Prostate Cancer:

diagnosis and treatment

Update of clinical guideline 58

Evidence review

Developed for NICE by the National Collaborating Centre for Cancer

This document is an update of the Evidence Review which accompanies NICE clinical guideline 58 (published February 2008) and will replace it.

Evidence has been reviewed on the diagnosis and treatment of men with cancer. New evidence which has been included as part of this update is highlighted in peach. You are invited to comment on this evidence only. Appendix L contains content from the 2008 Evidence Review which is being deleted as it has been updated.

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

Contents

1 Communication and Support

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

What are the communication methods that effectively inform men with prostate cancer (and their wives/ partners /carers /family) about treatment options?

Short Summary

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

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOMES
Men who need to make a decision about prostate cancer treatment options.	Information tools (e.g. DVD, written material, face to face meetings (such as contact with other prostate cancer patients, or support groups), courses, audio, video, websites, interactive and the more usual static types, nurse specialist or other MDT member)	▪ Usual care ▪ No contact person ▪ personalised' vs. generic information ▪ person vs. material vs. person plus material ▪ written vs. web based ▪ written vs. verbal ▪ other comparisons may have been evaluated and will be reported.	▪ Presence of communication between people and practitioners; ▪ decisional conflict; ▪ knowledge; ▪ realistic expectations; ▪ clarity of values; ▪ agreement between personal values for outcomes and choice; ▪ implementation of preferred choice; ▪ satisfaction with the decision, the decision making process, and the decision support provided; ▪ the actual choice made; ▪ health related quality of life; ▪ adherence to the chosen option; ▪ resource utilization; ▪ emotional distress (mechanisms for managing and coping with uncertainty related to cancer); ▪ anxiety (mechanisms for managing and coping with uncertainty related to cancer); ▪ depression; ▪ regret; ▪ Litigation rates.

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

Evidence Summary

The search found little evidence about the experience of culturally and linguistically diverse groups. A bias exists in the selection of only English language studies from the literature database search results.

The age group of men involved on the studies ranges from 65 to 75 years with a mean of 67years. This indicates that more evidence is required specifically about the men in the 70-75 year old age group.

The information provided to men varies in quality with evidence highlighting that high quality information is available but is often swamped by the vast quantity of low quality material that exists.

Evidence about information needs

The results of the systematic review of Echlin and Rees (2002) are presented below.

Content of information:

Davison (1995), Feldman-Stewart (2000), O'Rourke and Germino (1998), Krol (2000), Moore and Estey (1999), Heyman and Rosner (1996) and Gray (1997) provided survey data about the information about prostate cancer men want from their health services. This ranged from: likelihood of cure, stage of disease, types of treatments available, consequences of treatment failure, catheter care, pain control, and the management of urinary incontinence and impotence.

Context of information

Brandt and Moore and Estey provided survey evidence that the need for information before and after surgery differed. Before surgery, men expressed a need for information about comfort and activity restrictions during treatment and treatment efficacy. The areas of concern postoperatively were catheter care, pain control and the management of urinary incontinence and impotence.

Several men stated that they would have been able to cope better if they had been better informed. The participants stated that during treatment consultations and on the day of discharge from the hospital, they were too anxious to retain information.

Evidence about the quality of information

Fagerlin (2004), Rees (2003) and Meredith (1995) investigated the quality of the information provided to men (and others) about PCa. Both Fagerlin (2004), and Rees (2003) used defined criteria to evaluate the information material (Cochrane standards and the DISCERN instrument). Meredith (1995) made judgements using what oncologists, urologists, and patients reported as necessary and desirable information with what is currently in circulation for men and their families.

Fagerlin (2004) reported that 90% of patient education materials did not describe all standard treatments (watchful waiting, surgery, radiation, and hormonal therapy). 80% of the 44 materials that addressed standard treatments and underwent content review described anatomy, physiology, stage, and grade of cancer. 50% of the materials fully described radical prostatectomy and radiation therapy. One third of the materials included risks and benefits of each treatment; none explicitly compared outcomes of all treatments in a single summary. Information was accurate and balanced but did not include key content for informed consent.

Rees (2003) evaluated information leaflets for quality, readability and suitability using objective measures as described by the DISCERN instrument. The best five leaflets across the three conditions were identified using the scoring system of the DISCERN instrument. These included:

1. Screening for prostate cancer. The evidence by the NHS Centre for Reviews and Dissemination (CRD),
2. The treatment of prostate cancer. Questions and answers by the Covent Garden Cancer Research Trust,
3. Understanding cancer of the prostate by CancerBACUP,
4. Cancer of the prostate. Your questions answered by the Royal Marsden NHS Trust
5. Prostate cancer: everything you need to know by the Prostate Cancer Charity.

Meredith (1995) reported considerable shortcomings which included the lack of uniformity in form and content, topics of relevance to patients in the material examined. The terminology was often poor, and patients' experience was at variance with what their surgeons said. For example, only one fact sheet discussed the potential consequences of malignancy. Around 30% of men wanted more information on prostate cancer and 4% thought that the explanation of biopsy results was inadequate. Only six fact sheets discussed the possible changes in sexual sensation after transurethral resection of the prostate, stating that patients would feel no change, however, 35% patients reported a change and 12% were worried about it. Four thousand men were surveyed about their perspective on PCa information and 50 surgeons provided fact sheets used in their practice.

Evidence Tables

Echlin, K. N. & Rees, C. E. 2002 **Information needs and information-seeking behaviors of men with prostate cancer and their partners: a review of the literature** ***Cancer Nursing*, vol. 2002 Feb; 25, no. 1, pp. 35-41**
Design: Systematic review of combined study designs **Evidence Level**: 3
Inclusion criteria – The selection criteria for reviewed articles were as follows: (a) articles must address the information needs or information-seeking behaviours of men with prostate cancer and/or their partners, (b) articles must have been published between 1990 and 2000. This time frame was chosen to avoid historical artefacts resulting from the changes in information provision in recent years, e.g., since the Patient's Charter.
Exclusion criteria – Generic articles addressing the information needs of individuals with various forms of cancer are not included in this review because they are reviewed more globally elsewhere.
Population – See inclusion criteria
Interventions – The review included all types of information formats
Outcomes – Information needs of men with PCa and their partners: Types of Information Needed (pre-treatment, treatment related and post treatment) Information-seeking Behaviors of Men With Prostate Cancer and Their Partners: At Diagnosis, Treatment decision making and recovery
Results – Information needs of men with PCa and their partners: **Content**: *Davison* conducted a pilot study with 57 men newly diagnosed with prostate cancer to examine the types of information they considered important. Information preferences were determined by establishing the rank order of 9 information categories. The authors found that the 3 greatest areas of informational need were likelihood of cure, stage of disease, and types of treatments available. The effect of treatment on sexual activity

was considered least important.

Feldman-Stewart aimed to establish what questions men with prostate cancer wanted answered as they faced treatment decisions.

38 participants were recruited via urologists working in 5 Canadian practices (response rate =

68%) and were asked to complete a postal survey consisting of 93 questions pertinent to the treatment decisions of a man with PCa. Participants were asked to think back to the time just before their treatment decision and rate the importance of each question on a Likert scale.

The authors found low overall agreement about the subject matter participants believed was important to address (K= 0.17). The most frequently rated questions were

(a) If the treatment is not successful, what are my options?

(b) If the prostate cancer is not treated, will I die from it?

(c) If I delay treatments, is there a chance I can still be cured? and

(d) If the prostate cancer is not treated, how fast will it spread?

O'Rourke and Germino pilot study investigated the decision-making process as described retrospectively by 11 men with prostate cancer and 6 of their spouses. Men who had already made their treatment decisions and their partners were recruited from a self-help group to participate in focus group discussions. A single orienting question was asked of the participants.

The authors found that men with prostate cancer and their partners invested considerable time and energy attempting to obtain information about their disease, treatment options, side-effects, and the physicians who diagnosed and treated them.

Krol studied the information needs of 40 men with prostate cancer and 24 of their partners recruited from a Dutch hospital during a 2-month period.

Three questionnaires, found that both men with prostate cancer and their spouses wanted as much information about prostate cancer as possible.

Interestingly, the need for medical-technical information was higher than the need for psychosocial information.

The researchers found that spouses had a significantly higher need for information than patients, especially psychosocial information.

Moore and Estey explored the concerns of 63 men with urinary incontinence in the early weeks after radical prostatectomy. Men were recruited from 2 hospitals and participated in semi structured interviews. Follow-up visits were conducted with the participants until data saturation was achieved.

The major areas of concern postoperatively were catheter care, pain control, and the management of urinary incontinence and impotence.

Several men argued that they would have been able to cope better if they had been better informed.

Heyman and Rosner investigated the need for information about managing side effects and found that it was of immediate use after treatment.

Gray (in contrast to *Heyman and Rosner*) who investigated men's experiences with PCa self-help groups. Semi structured interviews were conducted with 12 men involved in 3 PCa sup-

port groups in Canada and found that once the treatment option had been made and the surgery completed the need for information was reduced.

Context (timing of information and delivery person) and Format:

Brandt explored the information needs of 22 men with prostate cancer recruited from a hospital undergoing brachytherapy.

The study found that the men had a diverse range of needs. For example, 24 hours before therapy, the greatest needs for information concerned the treatment, e.g., comfort measures and activity restrictions during treatment, and the efficacy of the treatment. In contrast, 24 hours after completion of therapy, participants required information about the side effects of treatment and the management of side effects.

Moore and Estey explored the concerns of 63 men with urinary incontinence in the early weeks after radical prostatectomy. Men were recruited from 2 hospitals and participated in semi structured interviews. Follow-up visits were conducted with the participants until data saturation was achieved.

The major areas of concern postoperatively were catheter care, pain control, and the management of urinary incontinence and impotence.

Several men stated that they would have been able to cope better if they had been better informed. Although the men had been informed about the consequences of treatment during consultations preoperatively and had received verbal and written information postoperatively, they were unprepared for the symptoms they experienced. The participants stated that during treatment consultations and on the day of discharge from the hospital, they were too anxious to retain information. This led to gaps and inaccuracies in knowledge between what the urologists believed their patients knew and the actual understanding of the patients.

General comments –

This review provides a critical review of recent literature pertaining to the information needs and information-seeking behaviours of men with prostate cancer and their partners.

It searches systematically for literature from various databases, and lists inclusion and exclusion criteria used for the evidence for the review. The results of the review are presented in a descriptive manner with no consideration to combining the results. (Although not possible from the different studies included in the review, mention of this may have provided some insight into the methodological rigour of the review).

If further details of individual studies included in this review are required please consult AM

Critical Appraisal of included studies:

Sample size restrictions applied for the following studies; Davison, Feldman-Stewart, O'Rourke and Germino, Krol, Brandt, and Moore and Estey.

Samples included in these studies are not representative of a wider population.

Feldman-Stewart and Moore and Estey included a homogenous population which does not encompass the diversity of perceptions within this group.

Davison, Feldman-Stewart and O'Rourke and Germino fail to establish the reliability and validity of their methods. O'Rourke and Germino, and Heyman and Rosner did not analyse the qualitative data independently to enhance the reliability of the analysis and did not conduct checks to ensure that their findings were valid.

Authors conclusions:

Despite the methodological limitations of the studies reviewed in this section, several conclusions can be drawn about the types of information needed by men with prostate cancer and

their partners throughout the cancer journey.

Before treatment, men with prostate cancer and their partners may require substantial information, particularly concerning the likelihood of cure, advance of disease, and treatment options. However, both the type and the amount of information required by this group may vary considerably between individuals. Although there is limited information about individuals' needs around the treatment phase, the greatest need for information appears to concern the treatment itself. After treatment, men with PCa may require information about managing the side effects of treatment and the issue of recurrence arises.

In the time immediately following diagnosis, information-processing abilities are generally low. During this time, men and their spouses are adjusting to the diagnosis and feel unable to take action. Information provided in this period may not be processed, leading to important deficits in knowledge. The participants of these studies did however overcome the overwhelming experience of a cancer diagnosis and compensate by seeking information rapidly. (this will be covered in more detail in a following question). Once the treatment decision has been made, the need for information is again low, while couples await therapy.

Information-seeking behaviour may increase immediately before and after therapy as information about the treatment and side effects becomes pertinent. Authors note that providing this information at earlier stages may be of little value if it is not processed.

There is some evidence that information-seeking behaviour continues after treatment as couples learn to manage their side effects.

Studies included in this Review:

Brandt B. Informational needs and selected variables in patients receiving brachytherapy. *Oncol Nurs Forum.* 1991;18:1221-1227

Davison, B. J., Degner, L. F., & Morgan, T. R. 1995, "Information and decision-making preferences of men with prostate cancer", *Oncology Nursing Forum*, vol. 22, no. 9, pp. 1401-1408.

Feldman-Stewart, D., Brundage, M. D., Hayter, C., Groome, P., Nickel, J. C., Downes, H., & MacKillop, W. J. 2000, "What questions do patients with curable prostate cancer want answered? *Medical Decision Making*, vol. 20, no. 1, pp. 7-19.

Gray RE, Klotz LH, Iscoe NA, et al. Results of a survey of Canadian men with prostate cancer. *The Canadian Journal of Urology.* 1997;4:359-365.

Heyman EN, Rosner TT. Prostate cancer: an intimate view from patients

and wives. *Urologic Nursing.* 1996;16:37-44.

Krol, Y., van Dam, F. S., Horenblas, S., Meinhardt, W., & Muller, M. J. 2000, "[Information needs of men with prostate cancer and their partners]. [Dutch]", *Nederlands Tijdschrift Voor Geneeskunde*, vol. 144, no. 9, pp. 431-437.

Moore, K. N. & Estey, A. 1999, "The early post-operative concerns of men after radical prostatectomy", *Journal of Advanced Nursing*, vol. 1999 May; 29, no. 5, pp. 1121-1129.

O'Rourke, M. E. & Germino, B. B. 1998, "Prostate cancer treatment decisions: a focus group exploration", *Oncology Nursing Forum* , vol. 1998 Jan-Feb; 25, no. 1, pp. 97-104.

Fagerlin, A., Rovner, D., Stableford, S., Jentoft, C., Wei, J. T., & Holmes-Rovner, M. 2004,

"Patient education materials about the treatment of early-stage prostate cancer: a critical review",

***Annals of Internal Medicine*, vol. 140, no. 9, pp. 721-728.**

Design: Systematic review of combined study designs (other), evidence level: 3

Country: US

Inclusion criteria

For print, and multimedia sources: National organizations

sources (including patient advocacy groups, government

organizations, pharmaceutical companies, insurance companies, health maintenance organizations, universities, and comprehensive cancer centres) were searched for materials. To be included, all materials must be widely available to the public at no cost.

For the Internet Material:

1. Web sites of prominent organizations

(including all of those identified during the print material, videotape, and CD-ROM search).

2. Web sites of pharmaceutical companies that had received approval from the U.S. Food and Drug Administration

to produce prostate cancer drugs.

3. A patient with prostate cancer strategy was adopted

using an open (broad-based) search strategy with Google

and Yahoo, which located more than 300 000 Web sites.

Exclusion criteria

Web sites composed of links to other Web sites or duplicated print materials previously reviewed. For example, the web site of the National Cancer Institute was not included.

Authors used the Cochrane criteria to eliminate all patient education materials that:

1) did not discuss the 4 standard prostate cancer treatments (watchful waiting, radical prostatectomy, radiation therapy, and hormonal therapy),

2) discussed only cancer in general, or

3) discussed only prostate cancer screening.

Population -

Interventions

The aim of this study was to assess the suitability (of publicly available patient education materials) to support informed decision making in early-stage prostate cancer.

Interventions included publicly available patient education materials about early-stage prostate cancer. This included material from the Internet, print and multimedia sources.

Outcomes

Assessments of the suitability (of publicly available patient education materials) to support informed decision making in early-stage prostate cancer.

Content and quality of this material was reported using criteria developed by authors based on Cochrane definitions and other literature sources.

For the content review the Cochrane-based criteria was applied and frequency of specific items presented was reported.

This criteria included:

1) All options must be presented (including, if appropriate, watchful waiting)

2) Potential harms as well as potential benefits must be presented?

A second-level detailed analysis, was also applied, this criteria was prostate cancer specific and included items such as:

- disease process,
- treatment information (description of clinical procedures,
- psychological effects and distinction between temporary and permanent outcomes.)
- participation in decision making,
- descriptions about the strength of evidence and
- quantitative representation of information.

These criteria formed the basis of the results section for the content review.

For the quality review the following factors were evaluated:

1) the accuracy of the information contained in the patient education material,

2) whether presentation of treatment options was balanced,

3) whether the information was comprehensible to the

average reader.

To determine the top-rated materials, a scoring system was developed that identified how many of the 54 essential criteria each piece of patient education material contained was conducted. To further evaluate the best materials identified through the simple content inclusion criteria, a health literacy expert performed an extensive plain-language review

on the top 5 print materials and top 5 Web sites. The review assessed characteristics of text and design that affect reading ease and comprehension, incorporating the widely used

Suitability Assessment of Materials system. Criteria included:

1) readability;

2) amount and organization of content;

3) writing style as it affects literacy demands;

4) graphics, layout, and typography;

5) evidence of learning stimulation;

6) cultural appropriateness.

Each criterion was evaluated according to specific sub characteristics rated on a 0- to 2-point scale (0=unsuitable; 1=adequate; 2=superior; or not applicable). Final scores were calculated as percentages based on a denominator of 44 possible points. The 0- to 2-point scale was then translated into grade level. Web sites were evaluated by using similar criteria.

Follow up

In the context of this review, the authors did report that several Web sites changed during the 4-month review period. The review described reflects assessment of Web sites between 1 September 2001 and 14 December 2001.

In April 2003, the top 5 and bottom 5 Web sites and brochures to determine whether they had changed substantially since our review. Outcomes of this update were not reported.

Results

The initial stage revealed 546 items and was reduced by

502 after applying the Cochrane criteria for all standard treatment options to be presented.

The remaining 44 materials (19 print materials, 19 Web sites, 4 videotapes, and 2

CD-ROMs) underwent a formal content and quality review. Discussion in this paper was restricted to print materials and Web sites because the authors describe that these are the tools most available to public audiences.

Content Review:

Disease process: 95% of print materials and 80% Web sites included basic information on prostate anatomy and physiology. 100% print materials and 95% of Web sites also discussed prostate cancer staging and grading (74% for print

and 84% for Web).

Treatment Information: 50% did not inform patients about the need for hospitalization (after radical prostatectomy) and only 53% of print materials and 21% of Web sites discussed the need for catheterization after a radical prostatectomy.

Many materials also did not include complete information on side effects. Most materials listed incontinence and impotence as side effects of treatments.

42% of print materials and 53% of Web sites discussed the likelihood of pain, nausea, or fatigue because of radiation therapy.

Few materials differentiated between permanent and temporary side effects, particularly for radical prostatectomy (26 % for print and 25% for web sites) or hormonal therapy (5% of print and 14% of web sites). For Radiation therapy the differentiation between permanent and temporary side effects, was more frequently reported. Approx 50% of print material reporting this and approx 42% for web sites.

Participation in Decision Making:

Most patient education materials (84% of print materials and 68% of Web sites) explicitly encouraged patients to be active decision makers. Support of shared decision making varied from simply stating that patients should talk with their physicians about their preferences and concerns to providing patients with questions for their physicians. The materials were adequate for describing treatment options but did not provide sufficient information to assist patients in their decision making.

Describing the strength evidence was addressed by identifying medical controversy that might exist about treatments, given that no clinical trial has revealed any differences in 10- to 15-year all-cause mortality across treatments for PCa, it is alarming to report that only 37% of print materials and 37% of Web sites described the lack of conclusive evidence.

Quantitative representation of evidence was lacking and none of the materials discussed recurrence or success rates; fewer than 50% of materials included any type of numeric or rate information. Only 1 Web site included graphical information.

For the Quality Review:

Accuracy and Balance of Print Materials:

No print patient education materials we evaluated had

clinically significant misstatements, although some references

were out of date because of the publication date. One case of clinically significant imbalance in the treatment descriptions was identified.

A general bias was found toward active treatment that minimized the role of watchful waiting. With the likelihood and impact of side effects were minimized.

Accuracy and Balance of Web Sites:

All sites reviewed were accurate, but some omissions were observed, typically underestimating side effects of

therapy. A paucity of content was observed in several sites which led them to generate somewhat misleading impressions.

Although a clinically significant imbalance

in treatment descriptions was not found in any Web site, a bias toward active treatment and minimizing the likelihood and effect of side effects was detected.

Plain-Language Evaluation:

Based on the content review, the top 5 web site and print materials were scored. Assessments made using the criteria outlined earlier, the readability level for all but 1 of the materials, was above the ninth-grade level. Authors state that this is acceptable for health information however; this level of reading difficulty is above the average reading ability of U.S. adults. They go on to suggest that upwards of half the population would have difficulty comprehending the material. Apart from the top 5 contenders, the other material used very clinical language, pages were text-laden and lacked design

elements to guide the reader. Most materials also lacked

visual appeal or illustrations to add human interest and

reinforce key points. And overall, the authors state that these materials did not follow guidelines for plain-language materials.

General comments

This study aimed to survey publicly available patient education materials and to assess their suitability to support informed decision making in early-stage prostate cancer. Using a systematic approach the review assessed and reported the content and quality of the material collected.

Authors point out that although shared decision making was encouraged as part of the content of the materials reviewed, suggesting this beneficial is not enough and that patients must be provided with guidance on how to engage in this process.

In 2004 (published year of this review) no decision aid was reported by this study.

The review describes the paucity of quantitative information found in the patient education materials may be due to the difficulty inherent in outcomes that are highly variable and hard to apply to a specific patient.

Limitations:

Only one reviewer was involved in judging the accuracy and balance issues of the material,

dual reviewing may have allowed for a more diverse perspective or quality assured the accuracy scores.

Unfortunately, this review was conducted in 2001 and no report of the 2003 update exercise was included. Given the rapid pace of health education materials, especially on the World Wide Web, it is necessary to continually provide the systematic and rigorous approach (as adopted in this study) to update this review.

Randomized controlled trials

Jones RB, J Pearson, A J Cawsey, D Bental, A Barrett, J White, C A White, W H Gilmour

Effect of different forms of information produced for cancer patients on their use of the information, social support, and anxiety: randomised trial

***BMJ* 2006;332;942-948**

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

Country: United Kingdom, setting: Secondary care

Inclusion criteria

874 patients identified from outpatient appointment diaries as starting radiotherapy treatment for breast, prostate, cervical, or laryngeal cancer were registered with the study, and their medical records were reviewed.

Of the 563 patients invited to take part, 400 (71%) consented. The 400 patients recruited comprised 275 (69%) women and 125 men with ages ranging from 28 to 82 years with mean age 59 (median 61).

Of these, 348 completed follow-up.

Patients had had their cancer diagnosed between five and 312 weeks before recruitment.

Two thirds (262, 68%) of the patients had breast cancer, and just under a third (118, 31%) had prostate cancer.

Exclusion criteria Reasons for exclusion included receiving palliative care, severe pain or symptoms causing distress, having cancer at other sites, having no spoken English, receiving treatment for psychological or psychiatric problems, visual or mental handicap, and case notes being unavailable, ambiguous, or illegible.

Population number of patients = 400.

Interventions (see attached table below)

The aim of this study was to explore the hypothesis that different methods of selecting and printing information for cancer patients could improve emotional support by affecting interaction with others, and so lead to improved psychological wellbeing.

Participants were randomised to 8 groups defined by the three binary factors under study:

(a) half received personalised information that included data from their medical records, whereas half had only general information from CancerBACUP for their cancer;

(b) half chose information interactively by selecting it with a computer at the oncology centre, and half had a larger volume of material in booklets that were produced automatically; and

(c) half had additional anxiety management advice, and half did not.

The patients given booklets that were produced automatically contained up to 40-47 sections and did not use the computer at the oncology centre.

Patients provided with general information only received the booklets Understanding Radiotherapy, Diet and the Cancer Patient, and the appropriate cancer-specific booklet (such as Understanding Breast Cancer)

Patients provided with general information and who selected information interactively could choose sections from the above three booklets and from three further CancerBACUP booklets (Cancer and Complementary Therapies, Feeling Better Controlling Pain, and Sexuality and Cancer). Patients were allowed to choose up to 10 sections from a menu. The anxiety management advice was an extra set of pages with self help advice based on work in cognitive behaviour therapy for anxiety.

The patients were allocated personalised information that was produced automatically received selected information from the three general booklets plus information from their medical records.

Patients were allocated personalised information that they chose interactively could select topics from their medical record such as problem list, treatment list, or your cancer.

For the patients who chose information interactively, sections chosen were recorded, and whether they required help with the computer, or whether they used the computer mouse or the touch screen.

Outcomes

Identification of information needs (content and format)

Social support requirement (as measured by the Helgeson's social support questionnaire (HSSQ) Helgeson's social support questionnaire produces four scores—instrumental, informational, and emotional support (20 = "best") and "negative interactions" (50 = "worst")

Anxiety and Depression levels (as measured using the hospital anxiety and depression scale (HADS). Scores ≥ 8 (cases or probable cases of anxiety or depression).

Follow up

Patients were sent follow-up questionnaires three months later.

The questionnaires included Helgeson's social support questionnaire, the hospital anxiety and depression scale, and questions about the patients' use and opinions of the booklets and their reported understanding of cancer.

Results

The aim of this study was to explore the hypothesis that different methods of selecting and printing information for cancer patients could improve emotional support by affecting interaction with others, and so lead to improved psychological wellbeing.

At recruitment, patients were asked to complete a questionnaire at home. From this questionnaire, there was no difference between the intervention groups in terms of anxiety, depression, social support, age, sex, or length of diagnosis.

Of the patients who answered the questions, 326/375 (87%) were satisfied or very satisfied

with the cancer information they had already received, 231/373 (62%) had read at least one CancerBACUP booklet. Only 52/382 (14%) had obtained health information themselves from the internet, but 67 (18%) had been given information from the internet by someone else, and 164 (43%) had never used a computer before.

199 Participants who interactively selected information the average time spent using the computer (including explanation given by the researcher) was 9 minutes (range 2-30). A third

required help in using the computer; two thirds chose to use the touch screen, and a third used the mouse.

Of the 82 (43%) patients who had not used a computer before, only two chose to use the mouse. The researcher operated the computer for four people. On average, patients chose eight sections (range 0-10); there was no difference by intervention or other factors.

The areas of information selected for PCa participants (n=29) included: Side effects, RT, understanding why RT was prescribed, healthy eating, PCa in general, possible PCa, general tips.

3 month follow up:

Patient opinions of booklets and perceived understanding:

The booklets produced automatically, which were larger than those produced interactively by patients, were more likely to be found useful and to tell the patient something new and less likely to be seen as too limited, but they were also more likely to overwhelm some patients than the booklets produced interactively.

The booklets with personalised information were more likely than those with only general information to tell the patient something new.

The patients given automatically produced booklets had higher overall satisfaction scores than those who produced their booklets interactively.

When asked to rate their current understanding of their cancer, 26 (8%) rated it less than they had done at recruitment, 188 (58%) rated it the same, and 110 (34%) rated it better, but there was no difference by any of the intervention factors.

113 participants (35%) made positive comments about the booklets, 38 (12%) made negative comments.

Patients with personalised booklets were more likely to mention the relevance of the information than those given only general information (41% vs. 15%; Chi Squared = 9.3, 1df; P = 0.002)

Use of the booklets with others:

Compared with patients with general information only, patients with personalised information were more likely:

- to show their booklets to their confidant (85% vs. 70%; Chi squared = 10.1, 1df; P = 0.001),
- to someone else in the household (32% vs. 19%; Chi Squared 2 = 6.8, 1df; P = 0.009), and
- to someone outside the household (33% vs. 22%; Chi squared = 4.3, 1df; P = 0.04).

There was no difference for the other two intervention factors.

Those with personalised information were more likely than those with general information only to think that it helped in discussing their cancer or its treatment (80% vs. 65%; Chi squared = 4.2, 1df; P = 0.04).

Changes in social support:

Patients' social support scores showed a considerable range of changes from baseline to follow-up. (From Helgeson's social support questionnaire)

Changes observed:

informational support ranged from - 12 to 12,

emotional support from - 10 to 7,

instrumental support from - 8 to 7, and

negative interactions from - 11 to 22.

There were unexpected differences by the intervention factors in those who had shown booklets to their confidant. The negative interactions scale showed 42% of patients with personalised information deteriorated, compared with only 24% of those with general information only.

Patients who were given anxiety management advice were more likely to have deteriorated on the instrumental support scale than those not given the advice (27% vs. 13%).

Changes in anxiety and depression.

At follow-up, 145 patients (45%) had improved anxiety scores.

General comments

This study has been included because it addresses issues that were deemed important to men with PCa and a substantial amount of men were included in the study. It must be noted that gender difference exist in responses and perceptions and this was not evaluated in the study.

Lepore, S. J., Helgeson, V. S., Eton, D. T. & Schulz, R. (2003) Improving quality of life in men with prostate cancer: a randomized controlled trial of group education interventions. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association,* 22: 443-452.

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

Country: United States, setting: Tertiary care

Inclusion criteria

Men with prostate cancer, living within 1 hour's driving distance of their institution. Of 362 eligible patients, 279 completed the baseline interview and agreed to randomisation.

Exclusion criteria

History of other (non-prostate) cancer, metastases at the time of diagnosis.

Population

number of patients = 279.

Interventions

Patients were randomly assigned to a control group, a group education intervention (GE), or a group education-plus-discussion intervention (GED). Group education was a series of 6 weekly lectures about prostate cancer topics of relevance to patients. The GED group also had a 45 group discussion after each lecture that was led by a clinical psychologist. The wives of the men in the GED arm also had separate discussion, led by a female oncology nurse.

Outcomes

Prostate cancer knowledge assessed using a 13 item quiz. Ratings of the lectures. Health behaviour index - questions to measure whether patients engaged in the recommended positive health behaviours. Quality of life, measured using the SF-36 scale. Depression was measured using the Center for Epidemiological Studies Depression Scale. Disease specific quality of life was assessed using the UCLA Prostate Cancer Index.

Follow up

29/279 patients (10%) were lost to follow up. Patients were interviewed at baseline, and at 0.5, 6 and 12 months after the intervention.

Results -

COMPARISON in Prostate cancer	Group education	Group education with discussion	Standard care	
Quality of life (SF-36)	Overall score not reported	Overall score not reported	Overall score not reported	No significant difference between groups at any time point (baseline, 0.5, 6 and 12 months) on mental and physical functioning items
Depression	mean (SD) CES-D score 0.54 (0.45) at baseline, 0.43 (0.42) at one year	mean (SD) CES-D score 0.49 (0.48) at baseline, 0.35 (0.44) at one year	mean (SD) CES-D score 0.46 (0.52) at baseline, 0.40 (0.49) at one year	No significant difference between groups at any time point (baseline, 0.5, 6 and 12 months).
Prostate cancer related quality of life	Overall score not reported	Overall score not reported	Overall score not reported	No significant difference between groups at any time point (baseline, 0.5, 6 and 12 months), statistically significant improvement with time for sexual and urinary functioning.

General comments

Mishel, M. H., Belyea, M., Germino, B. B., Stewart, J. L., Bailey, D. E., Robertson, C. & Mohler, J. (2002) Helping patients with localized prostate carcinoma manage uncertainty and treatment side effects: nurse-delivered psychoeducational intervention over the telephone. *Cancer,* 94: 1854-1866.

Design:

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

Country: United States

setting: Community

Inclusion criteria

Men with localised prostate cancer who were 2 weeks post catheter removal after RP or within 3 weeks of the start of radiotherapy. Men needed a telephone and an identifiable family member willing to participate. Men were recruited from 9 treatment centres**.**

Exclusion criteria

Cognitive impairment, other cancer.

Population

number of patients = 239, mean age = 64 years. (relatively young)

Interventions

A psycho educational intervention by phone to the men with prostate carcinoma, with or without supplemented delivery to a close family member. The intervention was directed at managing uncertainty and improving symptom control. The intervention was a weekly structured telephone interview with a trained nurse every week for 8 weeks. During the interview, symptoms and concerns were assessed and strategies were suggested. The control group received standard care only.

Outcomes

Uncertainty and uncertainty management programs (not reported in this appraisal). Number of symptoms, symptom intensity, control of urine flow, ability to have an erection and satisfaction with sexual function.

Follow up

Measurements were made at three time points: at entry into the study (baseline - T1), 4 months post baseline (T2) and 7 months post baseline (T3). Loss to follow up is not reported.

Results

Control over urine flow was rated on a 1 to 5 scale, 5 being complete control over urine flow.

COMPARISON	**Psychoeducational counselling (man only)**	**Psychoeducational counselling (man and carer)**	**Standard care**
in Men with erectile dysfunction after radical prostatectomy or EBRT			

Control over urine flow	Figures are group means (SD). At baseline 3.64 (1.16), at 4 months 4.52 (0.71) and at 7 months 4.56 (0.71)	At baseline 3.59 (1.19), at 4 months 4.59 (0.79) and at 7 months 4.73 (0.79)	At baseline 3.88 (0.93), at 4 months 4.41 (0.71) and at 7 months 4.51 (0.71)	In favour of the combined treatment groups at 4 months (Wilks lambda F=7.05; p=0.01), but no difference 7 months.

General comments Unclear who rated the symptoms (patient or nurse)

Davison, J. & Degner, L. F. 1997,

"Empowerment of men newly diagnosed with prostate cancer",

***Cancer Nursing*, vol. 1997 Jun; 20, no. 3, pp. 187-196.**

Design:

Randomized controlled trial (), evidence level: 1-

Country: Canada

Inclusion criteria

Diagnosis: newly diagnosed patients with prostate cancer who had been told their diagnosis and had not had their initial treatment consultation.

Exclusion criteria

Unable to read, speak, or write English; evidence of mental confusion.

Population

number of patients = 60,

age range 41 to 81 years.

Interventions

Consultation type: initial treatment consultation. Prior to the consultation (exact timing unclear), all patients were interviewed to introduce them to the idea that decisions would have to be made about treatment and that the investigator was interested in assessing the extent to which they would like to participate in making those decisions.

Baseline measurements were taken at this stage.

All patients were provided with the same written information package consisting of five brochures containing various types of information about prostate cancer.

Intervention group (n = 30):

Men in the intervention group were encouraged to consider what type of information they needed to assist them in deciding which treatment would be best for them.

Investigator and patient then examined a list of potential questions to ask the urologist.

They also reviewed the information package.

Additional questions that arose from the discussion were added to the list, and the final list of questions was given to the participant.

Each individual was given a blank audiotape and made responsible for asking the physician to tape their consultation. These men were also encouraged to bring their spouse/significant other to the treatment consultation.

Comparison group (n = 30):

Participants and their significant other were given the information package, showed what it contained and told that it might be helpful to read it before or after the initial treatment consultation with their physician. They were not given either support in its use or a consultation tape.

Outcomes

- Timing of outcome assessment: approximately 5 to 6 weeks after the initial interview.
- Psychology: the Spielberger State-Trait Anxiety Inventory (STAI), and the Centre for Epidemiologic Studies
- Depression Scale (CES-D).
- Participation: The Control Preferences Scale (CPS).
- Use and opinions of intervention: Sociodemographic Profile Questionnaire (SDQ) (Part Two).

Follow up

Part Two of the questionnaire was completed via a phone interview at approximately 5-6 weeks after the initial interview. Men in the intervention group were asked to evaluate the intervention at this time.

Part Two of the SDQ was completed to evaluate the intervention.

The CPS, CES-D, and STAI were sent out to all participants in a self-addressed envelope on the same day as the telephone interview.

Results

Objective: to determine whether assisting men with prostate cancer to obtain information would enable them to assume a more active role in treatment decision making and decrease their levels of anxiety and depression.

Method of analysis: Coombs' unfolding technique, chi-square test, Student's t-test.

Content:

various types of information about prostate cancer information that men thought they needed to assist them in deciding which treatment would be best for them.

Context:

Who: two consultants involved (urologist) and researcher (researcher and patient then examined a list of potential questions to ask the urologist.

When: initial treatment consultations with patients who had been previously told their diagnosis (exact details of this were not described).

Format:

written information package consisting of five brochures and audio tape of consultation with urologist.

Anxiety and/or depression

No statistically significant differential effect between the groups that received and did not receive recordings or summaries of their consultations.

Participation

A significantly higher proportion of participants in the intervention group assumed a more active role in treatment decision making than did participants in the control group.

Owing to the complex intervention, however, it is impossible to attribute this behaviour to the audiotape alone.

Use and opinions of intervention

- 26/30 (86.7%) people in the intervention group had their consultation audiotaped, of whom 22/30 (73.3%) listened to their tape from 1 to 4 times.
- 15/30 (50%) used the tape to review the consultation and to share information with their family.
- 8/30 (26.7%) used the tape to only review the consultation, and 1/30 (3.3%) used it only to share information with his family. 2/30 (6.7%) reported using the tape to assist them in treatment decision-making.

General comments

- Clinician and Assessor were not blinded
- Allocation concealment not used
- Randomisation: predetermined by block randomisation to ensure an equal number of patients for each
- physician (in fact, 34 were recruited from one physician and 26 from the other).
- Power calculation: not stated.
- Exact timing of the intervention delivery was unclear.
- The intervention was complex, having four main components (printed materials, question list, support and consultation audiotape). Hence, the significant differences in measured outcomes can only be attributed to the intervention as a whole.
- At pre-test I patients had significantly higher levels of state anxiety than C patients. This suggests that the groups were not comparable at baseline.
- Intention to treat analysis was not stated.

Johnson, J. E. 1996,

"Coping with radiation therapy: Optimism and the effect of preparatory interventions", ***Research in Nursing & Health*****, vol. 19, no. 1, pp. 3-12.**

Design: Randomized controlled trial, evidence level: 1-

Country: US

Inclusion criteria - Men scheduled to receive RT as an outpatient for localised PCa, written English language skills and at least 18 yrs old.

Exclusion criteria - Men could not have had previous or concurrent cancer diagnosis except basal cell skin cancer, no treatment of mental illness within the last 5 yrs,

Population –

62 patients receiving radiation therapy (RT) for prostate cancer met the inclusion criteria.

Sample number N = 62 (beginning of study)

Group 1. (Coping and self-care) = 22

Group 2. (Concrete objective) =20

Group 3. (Control) = 20

Mean age 69.6 yrs.

At all follow up points, n=62.

Clinical and demographic variables were distributed similarly amongst the groups.

Interventions –

3 intervention groups

1. Coping and self-care: ensuring that the man knows what he could do to deal with the experience of receiving RT.

2. Concrete objective: focussed toward allowing the patient to know what to expect and understand what would happen (helping him to deal with the experience of receiving RT)

3. Control: provision of information about treatment and the services provided by a cancer centre

The interventions were based on the self regulation model which asserts that “cognitive representations of impending experiences are instrumental to the process of coping”. And those cognitive representations consist of emotional, subjective and objective responses. The intervention for coping and self-care addressed the emotional/subjective responses (i.e. features included information about management of side effects and emotional stresses). The Concrete objective addressed the objective responses and provided information about treatment, duration of treatment, physical sensations to be expected).

Each of the 3 groups received 3 audio recorded messages delivered at:

a. prior to treatment planning
b. at the time of the second treatment
c. During the last week of treatment.

Men in all groups received written summary of information covered in each message.

The researcher delivered the messages and gave the intervention to the men (the author/researcher presumably).

Outcomes –

Expectancies: measured using an 8 item Life Orientation Test (LOT) with a 5 point scale; 4

strongly agree to 0 strongly disagree. Total scores ranged from 0-32.

Emotional Status: measured using a bipolar Profile of Mood States (POMS-BI). A list of 72 adjectives reflecting 6 moods. A 4 point Likert scale was used for each adjective. The higher the mood scores the more positive the mood, possible range -54 to +54.

Duration of usual activities: The Sickness Impact Profile (SIP), the score from this reflected the percentage of disruption in usual activities due to RT. Five categories made up the score and the category of recreation and pastime was the focus of this study (where the most impact was measured out of sleep/rest, mobility and social interaction and home management).

Clinical data focussed on presence or absence of side effects, and total number was the score allocated.

Mood and disruption of activities were assessed 3 times during and 3 times after RT.

Follow up At 2 weeks, 1 month and 3 months after termination of treatment.

Results

Content:

Group 1. Coping and self-care: ensuring that the man knows what he could do to deal with the experience of receiving RT (including the management of side effects).

Group 2. Concrete objective: focussed toward allowing the patient to know what to expect and understand what would happen during RT (helping him to deal with the experience of receiving RT) and including the experience of side effects.

Group 3. Control: provision of information about treatment and the services provided by a cancer centre.

Context/Format:

Each of the 3 groups received 3 audio recorded messages delivered at:

d. prior to treatment planning
e. at the time of the second treatment
f. During the last week of treatment.

Men in all groups received written summary of information covered in each message.

Results of the evaluation:

The self care instructions had no effect on mood or disruption of activities.

The concrete objective intervention (which described: simulation of treatment, experience of treatment (including side effects), changes in side effects) had a positive effect on mood among pessimistic men. The concrete objective information resulted in less recreation and pastime disruption in both optimistic and pessimistic men at the times they experienced the most RT side effects.

For ANOVA comparisons and numeric values please contact AM

General comments –

A combination of intervention group 1 and 2 would have been a valuable comparator to have included.

Although randomisation was performed, no allocation concealment was conducted and some blinding of the researcher was mentioned though not for the men involved.

Intention to treat analysis was not reported.

Power calculation was not included and from the sample size used, the study would have been underpowered. *Where statistical power analysis is a set of procedures and formulas (and includes sample size) that allow you to arrive at a number that says how likely it is that you would achieve statistical significance.*

Kim, Y., Roscoe, J. A., & Morrow, G. R. 2002, **"The effects of information and negative affect on severity of side effects from radiation therapy for prostate cancer",** ***Supportive Care in Cancer*, vol. 10, no. 5, pp. 416-421.**
Design: Randomized controlled trial, evidence level: 1- **Country**: US
Inclusion criteria -
Exclusion criteria -
Population – Men receiving RT as curative treatment for localised PCa as outpatients, having no previous or concurrent cancer diagnosis (except basal cell skin cancer), being able to speak and read English, having no history of mental illness or alcoholism, being capable of meeting daily basic needs independently (Karnofsky Performance status of at least 80%), and being 18 years or older. 184 men from 8 cancer centers were enrolled from 1991 to 1997; only 152 patients were fully evaluable. The mean age of the sample of 152 patients was 70.8 years (range 44–85 years). The distribution of disease stage: 13% with stage A, 66% with stage B, and 21% with stage C disease. Most of the patients (92%) did not receive hormonal therapy. Participants were randomly assigned to either the intervention group (*N*=77) or the comparison group (*N*=75).
Interventions – This study aimed to evaluate the efficacy of an informational intervention in ameliorating or preventing the development of side effects (from RT). The study works on the premise that: (a) a self-regulation perspective (side effects will be less severe and affect would be less negative for patients who receive an informational intervention than for

those who do not), and

(b) a negative affectivity perspective

(Severity of self-reported side effects would be positively associated with increased negative affect).

The intervention:

Men in both the intervention and the comparison groups listened to brief tape-recorded messages in the clinic before their first and fifth RT sessions.

The lengths of the audio-only tapes were 4 and 8 minutes, respectively, for these two treatments.

A member of the research staff stayed with each patient while the tape recordings were played.

The tape-recorded messages for the comparison group contained general and global information that was generally available to all RT patients, including resources available to them in the treatment setting.

The first message contained an explanation of the RT adapted from the pamphlet, "*Radiation Therapy and You*," it contained:

- Information about different types of RT,
- the use of high-energy X-rays to destroy cancer cells,
- how the type and dose of RT were matched to the type, location and size of the tumor.

The second message described the services available at the treatment facility (e.g. pharmacy for prescriptions, social services, etc.), the roles of the staff (e.g. treatment nurse, physicist, social worker, receptionist, and physician) involved in the patient's treatment, and a listing of community services available in the area (support groups, transportation, etc.).

The messages also included self-care instructions to help patients to control or lessen side effects. Clinic personnel answered all questions men had concerning their treatments.

After the first tape at the second treatment, the men completed the POMS and provided demographic and clinical information (POMS 1 early-treatment phase: time 1). At the last treatment, after the 5th treatment, patients were asked to fill out the POMS again and to complete the Severity of Side Effects Questionnaire (POMS 2 late-treatment phase: time 2).

Outcomes –

Severity of side effects: measured using a 5-point Likert scale (0=not at all, 5=extremely severe), for each of the following potential side effects: diarrhea, fatigue, skin changes and/or irritation in the treatment field, sleep disruption, and urinary problems.

Negative effects: measured by the tension-anxiety, anger-hostility, and depression-dejection subscales of the Profile of Mood States (POMS). 36 adjectives describe men's' feelings during the past week using a 5-point Likert scale (0=not at all, 5=extremely). An average score of the three negative emotions is calculated to create a composite level of negative affect.

Clinical and demographic data is collected.

Follow up –

Apart from the study procedure assessing men's responses throughout their RT, no follow up was done.

Results

Content:

Men in both the intervention and the comparison groups listened to brief tape-recorded messages in the clinic before their first and fifth RT sessions (i.e. 2 messages)

The first message contained an explanation of the RT adapted from the pamphlet, "*Radiation Therapy and You*," it contained:

- Information about different types of RT,
- the use of high-energy X-rays to destroy cancer cells,
- how the type and dose of RT were matched to the type, location and size of the tumor.

The second message described the services available at the treatment facility (e.g. pharmacy for prescriptions, social services, etc.), the roles of the staff (e.g. treatment nurse, physicist, social worker, receptionist, and physician) involved in the patient's treatment, and a listing of community services available in the area (support groups, transportation, etc.).

The messages also included self-care instructions to help patients to control or lessen side effects. Clinic personnel answered all questions men had concerning their treatments

Context:

Men in both the intervention and the comparison groups listened to brief tape-recorded messages in the clinic before their first and fifth RT sessions.

The lengths of the audio-only tapes were 4 and 8 minutes, respectively, for these two treatments.

A member of the research staff stayed with each patient while the tape recordings were played.

Format:

Audio taped messages.

Results:

The authors provide a concise summary:

Men in the informational intervention group reported less severe fatigue(marginally significant) and sleeping problems than those in the comparison group, and increased negative affect was positively associated with the severity of self-reported side effects, regardless of group assignment. However, skin problems were not associated with either group assignment or the change in negative affect. Baseline negative affect was not related to symptom development, although the development of side effects was associated with an increase in negative mood. The results suggest that men could benefit from increased knowledge about what to expect during their RT

No significant differences between the intervention and the comparison groups in age, disease stage, daily dose of radiation, total number of RT sessions, or field size.

The effects of information and negative affect on severity of side effects.

Group assignment contributed significantly to the severity of sleeping problems and was a marginally significant contributor to fatigue severity.

Group assignment was not significantly related to the other side effects or to change in negative affect. Subsequent t-test analyses revealed that patients in the comparison group reported more sleeping problems ($P<0.03$) and fatigue ($P<0.06$) than those in the intervention group. Thus the informational intervention reduced self-reported fatigue and sleeping problems, but it did not reduce negative affect or the three other side effects examined.

A change in negative affect would be related to side-effect severity was tested, this was true

fro diarrhoea, fatigue, sleep problems, and urinary problems, but not for skin problems.

The early-phase negative affect score was not significantly related to side-effect development in any of the analyses. Greater fatigue was associated with assignment to the comparison group (P<0.052) and with an increase in negative affect (P<0.02). Sleeping problems were also associated with being in the comparison group (P<0.02) and with an increase in negative affect (P<0.001). Urinary problems and diarrhoea were associated only with concurrent negative affect (P<0.002 for each), while skin problems were not associated with any study variables

The results of the present study indicate that specific side effects of RT for prostate cancer can be reduced by an informational intervention and are related to change in negative affect during the course of treatments.

General comments –

No blinding, allocation concealment, no power analysis was conducted.

Longitudinal data is required to assess the impact of side effects and psychological factors.

Overall an informative study, providing a useful intervention. Although conducted in the States it could be introduced in the UK, service arrangements might require adjustment. Applying this intervention in an actual clinic setting is required to assess if this can effectively applied.

Templeton, H. & Coates, V. 2004,

"Evaluation of an evidence-based education package for men with prostate cancer on hormonal manipulation therapy",

***Patient Education & Counseling*, vol. 55, no. 1, pp. 55-61.**

Design: Randomized controlled trial, evidence level: 1-

Country: UK

Inclusion criteria –

Men with a known diagnosis of PCa, who commenced HMT within the year 2000. From the sampling process. 60 men fulfilled these criteria.

Exclusion criteria –

Confused or terminally ill patients and patients who were unaware of their diagnosis were excluded

Interventions –

The aim of this study was to evaluate the effect of an evidence-based education package on the knowledge of disease and treatment, quality of life (QOL), coping and satisfaction with care of a sample of men with prostate cancer on hormone manipulation treatment (HMT).

A pre-test questionnaire assessed outcome listed.

The intervention was the delivered to the EG group of men after the pre-test.

The post – test questionnaire was conducted (timing not reported)

The intervention:

- Verbal information and a printed booklet were provided to the men.
- The researcher read through the information booklet with each participant.
- The men were asked if there was any information that they would like clarified and the main points were summarised.
- Other practical tips for promoting patient understanding of information were integrated into the delivery of the education package and included allowing the patient to decide the speed of the delivery of the intervention, respecting silence, repeating information as required and the use of simple language with simple explanations.
- Men were made aware of the means by which they could obtain further information.

Information included theoretical and contextual issues pertinent to PCa. Readability levels were assessed and diagrams were used to explain concepts. No exact details of the information were described only a description of these theoretical and contextual issues were listed.

Outcomes –

- Knowledge of PCa and HMT
- QoL using the FACT-P (Functional Assessment of Cancer Therapy-Prostate cancer version made up of physical, social/family functional and emotional well-being and prostate cancer specific (PCS) subscales.
- Coping Assessment: measured using the Jalowiec Coping Scale (JCS-40), which assesses affective and problem-oriented coping strategies.
- Patient satisfaction: measured with the Client Satisfaction Questionnaire (CSQ-8).
- Demographic details.

Follow up A post – test questionnaire was conducted (timing not reported)

Results –

Content:

Information included theoretical and contextual issues pertinent to PCa. Readability levels were assessed and diagrams were used to explain concepts. No exact details of the information were described only a description of these theoretical and contextual issues were listed.

Context:

The education package was delivered to the EG following completion of the pre-test questionnaire by the researcher.

Time taken to describe the booklet and its contents were not described.

Format:

Verbal information and a printed booklet were provided to the men.

Results of the intervention:

58 men participated:

- control group (CG) (*n*=29)
- experimental group (EG) (*n*=29)

At follow-up 55 men replied giving a response rate of 85%. (EG=28; CG=27)

Knowledge of PCa**:**

A potential score of 14 could be obtained.

CG pre-test mean score = 3.19 (S.D. =1.96) EG pre-test mean score = 4.04 (S.D. =1.88) No significance difference existed between the groups regarding their pre-test knowledge of disease (t=−1.644; df =53; P=0.106).

CG post-test mean score = 4.04 (S.D.=3.30) EG post-test mean score = 11.11 (S.D.=3.33)

When the pre-test and post-test mean scores for knowledge of the men in the EG were compared, a significant difference was observed (t=−12.769; df.=27; P<0.001)

No significant difference existed between these scores in the CG (t=−1.940; df. =26; P=0.063).

Knowledge of Treatment:

A potential score of 10 could be obtained.

For the pre-test mean scores:

EG = 2.89 SD=1.37,

CG = 2.41, SD=1.58

For the post-test mean scores:

EG = 7.46, SD = 2.33

CG = 2.67, SD = 2.27

QoL:

At pre-test, no statistical difference existed in any of these subscales between the EG and CG.

For EG, a significant difference existed in all subscales of the FACT-P between pre- and post-test

For CG, no significant difference existed in the majority of the subscales between pre- and post-test, apart from the PCS, which declined at post-test.

Coping:

The study reports that both the EG and CG used 'problem-oriented' coping mechanisms more often than 'affective coping' mechanisms at pre and post-test.

On further analysis, it was found that there was no difference in the coping mechanisms utilised by the CG (t=−1.35; df. =26; P=0.188) or the EG (t=−1.585; df. =27; P=0.125) between pre- and post-test.

Patient satisfaction:

With a possible cumulative score of 32 for the CSQ-8, the following were observed.

A significant difference between the groups at pre-test was found, with the CG more satisfied with their care (t=2.442; df. =53; P=0.018).

No significant difference existed between the pre- and post-test CSQ-8 scores of the CG (t=−1.925; df. =26; P=0.065).

Satisfaction with care was significantly improved in the EG between pre- and post-test (t=−6.476; df. =27; P<0.001).

No significant difference existed between the age groups, marital status and social class of

the CG or EG regarding satisfaction with their care.
General comments – Limits of this study include: Authors note: It was believed that interviewer presence at post-test could have introduced bias into the study. They suggest inclusions of a booklet only group in further evaluations. Stage of disease was not measured in this study, which could have yielded different results had it been administered prior to treatment. Ongoing long term effects would be valuable results to observe. Allocation concealment and blinding were not conducted in this study. Power calculations were not included. *Where statistical power analysis is a set of procedures and formulas (and includes sample size) that allow you to arrive at a number that says how likely it is that you would achieve statistical significance.* Further applicability will need to be tested with a larger, more diverse group of men. Generalizability to the UK setting is achieved.

Lepore, S. J. & Helgeson, V. S. 1999, **"Psychoeducational support group enhances quality of life after prostate cancer", *Cancer Research Therapy & Control*, vol. 8, no. 1-2, pp. 81-91.**
RCT, level 1- **Country : US** **Setting: community**
Inclusion Criteria: Men who had surgery or RT for localised PCa.
Population: Men from 4 physician led centres who had surgery or RT for localised PCa. 24 men participated. Control group: n=12 Intervention group: n=12 More men in intervention group had stage C PCa, and more men in control group had stage a (Jewett stage system used) Slightly more men in the intervention group had RT. 50% more men in the intervention group had hormonal treatment than the control group. No sig. diff was observed between the groups.

Age range of participants was not included, only a statement about the 'advanced age' of the group.

Both groups, at 1-2 weeks completed a pre-intervention interview (in men's' homes.)

At 2 weeks post-intervention, another interview was conducted.

Several outcomes were measured at each time point of pre and post-intervention (referred to as period) for each group control and intervention (referred to as group) – see outcomes

Intervention

This study investigated the efficacy of a psycho-educational support group intervention to improve the quality of life of men with PCa.

Men had received treatment (surgery or RT).

The intervention consisted of 6 weekly meetings.

Each meeting was a 40 minute lecture delivered by an expert in a different field. Followed by a 20 minute discussion time involving facilitators, men and their partners. For discussion time, men and women convened in separate rooms with separate facilitators.

Experts included a medical oncologist, a nutritionist, incontinence nurse specialist, urologist, clinical psychologist and oncology nurse.

Facilitators included a male clinical psychologist and a female oncology nurse.

Topic of weekly meetings included:

- Overview of PCa
- Cancer nutrition and exercise
- Managing Physical Side effects
- Stress Management
- Communication and Intimacy
- Follow-up care

Please ask AM for details of the content of each lecture.

The control group did not attend a series of weekly meetings.

Outcomes:

- Knowledge
- QoL: Physical and mental function (SF-36)
- Interpersonal conflict (Lepore Social Conflict scale)
- Intrusive and avoidant thoughts (Impact of Events Scale, IES)
- Self Efficacy (perceived personal control)

Results:

Knowledge:

Pre-test score for both groups was very low. A significant group X period was observed, $F(1, 22) = 20.85$, $p<0.001$. The intervention group showed a greater improvement in knowledge after the intervention compared to the control group.

QoL:

When a series of statistical test (ANOVAs) were conducted between group and period on, each of the different scales that make up the QoL outcome it found there was no significant differences.

A group by period interaction effect on mental health ($F (1, 22) = 5.15$, $p<0.05$). The intervention group had greater gains in their mental health scores over time that the control.

Psychosocial Outcomes

A significant difference between group by period interaction on the amount of conflict with spouse ($F (1, 20) =8.84$, $p<0.01$) and family/friends ($F (1, 22) =6.23$, $p<0.05$). That is, over time, controls reported increases in interpersonal conflict with wife and with family/friends compared to the intervention group, who reported no change in conflict with wife or family/friends.

A significant difference between group and period interaction ($F (1, 19) =4.57$, $p<0.05$) on self efficacy was observed. That is, over time, the intervention group had a greater increase in self efficacy that the control group.

Neither group showed a significant change in frequency of avoidance or intrusive thoughts about cancer. There was a significant difference between group and period interaction ($F(1,21)=4.63$,$p<0.05$) on ratings of distress by intrusive thoughts, that is, men in the intervention group tended to be less distressed by intrusions compared to the control group.

Social support:

The study examined the effect of participation in the psycho-educational support group and addressing unmet support needs. To do this, the interaction between social support (with wife and family/friends) and changes in mental health as a function of Group was analysed. Authors hypothesised that inadequate support would be associated with poorer mental health in the control group and not in the intervention group.

The analysis indicated that dissatisfaction with wife support and low levels of received support from family/friends were associated with poorer mental health in the control group. But not with the intervention group.

From this analysis authors conclude that men with unmet support needs benefited the most from the intervention, suggesting that education and emotional support can be provided in the form of a the psycho-educational support group to men who cannot get adequate information and emotional support from their social networks.

Follow-up:

At 2 weeks a post-intervention interview was conducted

COMMENTS

No blinding, allocation concealment, no power analysis was conducted.

Longitudinal data is required to assess the impact of group support intervention and psychological factors.

Authors point out that amidst the current thought (from literature and anecdotally) that men do desire to discuss their experiences, both emotional and practical, in a group discussion format. They based this point on the fact that they achieved an accrual rate of 83% and 100% follow-up rate (pre and post-test numbers). Given the small numbers involved in this study, it would seem a little presumptuous to make this claim. The intervention requires further assessment with larger numbers of men before a conclusive effect size can be deduced.

Prospective cohort study

Onel, E., Hamond, C., Wasson, J. H., Berlin, B. B., Ely, M. G., Laudone, V. P., Tarantino, A. E., & Albertsen, P. C. 1998, **"Assessment of the feasibility and impact of shared decision making in prostate cancer",** ***Urology*, vol. 51, no. 1, pp. 63-66.**
Design: Prospective cohort study (), evidence level: 2+ Country: United Kingdom, setting: Primary care
Inclusion criteria Patients presenting to any 4 physician practices with newly diagnosed PCa. 111 men viewed the video, 48 - 83 mean 67 97 men completed questionnaires. 95 of this group completed follow-up questionnaires.
Exclusion criteria Incomplete medical records or failure to complete the initial survey.
Population Number of patients = 111, age range 48 to 83 years, mean age = 67 years.
Interventions This study explored the feasibility of using a standardised video presentation in a busy practice in order to increase patients' understanding of their disease and treatment options. **Content**: The video presentation discussed risks and benefits of PCa treatment, details about potential treatment outcomes associated with radical surgery, EBRT, and watchful waiting. The video had 6 different version and were adjusted according to the risk factors of the patient (age, Gleason score, tumour grade) **Format**: 45 minute video presentation **Context**: Who: No information about who made the presentation. When: The video was played after the 30-minute standard consultation with an urologist in the practice or the patient could take the video home to watch (most elected to take it home to watch). After viewing the video, the patient then had a discussion with the treating physician.
Outcomes Knowledge assessment about familiarity with disease process and the different treatment op-

tions. Perceptions regarding patient participation. Satisfaction with decision

Follow up

A follow up questionnaire was conducted to assess final treatment decision and the impact of their discussion with their treating physician.

Results

A questionnaire recorded patients' responses before and after viewing the video. A follow up questionnaire was conducted to assess final treatment decision and the impact of their discussion with their treating physician.

Content:

The video presentation discussed risks and benefits of PCa treatment, details about potential treatment outcomes associated with radical surgery, EBRT, and watchful waiting.

The video had 6 different version and were adjusted according to the risk factors of the patient (age, Gleason score, tumour grade)

Format:

45 minute video presentation

Context:

Who: No information about who made the presentation.

When: The video was played after the 30-minute standard consultation with an urologist in the practice or the patient could take the video home to watch (most elected to take it home to watch). After viewing the video, the patient then had a discussion with the treating physician.

Results of the interventions:

Patient understanding of disease process (as reported by patients in the questionnaire)

Pre video 56% poor/fair
38% good/very good
6% excellent

Post-video 6% poor/fair
80% good/very good
14% excellent

Post-Physician 6% poor/fair
55% good/very good
40% excellent

Patient perceptions about participation in treatment decision.

For Surgery: 84% were satisfied with choice
82% indicated that they participated a lot
66% indicated they would choose the same treatment again

For RT: 94% were satisfied with choice
84% indicated that they participated a lot
55% indicated they would choose the same treatment again

For Hormonal treatment: 100% were satisfied with choice 82% indicated that they participated a lot 71% indicated they would choose the same treatment again For watchful waiting: 91% were satisfied with choice 75% indicated that they participated a lot 68% indicated they would choose the same treatment again 2 patients out of 97 expressed the desire to let the physician make a treatment decision.
General comments Limitation of study: Bias exists because of the lack of randomisation, assessment and questionnaires were not described so it is difficult to make an objective assessment of outcomes listed. It would be valuable to have had statistical analysis of proportions reported. As well as an analysis of the relationship between knowledge assessments and treatment decisions.

Flynn, D., van, S. P., van, W. A., Ahmed, T., & Chadwick, D. 2004, **"The utility of a multimedia education program for prostate cancer patients: a formative evaluation",** ***British Journal of Cancer*, vol. 91, no. 5, pp. 855-860.**
Design: Prospective cohort study, evidence level: 2- Country: UK
Inclusion criteria -
Exclusion criteria -
Population – The participants were 67 men recently (1 week or less) diagnosed with prostate cancer. The men were selected based on consultant urologists' assessment of their suitability for inclusion in the study. The age range was 48-89 with a mean age of 65.7 years (SD=7.95). The percentage of participants with secondary (school, aged 16), further (college, aged > 16) and higher education (university ages > 18) was, ages 50, 36 and 14% respectively. The majority were married (90%), retired (76%), resided in their own homes with at least one other person (84%) and attended the study session with their spouse (70%).

Interventions –

A multimedia program (MMP) was developed to educate patients with prostate cancer about their disease.

This study conducted a 'formative evaluation' by investigating the effect of the MMP on knowledge acquisition, psychosocial functioning, preference for participating in treatment decisions and information needs of patients recently diagnosed with PCa.

The authors state that a formative evaluation is an evaluation that takes place before actual implementation of a final product, and which influences the development of the product (a pilot study).

A within-subjects design was used to evaluate the utility of the MMP.

The study evaluated the intervention at: pre-trial - immediately before using the MMP post-trial - immediately after using the MMP.

Outcomes –

The outcome measures were the level of cancer-related knowledge, psychosocial functioning, treatment decision-making role and information needs.

Psychosocial functioning was assessed with 20 items describing common emotional states and coping strategies employed by cancer patients. A principle component analysis of the 20 psychosocial items yielded three components: distress, positive approach and non-acceptance.

Treatment decision-making role was assessed with the Control Preference Scale.

Information needs were assessed from a free text response on the questionnaires. Participants recorded their most important information need at pre- and post-trial. They were also asked to state the most important knowledge they had acquired at post-trial.

Follow up –

The study evaluated the intervention at: pre-trial - immediately before using the MMP post-trial - immediately after using the MMP

Results –

Content:

An MMP (developed using previous research on the information needs of prostate cancer patients, such as Davison 95) and a working committee consisting of two consultant urologists, a health psychologist, a psychologist specialising in human-computer interaction and a multimedia developer.

The MMP was comprised of six cancer-related modules:

(a) prostate anatomy,

(b) disease stages, aetiology and symptoms,

(c) diagnostic techniques,

(d) treatment options (surgery, hormonal therapy and radiotherapy) and side effects, which included a research update,

(e) coping strategies and

(f) further information (self-help groups, prostate cancer organisations, further reading and a cancer glossary).

Context:

The MMP was operated on a stand-alone PCa and participants navigated through the MMP using a mouse.

Participants were instructed how to use the MMP by a research assistant who was present throughout the study session. No time limit was imposed on patients for browsing the MMP

After the consultation where the diagnosis of PCa is delivered, the urologist or prostate cancer nurse informed the participant about the study and provided them with a study information sheet (that detailed the study aims and rationale) and a consent form.

Participants were given the choice of participating immediately, or within 1 week after the diagnosis consultation. They were also given the choice of attending the study session with a significant other or alone. A private room situated within the urology department was used to conduct the study.

Format:

The MMP combined text with sound, narration, images, animation and streaming video.

The interface used a selection of on-screen buttons (forward, back, exit) that controlled interaction and navigation through the MMP.

Results of the evaluation:

Knowledge:

After browsing the MMP significant increases in knowledge, that is, overall levels of correct responses significantly increased between the pre- and post-trial conditions (t [59]=4.49, P<0.001).

The following knowledge components all showed a significant increase from pre and post trial conditions: cancer in general, PCa anatomy, disease advancement, aims and side effects of RT and hormone treatment.

Knowledge did not change for aims and side effects of surgery.

A multiple regression analysis showed that being married was a significant predictor of overall knowledge gain between the pre- and post-trial conditions (R^2=0.10, P<0.05).

Psychosocial functioning (Distress):

A related t-test revealed that distress decreased significantly between the pre- and post-trial conditions (t [58] =2.35, P<0.05)

Treatment Decision Making:

In the pre- and post-trial study conditions, 68 and 71% respectively of participants preferred an active or collaborative role in treatment decisions.

No significant differences in treatment decision-making roles between the pre- and post-trial study conditions was observed.

A significant shift in preferences for a more active role in treatment decisions was reported for

(a) participants who attended the study session with their spouse or partner (z= -2.9, p< 0.05)

(b) participants who were married (z= -1.98, p<0.05)

Information needs:

A frequency analysis revealed six categories of primary information needs at pre-trial: likelihood of a cure (28%),

Treatment side effects (15%),

Coping strategies (13%),

Diagnostic tests (12%),

treatment duration (7%) and

Aetiology (4%).

In total, 19% stated that they had no information needs at pre-trial.

At post-trial, five categories of information needs displayed at least a 40% decrease, with only aetiology displaying a negligible increase.

Approximately 66% of the participants indicated that they required no further information needs at post-trial.

Seven categories were reported as the most important knowledge acquired:

Hereditary risks (30%),

Aetiology (24%),

Likelihood of a cure (4%),

Disease advancement (4%),

Coping strategies (2%),

diagnostic tests (2%) and

Treatment side effects (2%).

Approximately one third could not decide upon the most important knowledge they had acquired.

General comments –

Authors report that the findings of their study is consistent with other studies that have found that an interactive patient education interventions will significantly reduce distress, gain more cancer-related knowledge, and increase the desire for a more active role in treatment decisions. The authors point out that the reduction in distress is an important finding given that less distressed patients are better able to make sense of their experience with cancer and seek desired information (as reported by another study).

Other important conclusions about this study include:

Some inconsistencies with previous research which reports the majority of men within 0-13 weeks of receiving their diagnosis preferred a passive decision-making role (Davison et al 1995). However, more recent studies show similarity with the current study reporting that 68% (Davison and Degner 97), 75% (Wong et a) and as many as 93% (Davison et al 02) of men recently diagnosed prefer either an active or collaborative role in treatment decisions. This trend in the current study could be attributed to the relatively low mean age of the study participants (Davison et al 02), and/or spousal support that served as a catalyst to learn and take part in shared decision-making.

References cited above:

*Davison,B.J.; Degner,L.F.; Morgan,T.R.*1995 Information and decision-making preferences of men with prostate cancer. Oncology Nursing Forum 22: 1401-1408

Davison, J. & Degner, L. F. 1997, "Empowerment of men newly diagnosed with prostate cancer", *Cancer Nursing*, vol. 1997 Jun; 20, no. 3, pp. 187-196

Wong et al 2000 Men with prostate cancer: influence of psychological factors on informational needs and decision making. Journal of Psychosomatic Research. 49: 13-19

Davison et al 2002 Assessing information and decision preferences of men with prostate cancer and their partners. Cancer Nursing. 25:42-49 Limitations of this study include: Problematic sampling method (due to the selection by urologist the participants may have produced an unrepresentative sample as reasons for exclusion were not recorded. Generalizability to a wider population of men with PCa is difficult because the participants' disease stage and functional status was not recorded. Furthermore, given the generally late onset of prostate cancer, the mean age (66 years) of the study participants was relatively young. A research assistant supported the participants throughout the study session, which may have impacted upon the participants' level of distress and could possibly have impacted and biased the knowledge uptake and desire to participate in treatment decisions. The authors also recognise that this level of support needs to be evaluated for the effectiveness of the MMP.

List, M. A., Sinner, M., & Chodak, G. W. 1999, **"Improving knowledge about prostate cancer: The development of an educational program for African-Americans",** ***Prostate Cancer & Prostatic Diseases*, vol. 2, no. 4, pp. 186-190.**
Design: Prospective cohort study, evidence level: 2- Country: US setting: community
Inclusion criteria -
Exclusion criteria -
Population – Participants were recruited through advertisement within African American community networks. They included both men (not necessarily with PCa) and women
Interventions – To evaluate the content and format of an educational program about PCa. A one-hour educational seminar presented by a Health educator in conjunction with a series of slides. Content was made up of information about general on the prostate gland, BHP, PCa, methods (not sure what this means), controversies about screening and diagnosis, risk factors for PCa, early symptoms, common cancer myths, and treatment options. A baseline questionnaire recorded demographics and knowledge levels of PCa related issues. The seminar was delivered by a health educator and then a post-seminar questionnaire was completed by participants (assessing knowledge levels).

Outcomes –

Knowledge levels (pre and post-seminar).

The questionnaire used to assess knowledge was prepared in house in consultation with health care providers and men with PCa.

Results –

Content:

A one-hour educational seminar presented by a Health educator in conjunction with a series of slides. Content was made up of information about general on the prostate gland, BPH, PCa, methods (not sure what this means), controversies about screening and diagnosis, risk factors for PCa, early symptoms, common cancer myths, and treatment options.

Context:

Delivered by a health educator, specifically employed to deliver the seminar.

Timing is not described.

Format:

2-12 people attended the seminar program

Results of the evaluation:

52 African Americans completed the pre and post-seminar questionnaires. 71% were male, 90% with at least a high school diploma.

Pre seminar correct responses (mean) = 20.2% (+/- 15%)

Post seminar correct responses (mean) = 67.3% (+/-20%)

A significant difference was observed between these scores, $p<0.001$. The knowledge levels increased significantly after the seminar program.

Post seminar questions where only 50% or less of participants correctly answered questions were:

- Is it true/false that PCa is the most common cause of urinary difficulties in men?
- Which group of men will benefit most from PCa screening?
- Issues about side effects after surgery.

General comments –

This pilot study was able to provide some preliminary findings about the lack of knowledge of some African Americans and that an educational seminar could possibly address this issue.

The intervention requires further unbiased studies, e.g. controlled studies. Sampling was not adequate, purposeful sampling has a selection bias for specific types of people. Participant group was not exclusively men with PCa.

Authors note that they considered information to have been adequately conveyed if at least two thirds (65%) of participants responded correctly at Post seminar questionnaire. While only 3 areas were reported below 50% another 3 areas were below this limit. One of these important areas was about treatment option available to men with early stage PCa. *This reflects an inadequate proportion of knowledge about treatment options.* Authors do point out they are reviewing the wording, format and presentation that is associated with this area of the program.

Feldman, J. S. 1993, **"An alternative group approach: using multidisciplinary expertise to support patients with prostate cancer and their families",** ***Journal of Psychosocial Oncology*, vol. 1993; 11, no. 2, pp. 83-93.**
Design: Cohort Study, evidence level: 2- **Country**: United States, setting: Community
Inclusion criteria - men with metastatic PCa and family members
Exclusion criteria -
Population – 58 participants: 35 men with metastatic PCa and 23 family members 43-75 yrs: 46% in their 60s. The men were currently involved in a drug trial (suramin). No further details about sampling were provided.
Interventions – In order to address the psychosocial needs of the men involved in the suramin trial the researcher developed a support group intervention, The Suramin Club. The purpose of the Club was to provide a forum for men and their families to gain information about the drug they were taking, discuss problems, gain mutual support and reduce the isolation they experienced.
Outcomes – A Likert-scale was used to measure utility of the support group programs/meetings N=11 and trips/excursions N=4. (1= least useful to 4= very useful, beneficial)
Follow up Participants were interviewed about utility from 2 weeks up to 4 months after each program session.
Results – **Content**: Oral presentations/programs were provided at the meetings covering topics such as: ▪ Information about PSA ▪ Information about Suramin and the trial ▪ Relaxation therapies ▪ Coping with Cancer related stress

- Pain management
- Diet and nutrition
- Managing psychosocial responses to illness and treatment.
- Field trips/excursions.

Context:

- A clinical social worker and therapeutic recreation specialist led the group and co-ordinated the programs.
- A patient representative was also involved to bring this perspective to the development of the programs the Club provided.
- Programs were conducted by physicians, therapeutic recreation specialist, social worker, nurse specialists and dieticians.
- The Club met weekly. And continued for 15 weeks

Format :

Support Group which includes discussion groups, oral presentations and field trips/excursions.

Utility Scores:

No major differences between men and women's scores were observed, however, no statistical analysis was conducted.

Overall mean scores for

- Pain management
- Information about PSA
- Information about Suramin and the trial

Ranged from 3.4 to 3.6.

Overall mean scores for the trips/excursions ranged from 3.8 to 4.

General comments –

Several limitations exist with this study. Along with no hypothesis testing and the lack of random sampling and allocation of intervention, this study severely hinders the evaluation of how effective this intervention was at addressing the objectives. The evaluation conducted is limited and unsophisticated.

Given the general evidence base about the effectiveness of support groups for men with PCa, this study provides a very limited contribution.

Observational study

Meredith, P., Emberton, M., Wood, C., & Smith, J. 1995,

"Comparison of patients' needs for information on prostate surgery with printed materials provided by surgeons",

***Quality in Health Care*, vol. 1995 Mar; 4, no. 1, pp. 18-23.**

Design: Observational study (therapy), evidence level: 3

Country: United Kingdom,

setting: Secondary care

Inclusion criteria

87 surgeons selected from all NHS and independent hospitals performing prostatectomy in four health regions were included.

Men participating in a national prostatectomy audit were included in a 2 part survey study that asked about information needs. Part 1 was a closed response questionnaire and Part 2 was an open ended in-depth questionnaire.

Exclusion criteria -

Population -

Interventions

This study aimed to assess existing leaflets and factsheets on prostatectomy given by surgeons to patients, with specific attention to identification of strengths, weaknesses, and omissions in the material.

The design involved a comparison of content of leaflets and factsheets with patients' needs and discontents in a questionnaire survey as part of the national prostatectomy audit.

Outcomes

Collection of fact sheets used by surgeons when consulting with patients about treatment decision making.

The most important areas for inclusion in a patient information booklet.

Identification of information needs for men

Results

53 out of 87 surgeons selected from all NHS and independent hospitals performing prostatectomy in four health regions returned fact sheets. 25 different fact sheets were collected.

4226 out of 5361 men responded to the closed questionnaire and out 2000 randomly selected men, 807 responded to the open ended, in depth questionnaire.

Content

From the closed ended questionnaire 17 topic were identified as being the most important areas for inclusion in a patient information booklet. These were:

- physiology

- consequences of enlargement
- symptoms and clinical severity
- cancer
- clinical tests
- choice of treatment (TRUS or surgery or other methods)
- description of TRUS
- hospital stay
- catheter
- outcome
- adverse effects
- waiting time for TRUS
- post op pain management
- recovery
- return to activity
- sexual intercourse
- follow up

Format:

leaflets and factsheets

Results of evaluation:

22 out of 25 factsheets reported a description of physiology although there was inconsistency in the descriptions.

Only 6 / 25 fact sheets described prostate cancer and from the questionnaire responses 30% of men wanted more information about this. A further 4 from indepth responses indicated the need for more info about biopsy results and consequences.

4 factsheets mentioned tests required for diagnosis and 14% of questionnaire respondents indicated a need for more information. 4 % of in-depth responses criticised the poor communication about details and results of tests.

22 / 25 sheets described details about TRUS and surgery and only 4 included info about other treatment methods. But 26% questionnaire responses indicated the need for info about these other treatment methods.

Less than 10 sheets mentioned info about hospital stay.

24 sheets described the involvement of catheters only 3 actually mentioned the need to keep them clean. 21% of respondents indicated that required more information on this topic.

Although only 4 sheets mentioned adverse effects, changes in sexual function were described by 23. Some of the printed information was contrary to what the patients experienced, e.g. the incidence and severity of sexual side-effects. Although the printed information described the surgery itself and the function of the prostate well, they did not address topics like the side-effects of treatment and non-surgical treatment options.

Post op pain management was covered by 14 sheets but 13% of respondents expressed dissatisfaction with the lack of information. The severity and duration of pain was underestimated

by patients from the material they received

Recovery was described by 17 sheets but 28% of respondents said that it would be more helpful to have had more information about this issue and what to expect.

Overall, fact sheets did include some key issues that men identified as important but the details of this info was inconsistent, misleading, inappropriately phrased. A mismatch between what men wanted/needed and what was available from their surgeons. Generally, the information they received was lacking in depth and quantity and did not meet their needs.

General comments

The date of the publication does pose some limitations and it would useful to conduct this study in the present. Despite this major inconsistencies and mismatching was observed between what information surgeons provide and what men need or want. Authors point out that current standards of printed information do not meet the needs and requirements of patients undergoing prostatectomy.

The response rate of the questionnaire provided a valuable overview of men's experiences, needs and wants about information needs.

The UK setting also provides a useful backdrop to the study and allows applicability of responses to the current setting.

Although factsheets (printed material) were collected it is not clear exactly what the respondents of the questionnaire were responding about, i.e. written or verbal information. So understanding exactly what type of information they lacked and from whom they required it, is unclear from this study. The content however can be described from this study.

Hybrid Study (qualitative and quantitative study designs used)

Feldman-Stewart, D., Brundage, M. D., Van, M. L., Skarsgard, D., & Siemens, R. 2003, "Evaluation of a question-and-answer booklet on early-stage prostate-cancer", *Patient Education & Counseling*, vol. 49, no. 2, pp. 115-124.

Design: Hybrid Study (therapy), evidence level: 2+

Country: United States,

setting: Primary care

Inclusion criteria

Participants for Phase 1:

Eligibility criteria for the patients were: at least 18 years old, diagnosis of stage 1 or 2 prostate-cancer, PSA <20, Gleason score <8 and they had to understand English. Eligibility criteria for family were that the patient was eligible and the family member was at least 18 years old and could understand English. Close friends as identified by the patient were acceptable

family members.

Patients were recruited at four different locations, through two community urologists, one academic urologist, and three radiation oncologists at a cancer clinic.

Participants for Phase 2 study:

Eligibility criteria for the patients were: diagnosis of stage 1 or 2 prostate-cancer, Gleason <8, PSA <20. Patients attending their initial consultation at one of four locations were offered the study. The locations included two regional cancer clinics and two urology clinics. In addition, a family member/friend was offered the study if one attended with the patient.

Exclusion criteria -

Population –

Phase 1:

11 readers (6 patients and 5 family members) to identify features of the booklet that may be problematic.

Phase 2:

54 patients (79% response rate) and 33 family members (49% response rate)

Interventions

This study consisted of 2 phases that assessed the acceptability of a question-and-answer booklet about early-stage prostate-cancer created for patients and their family members.

The title of the booklet evaluated in this study was: Treatment choices for early-stage prostate-cancer in 1999, Patients' questions Doctors' answers.

Procedure of Phase 1:

After consenting, the booklet was given to the patient by the consulting doctor.

A semi-structured interview was a conducted by a research associate. The interviews were conducted on a 1:1 basis with separate interviews for the patient and the family member.

Assessment interviews were scheduled approximately 1 week after the second consultation (which typically occurs within a week or two after the initial consultation), when the treatment decision was made, usually readers had the booklet for a couple of weeks to read.

Phase 2. a quantitative study aimed to :

gain an overall evaluation of the booklet,

clarify the proportion of readers for whom the features identified in the first study were problematic,

provide insight into how and why readers were reading the booklet, and

determine if patients and family differed on any of the outcomes

An evaluation questionnaire was provided for each participant with the booklet that they were asked to fill in after they were finished using the booklet. The evaluation was then either mailed directly to our research unit or returned to the doctor

Outcomes

Phase 1.

Qualitative study:

identify features of the booklet that were problematic list suggested improvements on these features Phase 2. The survey reported levels of usage and overall opinion (for patient and family members) Evaluation of design features of the booklet (for patients only reported)
Results **Format**: Printed booklet **Context**: Provided by the consulting doctor to the patient. Booklet produced in consultation with related medical staff (three radiation oncologists and one urologist) Booklet given to patient after the initial consultation with the doctor in preparation for second consultation where a treatment decision is confirmed. (readers had the booklet for a couple of weeks to read) **Content** The title of the booklet: Treatment choices for early-stage prostate-cancer in 1999, Patients' questions Doctors' answers. The booklet was developed was based on the following well established principles (from earlier studies) : • The information must be relevant to audience • The information must be accurate • The information must be accessible, comprehensible, and acceptable • Identify further sources of information • Help the reader to judge reliability of information • Facilitate doctor patient/family communication • Facilitate application of the information For further details on booklet development please consult AM Some key points related to PCa and the development of the booklet: Relevant health professionals (urologists, radiation oncologists, nurses working in cancer centres, and radiation therapists) were consulted about the inclusion of relevant information required by a patient to make a treatment decision. Patients and families were also asked the same questions and consensus was reached about a final set of issues that are required for a treatment decision to be made. In order to make information as accurate as possible for each reader a personal-information form with the booklet on which the doctor recorded patient-specific details included. The details included disease characteristics along with other factors that might affect the patient's situation, such as age and co-morbidities, and individualized outcome estimates for seven probabilistic benefits and risks. To assist the doctor in providing outcome estimates most accurate for the individual, doctors were provided with a guide based on evidence from the literature when it existed, or a consensus opinion when there was no evidence. To provide the estimates for a particular patient, the doctor compared the patient's situation to the central

tendency of the most relevant subgroup and adjusted each outcome estimate accordingly.

Results of the evaluation:

Qualitative Study:

The thematic analysis of the qualitative data revealed a list of acceptable/positive and problematic aspects of the booklet.

A point of saturation was reported to be achieved after two consecutive interviews where no new information was revealed by the participants.

Acceptable/positive aspects:

- first impression
- colours used
- size
- weight
- binding
- layout of material
- font size
- ability to understand words and phrases
- ability to read the whole document or to choose specific sections
- help with understanding
- provision of information desired

Aspects that were problematic:

- The inclusion of the personal information form (with numeric values)
- glossary included terms that were already known and so was redundant
- Inadequate cross referencing of the Index
- inclusion of a notes section to write in the booklet
- repetitive nature of possible questions that a patient might want to ask a doctor
- comments page was unnecessary

Overall most participants expressed general satisfaction with the booklet with the exception of the areas identified above.

Quantitative Study:

68 booklets were distributed, 54 (79%) patients and 33 (49%) family members filled in evaluation forms independently, and one patient and family filled out the evaluation together.

Levels of use and overall opinion :

Overall opinion of the booklet did not differ between patients and family members (Chi 2<1) with a generally positive response to the booklet. 85% liked it, 9% found it acceptable, 3% thought it could be better, and 2% provided no response to the question.

85% patients reported that it helped to understand PCa and treatment options

88% family members reported that it helped to understand PCa and treatment options.

44% patients reported that it helped to participation in treatment decision

27% family members reported that it helped to participation in treatment decision

35% patients reported that helped with planning

9% family members reported that helped with planning

Chi squared =7.4, p=0.007

20% patients reported that the booklet provided better support to those around them

42% family members reported that the booklet provided better support to those around them

Chi squared = 4.9, p=0.03

61.1% of patients reported that the personal-information form was at least somewhat helpful compared to 39.4% of family members (Chi Squared =10.4, P=0.066).

Evaluation of design features of the booklet:

Results show that the glossary, the index, and the section question lists were all considered at least somewhat helpful by patients 71.2, 69, and 77% respectively.

For both the 'my unanswered questions' section and the comments page of the booklet, 75% of patients noticed but did not use these sections. (this finding is consistent with the qualitative study)

General comments

The results of this study indicate that overall, the booklet is helpful to both patients and their family members. It appears to be a reasonable strategy to provide information in a manner that allows individual readers to obtain particular details that are of interest and in a manner that facilitates the reader's ability to use the details to address their particular reason for needing the information.

The comparison of treatment options laid out side by side was unproblematic for the participants of this study and the authors recommended this format for information sources intended to provide information about more than one treatment.

The extra time taken for the doctor to use this booklet is negligible, where patient factors, treatment choices, support issues and side affects are already being discussed.

The booklet only focuses on early stage disease and associated treatment choices.

The booklet requires further evaluation in different settings, using a randomised controlled evaluation and with more men and their families.

Rees, C. E., Ford, J. E., & Sheard, C. E. 2003,

"Patient information leaflets for prostate cancer: which leaflets should healthcare professionals recommend?",

***Patient Education and Counseling*, vol. 2003 Mar; 49, no. 3, pp. 263-272.**

Design: Hybrid Study (therapy), evidence level: 3

Country: United Kingdom

Inclusion criteria

The inclusion criterion was that leaflets must discuss treatment options for men with prostate cancer.

22 men with PCa were identified by a consultant urologist at the City Hospital in Nottingham and invited to take part in a focus group discussion.

The men were selected purposively, i.e. on the basis of their range of treatments, age, social class and educational level to ensure that a broad spectrum of views would be elicited.

Exclusion criteria -

Population

Stage 2:

Eight men (36.4%) participated in the study.

Participants ranged in age from 63 to 82 years, all were white, the majority were married and came from socio-economic classes I and II (professional and technical occupations). The majority of men had undergone surgery of the prostate or testicles and 50% had undergone hormonal therapy

Interventions

This study evaluated 31 patient information leaflets (PILs) discussing treatment options for prostate cancer.

In stage one, leaflets were evaluated for quality, readability and suitability using objective measures as described by the: DISCERN instrument which generates a total score of between 15 and 75, where 15 was very poor quality and 75 was very high quality and in addition an overall rating of the quality of the publication as a source of information about treatment choices. This rating uses a five-point Likert scale from 1= low quality with serious or extensive shortcomings to 5 = high quality with minimal shortcomings;

Flesch formula for readability; and Suitability Assessment of Materials (SAM) instrument,). This instrument is composed of 6 categories: content, e.g.

'Scope is limited' (item 1c), literacy demand, e.g. Vocabulary uses common words (item 2c), graphics, layout and typography, learning stimulation and motivation and cultural appropriateness. Each item is scored from 0 (not suitable) to 2 (superior) and these scores are converted to a single percentage score, which could be rated as superior (70-100%), adequate (40-69%) or unsuitable (0-39%).

In stage two, eight men with prostate cancer took part in a focus group discussion or individual interview to outline their views regarding a number of leaflets, including the best five booklets or leaflets identified in stage one of the study.

Outcomes

The best five leaflets across the three conditions were identified according to the quality assessment measures specified.

Results

Context:

The most recent editions of patient information leaflets (PILs) were identified and collected from various sources such as cancer charities (e.g. CancerBACUP), healthcare professionals (e.g. consultant urologist), information providers (e.g. NHS Direct) and information producers

(e.g. Scriptographic).

Format: Print material : patient information leaflets (PILs)

Content: 31 PILs was evaluated and although the leaflets varied in terms of their scores on each measure, the best five leaflets across the three conditions were identified.

Results of the evaluation:

The total DISCERN scores for the 31 PILs ranged from 16 (Prostate brief. Prostate cancer) to 62 (Understanding cancer of the prostate (mean = 35:2, SD: 11:3).

None of the 31 PILs received the highest quality rating of 5 (high quality with minimal shortcomings).

The Flesch scores for readability of the 31 PILs ranged from 35.7 (Brachytherapy) to 68.5 (The Tenovus guide to prostate problems (mean = 52.8, SD 8.7)). Seven leaflets (22.6%) had a standard reading difficulty, 11 (35.5%) possessed a fairly difficult reading difficulty and 13 (41.9%) had a difficult reading difficulty.

The negotiated SAM percentage scores for the 31 PILs ranged from 12.5% (Prostate brief. Prostate cancer) to 83.3% (The treatment of prostate cancer. Questions and answers (mean = 52:8, SD 17:3)). Of the 31 leaflets, 6 (19.4%) were superior materials, 20 (64.5%) were adequate and 5 (16.1%) were unsuitable.

Overall for stage 1:

The quality, readability and suitability of the 31 PILs evaluated in the first stage of the study varied considerably. Less than half of the leaflets received quality ratings of moderate or above, suggesting that the quality of the information on treatment options was poor generally.

2 booklets: 'Understanding cancer of the prostate' by CancerBACUP and 'Prostate cancer: everything you need to know' by the Prostate Cancer Charity received moderate to high quality ratings, suggesting that these booklets possessed good quality information on treatment options.

A considerable number of the leaflets were fairly difficult or difficult to read. However, the SAM indicated superior or adequate scores indicating that the content, literacy demand, graphics, layout and typography, learning stimulation and motivation and cultural appropriateness were suitable.

By summing the ranks of the leaflets across the quality, readability and suitability conditions, the authors were able to discriminate between the leaflets in terms of their overall excellence. The best five PILs were:

1. Screening for prostate cancer. The evidence by the NHS Centre for Reviews and Dissemination (CRD),
2. The treatment of prostate cancer. Questions and answers by the Covent Garden Cancer Research Trust,
3. Understanding cancer of the prostate by CancerBACUP,
4. Cancer of the prostate. Your questions answered by the Royal Marsden NHS Trust
5. Prostate cancer: everything you need to know by the Prostate Cancer Charity.

In order to address the preferences of men with prostate cancer (which the PILs do not take into consideration) Stage 2 of the report was carried out. This study investigated men's' perception about 10 PILs which included the top 5 identified in stage 1. Focus groups were used and men were selected using purposive sampling.

All participants were sent a different combination (maximum of six) of 10 leaflets and booklets. Only the results concerning the best five were provided in this paper.

A semi-structured interview schedule was used to guide the focus group discussion and interview. Key questions included :

- what was liked or disliked about a particular leaflet,
- was anything missing from the leaflets and how could the leaflets be improved.

The interview data was analysed using a template analysis. This uses a pre-formed template which lists relevant and important themes. For this study, these included: what was liked and disliked about characteristics like readability, language, layout, graphics and content. Throughout the study, this list was re-assessed until a final templates list formed. The next step involved identifying and interpreting connections in the data, e.g. counting the number of men who made similar remarks about a particular leaflet and making comparisons and contrasts between the opinions expressed. The final step involved comparing the results with the quantitative findings from stage 1.

Stage 2:

Responses in the focus group discussions indicated that men were able to discriminate between the best five leaflets or booklets and identify their preferred booklets.

Clear readability, easy to understand, interesting, informative and comprehensive were the range of positive responses.

The negative responses included: Information was overwhelming, language to technical, criticisms about the illustrations in the booklets and the failure to support the text and how they trivialised important issues, illustrations were also frightening and off-putting, colour schemes were also

Taking both the quantitative and qualitative results into consideration, three booklets were rated highly in terms of their quality, readability, suitability and patients views.

From this study's findings authors recommend to Healthcare professionals to use 3 booklets to men with prostate cancer who want written information about their disease:

1. Understanding cancer of the prostate by CancerBACUP,
2. Prostate cancer: everything you need to know by the Prostate Cancer Charity and
3. The treatment of prostate cancer. Questions and answers by the Covent Garden Cancer Research Trust.

General comments

Some limitations exist for this study and include the lack systematic approach to identifying the PILs and some may have been missed. However, the study did include very relevant material. The qualitative study lacked a representative participant group of men with PCa.

Having 8 men in the focus groups could have allowed for further, more in depth interviews

Qualitative Study

McGregor, S. 2003,

"Information on video format can help patients with localised prostate cancer to be partners in decision making",

***Patient Education and Counseling*, vol. 2003 Mar; 49, no. 3, pp. 279-283.**

Design: Qualitative Study (therapy), evidence level: 3

Country: United Kingdom, setting: Community

Inclusion criteria

Part One:

All men were Scottish and living in the central belt of the country, with ages ranging from 49 to 74 years, with no prostate cancer

Part two:

12 patients who had been diagnosed with localised prostate cancer and had been given the standard information by their urologist, but had not had any treatment, watched the video.

Their ages ranged from 54 to 75 years and all were married.

Exclusion criteria -

Population –

Part One:

Participants were recruited from Rotary and Bowling Clubs were randomised to receive a copy of the video to view at home.

All men were Scottish and living in the central belt of the country, with ages ranging from 49 to 74 years. They represented a wide range of backgrounds, education and occupations.

None had suffered from prostate cancer and they were all interviewed in their homes.

N=10

Part two:

During a 5-month period, 12 patients who had been diagnosed with localised prostate cancer and had been given the standard information by their urologist, but had not had any treatment, watched the video.

Patients were referred by five consultants and came from areas across the central belt of Scotland. All consultants were asked to refer patients to whom they had given full

information on both the disease and possible management options.

Their ages ranged from 54 to 75 years and all were married.

Interventions

The aims of the study: To record the insight and knowledge that patients retained after their information-giving consultation with their urologist.

To establish the communicative effectiveness of providing information in a video format.

To discover the effect of a diagnosis of prostate cancer by comparing patients memory and

perceptions of the video with that of a healthy cohort.

To enable patients to understand the pertinent issues and empower them to ask questions and be an active partner in the management of their disease.

The intervention:

The video commenced with a few simple statistics of the incidence, investigations and recommended treatment for localised prostate cancer (as describe in the literature).

A diagrammatic map of the area, along with a simplified explanation of the function of the gland helped to demonstrate why various symptoms occurred while a voice over explained how and why urine problems resulted from prostate cancer.

The video involves 3 consultants (two urologists and a radiotherapist) introduced different methods of treatment, including information about the problems and benefits associated with each. And 3 patients who had early stage disease, who had completed treatment and were still in good health talked about their treatment and how it affected their life.

The study included two parts:

Part one: inclusion of healthy men and their responses to the video

Part two: men who were diagnosed with PCa and were considering treatment options.

Outcomes

The effect of the video on knowledge of PCa, extent to which the video aided the treatment decision, description about how the video influenced treatment decisions.

Follow up

Before and after assessments were reported.

Results

Content:

The video commenced with a few simple statistics of the incidence, investigations and recommended treatment for localised prostate cancer (as describe in the literature).

A diagrammatic map of the area, along with a simplified explanation of the function of the gland helped to demonstrate why various symptoms occurred while a voice over explained how and why urine problems resulted from prostate cancer.

The video involves 3 consultants (two urologists and a radiotherapist) introduced different methods of treatment, including information about the problems and benefits associated with each. And 3 patients who had early stage disease, who had completed treatment and were still in good health talked about their treatment and how it affected their life.

Context:

Provided by the urologist after the first consultation where the diagnosis of PCa has been delivered and before the next consultation where a treatment decision is required.

Format:

Video (to be played at home however many times the man desires)

Results from the thematic and content analysis of the data.

Part one:

Before viewing, all men were asked questions about the prostate gland and prostate cancer.

Ten men were interviewed on tape, using a semi-structured questionnaire, before and follow-

ing viewing.

Before the viewing the video:

Only one man knew the position and function of the gland.

Authors suggest that people constantly reconstruct illness understanding in context of their daily life and these men who had been engineers put their explanations in the context of their life experiences.

Radiotherapy was the most commonly suggested treatment, although six described it as radium treatment. No one suggested surgery.

After watching the video:

Everyone remembered the three methods of managing the disease and decided which they would prefer should they be diagnosed with prostate cancer. The reasons were often

because of perceived negative aspects of the other options.

All men remembered the possibility of sexual dysfunction, and this caused concern.

Remembering the various treatments was strongly associated with the characteristics of the patients in the video. Associations and judgements were made about each of them and this influenced the perceived effect of each treatment.

Part two:

All men had kept the video for 1 week; three had watched it once, five had viewed it twice, three watched it three times while one man watched it four times. Before the interview two men had decided and were booked to have a radical prostatectomy, three had absolutely no idea what treatment they wanted, five wanted surgery and two radiotherapy. All patients talked of their symptoms, investigations, confusion and perceptions of what was happening. None felt ill and symptoms were mainly around having to go to the toilet.

The thematic and content analysis of the data revealed:

After being diagnosed with localised PCa and been given the standard information by their urologist, but not had any treatment, before watching the video.

Patients talked of surgery, radiotherapy, chemotherapy, steroids, seed implants, laser treatment and hormone treatment. Only two remembered being told that 'wait and see' was a management option.

For the majority of people radiation is an unknown procedure and patients often misinterpret explanations, but three were aware of this, suggesting; "we're all kind of ignorant, us working class folk".

Eleven had discussed their disease and treatment options with their wives, five of whom were present during the interviews.

When talking about future decisions they talked about "us and we". Their disease affected their wives and decisions were taken together.

Only one man was sure he knew where the gland lay and what organs were close by. He had received a booklet from his son.

Three had no idea what the side effects of surgery or radiotherapy might be, while one had the side effects of radiotherapy explained with the understanding that he could have an appointment with an oncologist should he require further details. He was given the weekend to decide on a treatment option and only when surgery was chosen were these side effects listed. Eight patients noted that radiotherapy and surgery could result in both incontinence and impotence. Two felt that their surgeon was rather vague when talking about the possibility of being impotent. 4 men had been given leaflets describing the processes and potential side

effects following radiotherapy, but only 2 seemed to remember what they might be.

After viewing the video:

6 men could describe the physiology of the gland and associated names of the ureters.

All remembered the three management methods. All commented on the presence and position of the nerve bundles on either side of the prostate gland. Although very few had indicated that they would be concerned to be left impotent the importance they attached to the ability of the surgeon to preserve those nerves was evident.

Diversity and some confusion in what the men remembered about the different treatments and side effects was observed. The need to go home with a catheter in place was accepted without a perception of any undue distress. Watchful waiting was described by everyone as a 'wait and see' and all mentioned the need for regular blood tests.

Only one man radically changed his mind as to his preferred treatment after having watched the video. He expressed the need to speak with his urologist to review his treatment decision.

Three felt that they had limited knowledge of their disease and management; they expressed problems with understanding information and felt responsible for their lack of knowledge.

Patients it would seem place more emphases on their competence in obtaining information rather than on the health care team in providing it.

The author note that even though all patients had received the standard 'information-giving' consultation from their urologist and had attended a urology clinic for some considerable time but still most became aware of gaps in their knowledge. Information outlined on the video helped to create a mental image that was remembered.

General comments

General conclusions to be drawn form this study:

- The video was able to consolidate information for the men who had gained prior knowledge from other sources.
- It provided confidence to the men with PCa to discuss treatment options and side effects with their partners.
- The specialty field of the doctor had an influencing effect on the amount of information provided to a man about other treatment available.
- The healthy men would prefer to choose watchful waiting as a treatment compared to men with PCa, who preferred RT or surgery.

The visual images and the insights into the process PCa and management of it allayed anxiety for men and gave them a sense of control over their condition.

The men with PCa felt they had sufficient understanding to ask their urologist questions although most considered that the video had addressed all general queries.

All felt they had learned something of value in a user friendly way and welcomed the acquisition of knowledge that it made possible.

Most patients expressed the ability to decide on a definitive course of treatment, while those who still could not, felt they had a greater understanding of the pertinent issues.

All participants remembered and drew inferences about the patients, who participated in the video; they made comparisons, found parallels and developed an affinity towards them.

Overall, this study was able to demonstrate that the video did enable knowledge gain, and influence treatment decision making in an effective, appropriate manner.

Rozmovits, L. & Ziebland, S. 2004,

"What do patients with prostate or breast cancer want from an internet site? A qualitative study of information needs",

***Patient Education and Counseling*, vol. 2004 Apr; 53, no. 1, pp. 57-64.**

Design: Qualitative Study (therapy), evidence level: 3

Country: United Kingdom,

setting: Community

Inclusion criteria

Participants were selected by way of the voluntary sector to contribute to a focus group discussion FGD.

Two participants from each focus group were selected to take part in a follow-up interview.

4 FGD were conducted involving a total of 28 people were conducted in London, Scotland, Wales and the north of England. Every prostate cancer participant was a regular member of a support group. Where possible the evidence from PCa patients was extracted reported. 13 of the total number involved in the FDG were men with PCa.

Out of 8 indepth interviews, 4 were men with PCa.

Participants were asked to think of at least one information need they had had at some time in their cancer experience.

Exclusion criteria -

Population

number of patients = 28, age range 59 to 75 years, mean age = 65 years.

Interventions

This study examined :

- contextual and content issues of information delivery
- the utility of the DIPEx website for men PCa.

The Dipex website presents data from qualitative interviews with people about their experiences of health and illness. The site covers cancers, heart disease, mental health, neurological conditions, screening programmes, pregnancy, teenage health, chronic illnesses and many others.

Each module in the website is based on a purposive sample of 40-50 narrative interviews which are video or audio-tape recorded. The interviews are analysed using qualitative thematic methods and the results are presented as topic summaries, which are illustrated with video, audio and written clips from the interviews, according to the preference and consent of the participant.

Outcomes

Men in the FDG were asked to discuss:

the information needs they experienced at various stages of their illness, treatment and recovery period and to reflect on how well or poorly these needs were met.

For indepth interviews, men were shown the DIPEx module for breast or prostate cancer and asked to consider whether it could have met their unmet information needs had they had access to it at the time of their illness.

Follow up

not conducted.

Results

Context:

Information from consultants was trusted by the men.

Consultants were considered not to be the best source of information. Reasons included: lack of time, preference for particular forms of treatment, and poor communication skills were common problems.

Consultants were forthcoming with answers to specific queries but did not routinely volunteer information or initiate wider discussion of treatment options. Authors indicated that this could be problematic for those who felt they did not even have enough information to know what to ask.

Specialist nurses were generally highly regarded as sources of information. Because they provided specialist knowledge, they are more approachable and less busy than consultants.

Some concern was also expressed about inconsistency of information delivery by specialist nurses and a lack of clarification for patients of the specialist nurse role.

Some suggested that specialist nurses should have a checklist of topics that should be routinely covered with patients so that vital information was included.

GPs were considered generally positive but not reliable information providers.

Format:

Provision of information from the voluntary sector was not routinely made available. This included information from CancerBACUP, and other PCa support groups currently operating.

Awareness of these sources were found by accident.

Virtually all participants felt that coming into contact with a relevant voluntary sector organisation had greatly improved their situation and had given them access to a wealth of information unavailable to them previously.

Internet use:

Non-commercial to commercially sponsored websites were preferred.

'Centres of excellence' or institutions with established reputations were much sort after by nearly all participants.

Sites supported by the NHS or Department of Health were trusted.

Content:

Participants understood the limitations of applicability of US websites to the UK about treatment available.

Consultant Patient Group:

Access to the experiences of other patients was generally valued as it provided both reassurance and access to a wealth of practical information that health professionals tended to omit.

Many people said it was virtually impossible to get information about the impact of cancer on families and family life.

Focus Group Results:

The results presented describe the experience with information providers, support groups and specific sites on the internet (e.g. NHS sites), other patient experiences.

Indepth Interviews:

Interviewees liked the combination of reliable health information and patient experience on the DIPEx website (since it meant that one resource answered two major kinds of information need).

All participants, including those who had no previous interest in the Internet, said they would recommend DIPEx to other cancer patients, family members, or others just wanting to know more about an illness.

Participants with and without familiarity with the Internet mentioned several features of DIPEx that they saw as beneficial:

- the ability to learn from the experiences of others about what it is like to go through different treatments,

- access to many features of a support group without the emotional demand of attendance

- The 24 hour, 7 days a week availability of the site over the Internet.

Some gaps still exist with DIPEx and include:

- explanation of the role of the nurse specialist

- list of suggested questions to ask health professional

- practical info about what is needed in hospital

- resources for teenage children (whose parent has cancer)

- suggestions about how to talk to children about cancer

- Access to DIPEx without the internet.

DIPEx provided the opportunity for people to select patient experiences of a particular age, stage, survivors, and similar treatment choices. This greatly reduced feelings of fear and isolation during their illness.

Most commented that had they had the benefit of such information at the time of their illness it would have saved them time, trouble, worry, or difficult decision-making. Similar benefits for family members and friends of people with cancer were also described.

DIPEx allowed the screening out of unwanted information.

The benefits of support group were described, where input without having to attend a group was available. DIPEx was also considered valuable for patients and others who were reluctant to seek information, but who still required and wanted it.

People liked the fact that DIPEx provided access to personal information that could be viewed in total privacy.

A general positive response was reported about how DIPEx encouraged people to be more active participants in decision-making about their treatment (through the access to the infor-

mation and patient experience that DIPEx provides). DIPEx made participants feel more informed. Even for people with limited or no experience of computers DIPEx was reported as being approachable. Experienced computer users thought the site was generally good. Accessing DIPEx in a public location such as a library or outpatient department was not seen as problematic or a cause of discomfort. Although some expressed the need for a private or partitioned area. Most expressed the need for an introduction to the resource particularly if the user was unfamiliar with computers.
General comments Limitations of this study include: Selection bias of sample. Ethnicity of participants is not revealed Although the reports from DIPEx are from men of culturally and linguistically diverse backgrounds, it is only reported in English, therefore biasing access to men who can only read and understand English. Men involved had a diagnosis and treatment of PCa some time prior to the study, therefore men who are currently undergoing a treatment decision process or who have just been given the diagnosis could respond differently.

Diefenbach, M. A. & Butz, B. P. 2004, **"A multimedia interactive education system for prostate cancer patients: development and preliminary evaluation",** ***Journal of Medical Internet Research*, vol. 6, no. 1, p. e3.**
Qualitative Study, evidence level 3
Inclusion Criteria: Men who have been diagnosed with early-stage prostate cancer.
Population: The first 3 focus groups consisted of 18 prostate cancer survivors. A preliminary evaluation through 5 separate focus groups with prostate cancer survivors (N = 18) and their spouses (N = 15). Men were on average 67 years old and had at least a high-school education (33%), a large majority was married (83%), and had completed treatment (83%). External beam radiation was chosen by 72%, 22% chose surgery, and 6% chose brachyther-

apy.

The remaining 2 focus groups were held with spouses of prostate cancer survivors (N = 15). The women were on average 60 years old and 50% had a college or postgraduate degree

Intervention

This study aimed to introduce the development and preliminary evaluation of a novel highly-interactive multimedia-education software program for patients diagnosed with localized prostate cancer.

Outcomes:

Utility of the interactive multimedia-education software program.

Ratings were collected using a 5-point scale, with higher scores indicating higher levels of interest.

Results:

Format:

The system is CD-ROM based but could be made available over the Internet. This system can provide a computer characterisation of a man which is altered by an expert system. In turn, the expert system, analyses how the patient interacts with the software and reports this in the results folder. The results folder contains information that the expert system will use to generate a report to the psychologist.

The prostate interactive education system (PIES) is an interactive multimedia expert system that uses the metaphor of rooms in a virtual health centre (i.e., reception area, a library, physician offices, group meeting room) to organize information. Text information contained in the library that is both up to date and tailored to a person's information-seeking preference (i.e., high versus low information seeker).

When the man first enters the program and information specialist welcomes him and shows him around the PIES virtual Health Centre. The man is able to interact with virtual physicians, support groups or sex therapists who can answer specific questions. The man can query various physicians (e.g., surgeons, radiologists), therapists and groups. The physicians and others "consult" with the man through digital video sequences as well as through interactive multimedia question-and-answer sessions.

After showing the man the Health Centre layout, the information specialist asks the man to complete a questionnaire. The questionnaire requests data that the expert system will need to tailor the Health Centre for his needs. It is capable of determining how much information men desire about a topic and provides it. Affectively it is able to tailor information to low or high information seekers.

Finally, each man is provided with a decision aid that will assist him in treatment decision making.

Content

The library is a highly-interactive area where a man may obtain, and interact with, educational material and other information. The library consists of books and videos.

An example: a book entitled Brachytherapy contains information about radioactive-seed implant treatment. A chapter gives an overview of brachytherapy; another chapter focuses on side effects, while another one describes the rationale behind a particular treatment regimen.

Other books available contain information about psychosocial functioning, such as how to deal with impotence and incontinence, the use of alternative medicine, clinical trials, and the

impact of prostate cancer on the family.

The video section contains short videos (up to 5 minutes) that show facilities (e.g., a surgical suite) and describe specific treatments.

All information provided has been quality assessed for readability, accuracy and current.

The physician offices:

Experts in a treatment area (i.e., surgeons, radiation oncologists, and a brachytherapy specialist) are available to provide information about different treatment modalities.

Risk factors for treatment modalities, the likelihood of side effects, success rates, recovery time, and expected quality of life are issues discussed.

The Group Meeting Room

When a man participates in a group meeting of prostate cancer survivors (men who have experienced the range of treatment options).

A range of issues are covered in the discussions available (treatment decision-making processes and influencing factors, sexual and incontinence problems, issues with intimacy, the effect of the disease on the partner, the influence of the spouse on treatment decision-making, experience with different treatments, and the use of alternative therapies.)

Context:

Ideally, these PIES should be made accessible to men when they have received confirmation PCa diagnosis and treatment options are being considered.

Results: (Feedback on the concept of PIES)

Ratings were collected using a 5-point scale, with higher scores indicating higher levels of interest. Both men and spouses, uniformly stated that they were "very much" interested in the software (mean = 4.71; SD = 0.59; range, 3-5), and that it was "very" useful (mean = 4.71; SD = 0.47; range, 4-5).

Overall Results from men

- Men indicated that they would spend between 1 and 2 hours with the program and were willing to pay an average of $50 for it, (if commercially available).

- From the focus groups, participants' comments revealed a general positive repose to the concept. Obtaining information from the virtual rooms or offices was reported as intuitive and appealing. Participants appreciated the variety of information that was provided.

Results for each component:

Introduction

- Very positive responses to the Introduction to PIES were reported by men and spouses; they found it easy to follow.
- They particularly liked the possibility of accessing information in any order they liked and

the program's capability of tailoring the information to their information-seeking needs.

- Participants also mentioned that they value an interface that mimics an interaction with a human. There was some suggestion about the inclusion of a guide who follows the user as he/she navigates the program and is able to be asked questions.

The physician's offices

- 90% for each of men and spouses indicated that they would visit the physician's offices first, before going to any other room.
- Participants liked the opportunity to type in a question, (which will prompt the program to retrieve the appropriate video with the physician answering the questions).
- However, a majority of patients also requested an overview of available physician answers. As one man stated: "After a diagnosis I didn't know what type of questions to ask. An index of available information from the physician would be very helpful."
- Other men didn't like the physician sitting behind a desk, which increased the perceived distance between patient and physician.

Library

- Again very positive responses from participants about the layout of the library.
- The provision of information in book form was reported as being very appealing. The combination of written text with illustrations and short video clips was acceptable.
- Some interest in watching video clips of surgical or seed-implantation procedures was noted.
- Others, in contrast, indicated that they would not be interested in such a level of detail.
- Both men and spouses liked that some medical terms were hyperlinked to the Glossary, which provided short one-sentence explanations of the term.

Support Group

- Overall, men indicated great interest in watching video clips of prostate cancer survivors sharing their experience.
- In the initial format there were 3 men sitting behind a table answering questions that were keyed in by the patient. While about half of the patients appreciated the opportunity to interact with each man directly in the support group, the other half was interested in watching the men exchanging their ideas.
- The current version of the software includes videotapes of men discussing certain topics, such as treatment decision-making, treatment experience, and post-treatment quality of life.

Spousal feedback

- Certain topics were specifically mentioned in the focus groups with spouses.
- Spouses advocated for a room that provided information specific to their information needs.
- Topics of interest were information about:

  - nutrition (e.g., soy, lycopenes),

  - emotional support (both resources for support, as well as learning from the experience of other spouses),

  - instrumental support (particularly with care-giving after treatment).

♦ Spouses were also interested to receive information about sexual issues: - intimacy, - communicating to one's spouse about sexual issues, - the use of devices to assist a patient with erectile dysfunction.
COMMENTS Needs to be trialled with men (and spouses) currently going though a decision making process.

Matsunaga, D. S. & Gotay, C. C. 2001, **"Characteristics contributing to an enduring prostate cancer support group in an Asian and Pacific Islander community.",** ***Journal of Psychosocial Oncology*, vol. 22, no. 4, p. -30.**
Design: Qualitative Study ,evidence level: 3 Country: US setting: community
Inclusion criteria Men who participated in the ethnically-orientated community support group
Exclusion criteria .
Population 24 participants: 71% Asian or Pacific Islander. 55 – 85 yrs old: 75% was 70+ years.
Interventions Community Support group (for Asian and Pacific Islanders)
Outcomes Semi structured interviews of men who participated in this ethnically-orientated community support group elicited information about: ▪ Perceived Benefits of the Support Group ▪ Aspects of the Group that contributed to its success

- Aspects that enable the Group to relate to the broader community

Follow up

Not reported

Results

Content:

provision of information about PCa through written sources, or verbally from experts about treatment choices, side effects, coping mechanism (treatment or psychosocial).

Details of the content were not described in details the information here has been gleaned from the reports of the interviewees in the study.

Format:

Community based Support Group meetings conducted monthly.

Context:

Inclusion into the group was not specified and details about when this took place were not included.

Results from interviews:

Perceived Benefits:

- Experiencing comfort and camaraderie.
- Receiving practical information from peers
- Enhancing their coping ability
- Provision of the opportunity to discuss their experiences with physicians and medical care.

Aspects of the Group that contributed to its success:

- Peer leadership
- Characteristics of the participants (particularly members who were physicians)
- Members' participation in group activities.

Aspects that enable the Group to relate to the broader community:

- Occasional attendance of women and other family members.
- Annual functions with invitation to the wider community
- Activities outside of the meetings that engage and encourage fellow members to attend meetings or other associated events that support fellow members through their disease.
- Addressing the issues of a multiethnic community. And being responsive to diverse expectations and behaviours.

General comments

The authors describe limitations of this study and points out that the interviewer was a relative of a peer leader of the Group. They describe the bias involved however recognise that without this link, access to this Group would have been severely limited.

The interviewer attempted to reduce bias by reporting responses as an aggregate and preventing her from identifying who the responders were and not attributing any additional knowledge to their responses (through her relationship to the peer leader).

Another bias not discussed was that the participants of this study were self selected group

and therefore introduces a selection bias where a somewhat skewed representation of responses is reported.

This study provides insightful understanding of how and why this multiethnic support group is successful. It offers a useful model for other support groups to be based on and demonstrates the positive outcomes that can be achieved for men with PCa.

Snow, S. L., Panton, R. L., Butler, L. J., Wilke, D. R., Rutledge, R. D., Bell, D. G. & Rendon, R. A. (2007) Incomplete and inconsistent information provided to men making decisions for treatment of early-stage prostate cancer. Urology, 69: 941-945.

Design: Prospective case series (other), evidence level: 3

Inclusion criteria Men, treated for localised prostate cancer (T1-T2, N0, M0), who returned a postal questionnaire.

Exclusion criteria -

Population number of patients = 270, age range 50 to 85 years, mean age = 66 years.

Interventions Men had received either radical prostatectomy or radiotherapy for prostate cancer. They were mailed a questionnaire which aimed to asses their needs for prostate cancer information.

Outcomes Patients rated the importance of information on various prostate cancer topics (1 - not important to 5 very important). Patients also rated how well they knew each topic (1 not very well to 5 very well). The difference between these two measures was used to calculate the information gap for each topic.

Follow up Questionnaire response rate was 51% (138 men)

Results Unsurprisingly the ratings of importance and knowledge differed statistically for all 6 information subsections (treatment choices, surgery treatment details, radiation treatment details, surgery risks/benefits, radiation risks/benefits and personal considerations). There was no analysis to identify whether there were specific subsections where the difference was more marked.

General comments Unclear whether this study's concept of information gap has any validity.

Sharpley & Christie . Patient information preferences among breast and prostate cancer patients. Australas.Radiol. 51[2]. 2007.

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

Country: Australia, setting: Tertiary care

Inclusion criteria Patients treated for either breast or prostate cancer within 4 years of the study questionnaire.

Exclusion criteria -

Population number of patients = 845.

Interventions All patients received radiotherapy; some also had surgery, chemotherapy or hormonal therapy. All were sent a survey designed to collect self reported data on participants ratings of 5 different types if informational materials and anxiety and depressions symptoms.

Outcomes Participants ratings of informational materials (using a five point scale: 1 very poor to 5 very good). Anxiety and depressions symptoms. Outcomes were measured at the time of the survey and (retrospectively) at the time of treatment.

Follow up Return rate for the questionnaires was 195/400 (49%) for the prostate cancer patients and 197/445 (44%) for the breast cancer patients.

Results Only results for the men treated for prostate cancer are included in this appraisal.

Most preferred information format was the Doctor interview (average rating 4.44/5) followed by the information booklet (3.91), the educational video (1.71), the guided hospital tour (1.47), and the individualised training session (1.24) and no information (0.04).

There was no statistically significant difference in anxiety or depression scores according to the type of information men had received. clinically depressed men tended to rated receiving no information more highly.

General comments Low survey response rate, extensive post-hoc subgroup analysis: substantial possibility of bias.

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.

1.2 Decision support

How effective are decision aids at informing men with prostate cancer (and their wives/partners/carers/family) about treatment options?

Short summary

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

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOMES
Men who need to make a decision about treatment options.	Decision aids	No decision aid	▪ Presence of communication between people and practitioners; ▪ decisional conflict; ▪ knowledge; ▪ realistic expectations; ▪ clarity of values; ▪ agreement between personal values for outcomes and choice; ▪ implementation of preferred choice; ▪ satisfaction with the decision, the decision making process, and the decision support provided; ▪ the actual choice made; ▪ health related quality of life; ▪ adherence to the chosen option; ▪ resource utilization; ▪ emotional distress; ▪ anxiety; ▪ depression; Regret; and Litigation rates.

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

Evidence summary

Evidence about the effectiveness of decision aids comes from a systematic review of randomised trials in range of conditions (O'Connor *et al.* 2003), but most of the included randomised trials were not of prostate cancer treatment decision aids.

Decision aids consistently knowledge about treatment options, procedures and side effects. More realistic expectations were reported, reduced proportions of people feeling of uninformed, reduction in the proportion of people who assumed a passive (practitioner-controlled) role in decision making, lower numbers of people who remained undecided post intervention, consumers' general satisfaction, readability and ease of use was also reported.

Although applicability is limited the review provides insight into; what could be effective and acceptable to patients, and the complexity of the decision making process.

Observational studies evaluating decision aids for men with prostate cancer who need to make treatment decisions provided the most applicable evidence (Brink *et al.* 2000; Feldman-Stewart *et al.* 2001; Feldman-Stewart *et al.* 2004; Holmes-Rovner *et al.* 2005; Schapira *et al.* 1997). There was evidence that decision aids are associated with an improvement in:

- Knowledge uptake about treatment options, procedures and side effects,
- Participation in patient controlled decision making processes,
- Self-efficacy
- Cognitive processing (identifying attributes that are important and influence decisions; identifying shifts in attributes throughout the decision making journey; identifying treatment preferences and associated shifts in preferences throughout the decision making journey; and involvement of regret in the decision making process)

Evidence Tables

O'CONNOR, et al 2003
Design: Systematic review of RCTs (therapy), evidence level: 1++ **Inclusion criteria** Decision Aids (DA) meeting the inclusion criteria were described according to the following categories: a) Publication Information: title of decision aid, copyright holders, contact information, availability, and current use; b) Developer Information: credentials, link to systematic review group and/or guidelines group; c) Source of Funding/Sponsorship; d) Timing of Publication: year of publication; update policy; e) Potential Users: target audience; skills required (computer, literacy). Literacy was calculated by using a table of random numbers to choose three pages from the decision aid. The three pages were typed into an MS Word program and the readability calculated by the program; f) Delivery Method: medium (format of aid with length), level of interactivity, use in relation to counselling; g) Elements of the Decision Aid; h) Practitioner Support: inclusion of materials or tools to guide practitioners in using decision aids with patients; i) Development Process: use of needs assessment, evidence reviews, expert review panels, and user review panels; j) Evaluation Data; and k) Publications. All decision aids identified were assessed using the CREDIBLE criteria for quality of development and evaluation of decision aids (Stacey 2001) A comprehensive inventory of DA was produced in this review, please AM for a list of relevant PCa DAs. **Exclusion criteria** Interventions that focused on decisions about lifestyle changes, clinical trial entry, or general approaches to treatment if the person should become unable to participate in decision-making in the future; education programs not geared to a specific decision; and interventions designed to promote adherence to or to elicit informed consent regarding a recommended option, were excluded from the analysis. Further exclusion, also included: a) the study was not focused on making a choice; b) the intervention offered no decision support in the form of a decision aid; and c) the decision was hypothetical with participants not actually at a point of decision making.

Population –

Types of studies

For the systematic RCT Review, all studies were included that used a randomized controlled trial design comparing decision aids to no intervention, usual care, alternative interventions, or a combination.

Types of participants

Studies were included that involved people over the age of 14 who were making decisions about screening or treatment options for themselves, for a child, or for an incapacitated significant other. Authors excluded studies in which participants were making hypothetical choices.

Interventions

DAs were defined as interventions designed to help people make specific and deliberative choices among options (including the status quo) by providing (at the minimum) information on the options and outcomes relevant to a person's health status.

The aid also may have included:

- information on the disease/condition;
- costs associated with options;
- probabilities of outcomes tailored to personal health risk factors;
- an explicit values clarification exercise;
- information on others' opinions;
- a personalized recommendation on the basis of clinical characteristics and expressed preferences;
- and guidance or coaching in the steps of decision making and in communicating with others.

Outcomes

- Presence of communication between people and practitioners;
- decisional conflict;
- knowledge;
- realistic expectations;
- clarity of values;
- agreement between personal values for outcomes and choice;
- implementation of preferred choice;
- satisfaction with the decision, the decision making process, and the decision support provided;
- the actual choice made;
- health related quality of life;
- adherence to the chosen option;
- resource utilization;
- emotional distress;

- anxiety;
- depression;
- regret; and
- Litigation rates

Follow up – differed for each study

Results 34 RCTs were evaluated in this Review, 31 different decision aids were covered. Most are intended for use before counselling. 7 RCTs focused on conditions of the prostate (treatment decisions or BPH or PSA screening), only one of the 7 RCTs included prostate cancer patient's treatment decisions.

Using the CREDIBLE criteria to evaluate the quality of the decision aids: a) most included potential harms and benefits, credentials of the developers, description of their development process, update policy, and were free of perceived conflict of interest; b) many included reference to relevant literature; c) few included a description of the level of uncertainty regarding the evidence; and d) few were evaluated.

Thirty of these decision aids were evaluated in 34 RCTs and another trial evaluated a suite of eight decision aids. An additional 30 trials are yet to be published.

Overall Results for all trials including results for PCa trials (indicated by)*:

Among the trials comparing decision aids to usual care, decision aids (DA) performed better in terms of:

a) greater knowledge

DA had a significantly higher average knowledge scores, gains from 9 to 30 percentage points. WMD 19 points, 95% CI: 13 to 24);

Comparing detailed to simpler DA: a stat significant greater knowledge gain was observed from using detailed DAs, WMD 4.4 percentage points, 95% CI 2.4 to 6.2.

b) The pooled relative risk of having more realistic expectations (reported by way of measuring perceived probability of outcomes) after using a DA compared to usual care was 1.4, 95%CI: 1.1 to 1.9.

The pooled relative risk of having more realistic expectations after using a detailed DA compared to a simpler DA was 1.5, 95%CI 1.3 to 1.7.

c) Lower decisional conflict related to feeling informed was the most consistently observed effect of DA compared to usual care. A stat significant reduction in feeling uniformed about options, benefits and harms by 5 10 16 percentage points (pooled WMD -9.1 of 100, 95%CI: -12 to -6);

No stat significant reduction for feeling uninformed about options, benefits and harms was observed between detailed and simpler DA.

d) * Five out of seven studies showed a 26 to 70 % reduction in the proportion of people who assumed a passive (practitioner-controlled) role in decision making with two trials that were stat significant (PCa trial) and three that were not. The other two studies showed no difference. The pooled RR = 0.7 (95% CI: 0.5 to 0.9).

For individuals assuming an active (patient-controlled) role in decision making. Three of the seven studies (includes the PCa trial) reported relative risks ranging from 2.8 to 7.6, indicating a significant impact on the assumption of the patient-controlled role, two indicated an increase that was not statistically significant, and there was no difference for the other two studies (pooled RR 1.49, 95% CI: 0.99 to 2.25). The proportion adopting a shared decision making role

was more variable (pooled RR 0.9, 95% CI: 0.7 to 1.1)

e) The studies reporting on the proportion of people who remained undecided post intervention showed statistically significantly lower proportion in the decision aid group. The

Pooled relative risk was 0.43 (CI: 0.3 to 0.7).

f)* The PCa study found no significant difference between groups for depression, measured on the previously validated 20-item Centre for Epidemiologic Studies Depression Scale (Radloff 1977).

Decision aids appeared to do no better than comparisons in affecting satisfaction with decision making, anxiety, and health outcomes.

Decision aids had a variable effect on which healthcare options were selected.

Analysis where the Prostate Cancer Treatment Decision Aid was evaluated (Davison 1997):

Seven studies (which include Davison 1997) compared the effects of decision aids to usual care in terms of participation in decision making. The Davison paper used the Control preferences Scale (Degner 1992). The scale measures the preferred or actual role in decision making using five response statements - two represent an active or patient controlled role, one a shared or collaborative role, and two response statements represent a passive or practitioner controlled role.

Five of these seven studies showed a 26 to 70 percent reduction in the proportion of people who assumed a passive (practitioner-controlled) role in decision making with two trials that were statistically significant (including the Davison 1997) and three that were not.

COMPARISON IN MEN WITH PROSTATE CANCER WHO HAVE TO MAKE A TREATMENT DECISION	DECISION AID (A CONSULTATION, AUDIOTAPE, AND FIVE HANDOUTS ABOUT PCa TREATMENT OPTIONS)	USUAL CARE (THAT WERE PROVIDED WITH GENERAL INFORMATION)	OVERALL RESULT
participation in decision making (patient controlled)	17/30	5/30	Favours DA, RR = 3.4, 95% CI 1.44 to 8.03 (pooled RR 1.49, 95% CI 0.99 to 2.25)
participation in decision making (shared)	10/30	15/30	No stat sig. result, RR = 0.67, 95%CI 0.36 to 1.24 (pooled RR 0.9, 95% CI: 0.7 to 1.1)
participation in decision making (practitioner controlled)	3/30	10/30	Favours usual care, RR=0.03, CI 0.09-0.98. pooled RR = 0.7 (95% CI: 0.5 to 0.9)
depression			No significant difference between groups for depression, measured on the previously validated 20-item Centre for Epidemiologic Studies Depression Scale (Radloff 1977).

General comments

Overall conclusions about the effectiveness of DA are restricted because of the variability in

the decision context (screening, disease), the design used, the comparison used in the evaluation, outcomes included and the measurement of them.

In spite of these limitations, the trials consistently demonstrated that DA do better than usual care interventions in improving people's knowledge regarding options (19% absolute improvement), enhancing realistic expectations about the benefits/harms of options (40% relative improvement), reducing their decisional conflict, decreasing the proportion of people remaining undecided, and stimulating people to take a more active role in decision making.

Compared to simpler versions, DAs improved knowledge only marginally, but had other benefits such as increasing realistic expectations and agreement between values and actual choices.

The impact of DAs on increasing or decreasing references for particular options is more variable, which might be expected given the balanced information presentation within the DA and potentially variable preference rates at baseline. The review points out that most studies report that DAs reduced people's enthusiasm for major elective surgery in favour of more conservative options.

There has been no impact on satisfaction with the decision making process or with the actual choice, nor has there been an impact on health outcomes such as anxiety, general quality of life, or condition-specific quality of life.

There are too few studies to determine effects of DAs on persistence with the chosen therapy, costs, resource use, or efficacy of dissemination strategies.

Brink, 2000

Design: Observational study (therapy), evidence level: 2-

Inclusion criteria men with PCa and their female partners

Exclusion criteria not mentioned

Population number of patients = 43.

Interventions

CD ROM decision aid: an interactive CD-ROM that educates patients and facilitates treatment decision-making.

Outcomes

- self-efficacy (participants confidence to discuss issues about treatment with doctor),
- knowledge (about staging and brachytherapy) and
- program elements (CD_ROM usability)

Follow up

A pre-test questionnaire was conducted with men and their partners, the CD-ROM was then used by the participants and then a post-test questionnaire was administered to evaluate the

stated outcomes.

Results

For both groups: men with female partners and men only, almost half did not know the stage of their disease.

- For self efficacy and knowledge:

Significant difference was observed between pre-test and post-test

- Program elements:

Between 79 - 95% of participants approved of the following elements; title of program "Charting you course", presentation layout and design on screen, narration used, amount on information provided.

- Participants commented that more in depth information would be preferred.
- Only 62% of participants liked the 'personal story' or the navigation process of the program.

COMPARISON IN PROSTATE CANCER PATIENTS	CD-ROM DECISION AID	PRE-TEST	POST-TEST	OVERALL RESULT
self efficacy		mean test score 2.10	mean test score 1.61	p=0.016, CD ROM improves participants self efficacy in interactions with doctor about treatment.
knowledge (staging)		mean test score 0.73	mean test score 0.82	p=0.020, CD-ROM improved knowledge of staging.
knowledge (brachytherapy)		mean test score 0.46	mean test score 0.75	p=0.000, CD-ROM improved men's' knowledge of this treatment
COMPARISON IN PROSTATE CANCER PATIENTS AND THEIR FEMALE PARTNERS	CD-ROM DECISION AID	PRE-TEST	POST-TEST	OVERALL RESULT
self efficacy		mean test score 2.19	mean test score 1.66	p=0.002, CD ROM improves participants self efficacy in interactions with doctor about treatment.
knowledge (staging)		mean test score 0.73	mean test score 0.82	p=0.018, CD-ROM improved knowledge of staging.
knowledge (brachytherapy)		mean test score 0.51	mean test score 0.78	p=0.000, CD-ROM improved men's' knowledge

of this treatment

General comments

This is a pilot study of a CD-ROM DA. A prototype of the complete version of the CD-ROM DA was evaluated. The truncated version included self-efficacy (subject's perceived self efficacy in interacting with doctors about treatments), knowledge (about staging and brachytherapy) and program elements (CD-ROM usability).

The limitations of this pilot study include: evaluation was not done including all components of the DA, so we are unable to gauge how effective the whole thing is, and the evaluation was done with only a small sample that was not randomised. We would want to know how effective this study was in a larger sample.

Given the limitations and outcomes of this pilot, there are encouraging results for this CD-ROM DA.

Feldman-Stewart, 2001

Design: Observational study (therapy), evidence level: 2-

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

Inclusion criteria

The decision aid was tested with men who were in the age group of most newly diagnosed prostate cancer patients (at least 50 years old). The participants acted as surrogate decision makers as they had not been diagnosed with the disease.

The participants were a convenience sample of men at least 50 years old, never diagnosed with prostate cancer, who could understand English.

A purposeful sampling strategy was used to ensure presentation of those with and those without post-secondary education.

Exclusion criteria not specified

Population number of patients = 69, age range 50 to 83 years, mean age = 61 years.

Interventions

The DA: This decision aid is an interview, administered on an individual basis that is intended to be an adjunct to the normal doctor-patient consultations.

It fits between an initial consultation when the doctor presents the treatment options and a second consultation that occurs about 1 week later when the treatment decision is made.

This DA is based on the psychological theory of decision making, Svenson's Differentiation and Consolidation Theory (DiffCon). Decision aids guided by DiffCon, aim to reduce the risk that patients' decisions will cause them regret and/or cognitive dissonance by facilitating pre-decision differentiation and post-decision consolidation processes.

The aid includes three components:

1) the structured presentation of information

2) exercises designed to help the patient determine which attributes are important to his decision and

3) Exercises designed to help clarify the value of each of his important attributes as they are integrated into the larger picture.

Outcomes This is a preliminary evaluation of the aid.

Outcomes included:

- Comprehension: to determine if participants would be able to understand the information presented (evaluated by using a comprehension test at initial step of DA and decisional conflict assessment at the end of DA) ,

- To identify what is important to their decisions, and to weigh the attractiveness of the treatments on their important attributes (evaluated using a pre and post info test),

- To clarify the value of each of his important attributes (evaluated using trade-off "flip point" exercises)

- Indication of a preferred treatment options (TPA using an ordinal scale)

- To show evidence of differentiation (between initial attributes identified and if changes occurred during the DA interview).

Follow up no follow-up conducted after the interview

Results

All participants completed all aspects of the interview. They answered an average of 10 comprehension questions each, with a mean of 94.7% correct without a prompt. Each attribute in the information presented was identified by at least one participant as important to his decision.

Participants identified a median of five attributes as important (ranges 1-14) at each of three points during the interview, 75% changed at least one important attribute during the interview. Forty-nine per cent of participants also identified attributes as important those were not included in the presented information. Participants showed a wide range of values in each of seven trade-off exercises. Eighty-eight per cent of participants showed evidence of differentiation; 75% had a clear treatment preference by the end of the interview.

General comments

This is a pilot study for the Feldman-Stewart 2004 study (see following table for more relevant results). It was conducted with men who did not have PCa and a full description of the DA is attached.

The results observed will represent a population that does not meet the PICO specifications which has a risk of not capturing real time responses of men facing treatment decisions. In order to assess the effectiveness of this DA it would be more advantageous to evaluate the findings from the Feldman-Stewart 2004 study which involved men with PCa facing treatment decisions.

Feldman-Stewart, 2004

Design: Observational study (therapy), evidence level: 2-

Country: Canada (federal state, Commonwealth Realm), setting: Community

Inclusion criteria

Men attending an early consultation where the doctor is presents the treatment options.

After the patient consented to participate in the study, his physician identified which of the three treatment options were being offered, and some patients considered only two options while others considered three. Because the study was run in a cancer centre, all patients were offered radiation treatment, but not all offered either surgery (because of co-morbidities) or offered no treatment for now (often because the doctor felt the patient was too young).

Population number of patients = 60, mean age = 66 years.

Interventions

The decision aid is a one-to-one interview with a research assistant,

It occurs between an initial consultation when the doctor presents the treatment options to the patient and a second consultation that occurs about 1 week later when the treatment decision is made.

This DA is based on the psychological theory of decision making, Svenson's Differentiation and Consolidation Theory (DiffCon). Decision aids guided by DiffCon, aim to reduce the risk that patients' decisions will cause them regret and/or cognitive dissonance by facilitating pre-decision differentiation and post-decision consolidation processes. The aid is intended to help the patient become clearer about which treatment option he prefers in order to make the decision with his doctor at his next visit.

This study involved the decision-aid interview, a first follow-up interview (follow-up 1) that occurred after the patient made his actual treatment choice with his doctor, and a second follow-up interview (follow-up 2) that occurred about 3 months after the treatment decision, when the acute side-effects of the active treatments would have resolved.

The objectives of the intervention evaluation:

(1) To identify attributes that the patients considered important to their decision,

(2) To determine what patients identify as particular challenges as they make their decisions,

(3) To describe the proportion of patients that appear to show differentiation and consolidation through:

(a)changing which attributes were important to their decisions, and

(b) changing their ratings of how attractive the various treatment options are,

(4) To identify aspects of cognitive processing that are associated with:

(a) the stability of the preferred treatment option; i.e. the likelihood that the patients' actual treatment decision was the treatment they preferred at the end of the interview, and

(b) Regret as scored after they had completed their treatment.

Outcomes The attached flow diagram indicates the outputs of the DA that addressed the objectives of the evaluation. This was achieved by measuring attributes contained in the following lists:

Pre-Info List *

Post-info List *

Drop-option List *

Remaining-option List *

Flip Differences

* Objectives are the focus of this report.

Follow up a first follow-up interview (follow-up 1) that occurred after the patient made his actual treatment choice with his doctor (approx 1-2 weeks), and a second follow-up interview (follow-up 2) that occurred about 3 months after the treatment decision, when the acute side-effects of the active treatments would have resolved.

Results

Objective 1 - attributes important to the decision

60 participants identified 34 different items as important to their decisions when they were selecting their most preferred option. These were ranked and 18 different attributes were considered the most important attributes to the decision. The wide variation in important attributes is further demonstrated by the fact that only two attributes were important to more than 50% of patients (effect on bladder functioning, and effect on bowel functioning). A median of 4 attributes in the pre-info list (range 1-16) and 4 in the post info list (1-10) were reported.

32 patients completed the drop-option list (a list of attributes important to dropping the least-preferred option). The median number of attributes underlying the drop for the 32 patients was 2 (range 1-4); including 10 of these patients who reported non-board items (median 1, range 1-3). Nineteen of the patients (58%) identified at least one attribute on their drop lists that was not identified on any of their other lists and for 11 of the patients (33%), none of the attributes on their drop list was on any of the other lists. The most common attribute underlying the drop was 'the procedure involved' and that was important to 14 patients (42.4%).

Overall, 37 of the 60 patients (61.6%) identified non-board items in at least one of their important attribute lists.

Objective 2 - cognitive challenges

Insight into the cognitive challenges faced by patients was addressed from responses to the three items of the Decisional Conflict Scale identified in the methods. At the end of the decision-aid interview 92% of the participants (strongly) agreed that they were clear about the importance of the benefits of the options and 88% (strongly) agreed that they were clear about the importance of the risks and side-effects of the options. However, 47% (strongly) agreed that it was hard for them to decide if the benefits or the risks were important to them in the decision-making.

Objective 3(a) - changes in important attributes over decision process

A considerable number of important attributes were changed during the decision process: almost half of the patients (45%) added to, and a similar proportion (48%) dropped attributes from, the Pre-Info list when they listed their important attributes on the Post-Info list. Of the patients offered only two options, 78% changed at least one attribute between the two lists. Similarly, almost one-third of those completing the Remaining-options list dropped attributes from their Post-Info list and 25% added more. Overall, 49 (81.7%) patients changed, at some point in the interview, the attributes that they reported as important to the selection of their treatment choice.

Objective 3(b) - differentiation and consolidation: changes in treatment ratings :

Over the three assessments during the decision-aid interview, 43 (71.7%) patients changed at least one of their TPA ratings of the treatment options offered to them. Between the interview

and follow-up 1, 45 patients (75%) changed at least one of their TPA scores, and between follow-up 1 and follow-up 2, 34 (57%) changed at least one of their scores.

The average TPA scores for the most preferred option and for that of its closest competitor across the 56 patients who had completed the TPAs at all five time points (i.e. 5 TPA scores that were collected throughout the study) was assessed. The difference between mean TPA score for the most preferred option and that of its nearest competitor grew significantly over the five time points: the score of the most preferred option increased gradually over the entire time, while that of its closest competitor dropped [$F(4,220) = 16.6$, $P < 0.001$]. As described by the theoretical framework that the DA is based, the difference in the attractiveness of the most preferred option when compared with its nearest competitor continued to increase over the whole of the study.

Objective 4(a) - cognitive processes associated with stability of preferred treatment option :

At the beginning of the interview 17 (28%) of the patients did not have a clear treatment preference, as indicated by ties in top TPA scores; by the end of the interview, only five of them still did not have a treatment preference. At the end of the interview, 50 (83%) patients had a clear treatment preference.

Of the 50 who had a treatment preference at the end of the interview, 38 (76%) chose that preferred option as their actual treatment, and we describe their having the same preferences at the two time points as their preferences being consistent. Consistency of the preference was not associated with the size of the difference in TPA scores between the most preferred option and its nearest competitor, as measured either at the end of the interview (odds ratio 1.38, 95% CI: 0.80-2.37) or at the time of follow-up 1 (odds ratio 0.87, 95% CI: 0.44-1.72). However, the consistency was associated with increasing differences in the TPA score between the most preferred option and the TPA score of its nearest competitor between the interview and follow-up 1 (odds ratio 2.1, 95% CI: 1.40-3.14).

Mean TPA scores for most preferred option and for its nearest competitor during the study showed that the mean TPA score for the most preferred option increased in a linear manner throughout the decision-aid interview, and continued to do so after the actual decision was made. Results also show how the mean TPA score for the nearest competitor dropped in a step fashion between the end of the decision-aid interview and follow-up 1, when the treatment decision was made.

It appears that the relationship between TPA scores and whether patients actually chose the option that had the highest TPA score at the end of the interview is complex. The association appears to be with the shift in the difference between the preferred option and its competitors rather than with the size of the difference at any particular point in time.

Objective 4(b) - cognitive processes associated with regret :

The range of regret scores was 5–14 (where the scale is 5–25) with a mean of 8.4. The degree of regret was not associated with the difference in the TPA scores of the most preferred option and it nearest competitor, as measured at either follow-up 1 or at follow-up 2. However, regret scores were negatively associated with the shifts in the difference in the two TPA scores: regret scores decreased as the difference in TPA scores of the most preferred option and its nearest competitor increased from the interview to follow-up 2 ($P < 0.05$) and from follow-up 1 to follow-up 2 ($P < 0.01$).

Results suggest that patients experience less regret as the difference in the TPA scores between the two highest options increases. In other words, if differentiation is increasing, patients tend to feel less regret.

Overall Conclusions from the study:

Generally, the study demonstrated that a wide variation from one patient to the next in attributes that affect their treatment decisions exist. Furthermore, the extent of changes in attributes and in treatment ratings demonstrated in this study emphasizes the dynamic nature of

the decision process.

Authors note that by capturing the detail of differentiation and consolidation of attributes and when there are more than two options, if screening out options is not explicitly built into the process, important attributes may be overlooked and we may in turn increase the complexity of the decision for the patients. Further to this, both the stability of the patients' treatment choices and the extent of their regret after the decision appear to be related to whether the patients' evaluations of the options were still increasingly in favour of their initial treatment preference.

The authors believe that the approach of basing decision-aid development on a cognitive process theory of decision-making helps to create a product that could both help patients and provide health practitioners with some insight into patients cognitive processing that may, in turn, help practitioners to be even more effective. Guided by Diff Con, observations of differentiation/consolidation and its relationships to stability of choice and to regret suggest that values clarification exercises in decision aids may want to focus on encouraging differentiation processes. Study observations that decision processes are related to regret, support the use of regret as a primary outcome for the evaluation of decision aids.

Repeatability Study:

In order to detect any possible shift in attributes identified by the men in the study, 10 men were approached to repeat the formation of a post-info list and the remaining option list. This was conducted at the time of follow-up interview 1.

This set of men identified a mean of 4.3 (range 2-8) important attributes at the end of the original interview and a mean of 4.5 (range 3-7) in the follow-up interview. Of the total number of items identified at both times, a mean of 69.2% appeared on both lists; a mean of 85.6% of original interview attributes were repeated in the follow-up interview. Thus, the overwhelming majority of attributes identified as important at the original interview continued over the time to be identified as important; changes over time (either due to our measurement method or to a real shift in what was important) were more often in the direction of adding new attributes to the list.

General comments

Author's conclusions:

The decision process appears to be dynamic for the patients with great variability across patients in what is important to the decision. Increasing stability of choice and lack of regret appear to be related positively to increasing difference over time in how attractive the preferred option is over its closest competitor, rather than to the size of the difference at any one point in time.

The authors point out that understanding how patients weigh up benefits and harms and integrate this into their decision making processes requires further investigation.

Reviewers comments:

While this DA offered a tool that was able to address the complexity of associated with the variability and shifts in patient preferences, values and information intake, it requires an unbiased evaluation before it could be used to guide a clinical recommendation.

The DA interview is estimated to take an hour and a half to complete, the appropriateness of this aid in a busy clinic setting is questionable.

Holmes-Rovner, 2005

Design: Observational study (therapy), evidence level: 2-

Country: United States, setting: Secondary care

Inclusion criteria men recently diagnosed with PCa

Population number of patients = 60, mean age = 62 years.

Interventions

- Decision Aid for men (who have recently been diagnosed with PCa) and are at the point of decision about treatment options.
- Different designs were also evaluated (internet, audio and booklet).

Outcomes

- Knowledge (of patient) about own PSA test result, stage and grade of PCa, treatment options and side effects.
- Assessment of the balance, clarity and length of DA

Follow up no follow-up was conducted

Results

- The responses of men who received the 3 different designs of the DA (internet, audio and booklet), were reported to be virtually identical across all survey items with exception that those who received the audio version were less likely to share it with family and friends (data was not shown).
- Knowledge of the treatment options was not significantly different between the groups.
- Discussion of treatment options with the physician showed a significant increase in surgery discussions (98% in DA, 89% in control, p=0.019)
- Of the men that received the DA, 96%reported that the DA was mostly or all clear (with respect to the wording of the DA) with 76% of men reporting that the DA influenced their decision making, ranging from moderately to a lot).
- 86% reported sharing the DA with their spouse or partner, 22% with other family members, 14% with friends.
- 72% reported that they were more likely to take an active part in treatment decisions.

COMPARISON IN MEN WITH PROSTATE CANCER WHO HAVE TO MAKE A TREATMENT DECISION	DECISION AID	DA SAMPLE	HISTORICAL CONTROL	OVERALL RESULT
knowledge (treatment options)		98%	89%	Discussion of treatment options with the physician showed a significant increase in surgery discus-

	sions (98% in DA, 89% in control, p=0.019)

General comments

This study investigated the effectiveness of a DA to increase men's knowledge about their own PSA test result, stage and grade of PCa, treatment options and side effects. It also evaluated the balance, clarity and length of the DA.

Author's comments: The plain language DA presenting medical evidence in text and numerical formats appears acceptable and useful in decision-making about localized prostate cancer treatment. Further testing should evaluate the impact of all three media on decisions made and quality of life in the survivorship period, especially among very low literacy men.

Some limitations exist:

- The sample size limited the measurement of effect size and there was no randomisation of the DA. The comparison group was a group of historical controls. No description about the historical control group was provided and we are to assume they are a similar group of men who were not given the DA and who received usual care.
- There was a lack of analysis (for significance) when evaluating the different designs of the DA (internet, audio and booklet) as well as the assessment of the balance, clarity and length of DA.
- The data about the actual decision made by the test group was not available.
- No confidence intervals were reported.

In spite of these limitations, the study provides some insights into the make up of an effective DA.

Schapira, 1997

Design: Observational study, evidence level: 2-

Inclusion criteria A convenience sample of 32 men aged 50-85 years who did not have prostate cancer. Subjects for evaluation were recruited from men who were in primary care outpatient clinics.

Exclusion criteria – not stated

Population number of patients = 32, age range 50 to 85 years.

Interventions A videotape decision-aid: It incorporates role modelling and is designed to help patients understand treatment options and enhance the process of informed patient decision-making.

The content of the script included the following areas:

- Anatomy of the prostate gland, epidemiology of

- Prostate cancer, treatment options and outcomes,
- Efficacy of treatment and management of possible
- Treatment side effects.

Drafts were revised based upon comments from members of the expert panel until consensus was achieved regarding, the final form of the videotape script.

The video portion of the script was designed to complement the audio portion by the use of role modelling, the reinforcement of quantitative data with visual presentations, and footage of the operating room, radiation suites, and other medical and community settings.

The videotape was 20 min in length.

Outcomes

Knowledge scores:

The subjects completed a pre- and post-viewing knowledge and approach to decision-making assessment and a post-viewing evaluation of the videotape. The videotape was viewed only once by subjects. The knowledge assessment instrument included 20 multiple choice questions developed by the investigator and based on the videotape content.

Topics covered by the questions included anatomy and physiology of the prostate, risk factors and epidemiology of prostate cancer, common short-term and long-term side effects of radiation and radical prostatectomy, the definition and indications for watchful waiting and the relative efficacy of surgery and radiation.

Subjects were asked to both identify the most common side effects of specific treatments and to identify the expected frequency at which these side effects would occur. Differences between pre-test and post-test responses were analyzed with McNemar's test for matched pairs.

Decision-making process:

Approach to decision-making was assessed by responses to open-ended questions.

Follow up – not conducted

Results The analysis found a significant improvement in knowledge regarding prostate cancer and treatment options after viewing the videotape compared to responses of subjects prior to viewing the videotape.

The specific areas where a significant difference occurred include:

Knowledge about side effects (both quantitative and qualitative issues associated with fatigue and impotence after RT)

Knowledge about side effects (qualitative issues associated with impotence after prostatectomy)

Awareness about impotence and incontinence.

Indications for watchful waiting.

Analysis of the qualitative section of the instrument demonstrated five major factors influencing the approach to treatment decision-making.

These factors were:

(1) deferment of the treatment decision to the physician,

(2) information seeking such as asking a second opinion,

(3) joint decision-making discussions between the physician and patient,

(4) family advice (inconclusive evidence shown in study)

(5) consideration of treatment side effects

COMPARISON IN MEN WITHOUT PCa	DECISION AID (VIDEO)	PRE-TEST NUMBERS OF MEN	POST-TEST NUMBERS OF MEN	OVERALL RESULT
knowledge		About fatigue after RT: 28%	About fatigue after RT: 59%	The DA significantly improved qualitative knowledge about fatigue after RT, p<0.05
knowledge		About impotence after RT: 44%	About impotence after RT: 84%	The DA significantly improved qualitative knowledge about impotence after RT, p<0.05
COMPARISON IN MEN WITHOUT PCa	DECISION AID	PRE-TEST NUMBERS OF MEN	POST-TEST NUMBERS OF MEN	OVERALL RESULT
knowledge		About impotence after radical prostatectomy: 56%%	About impotence after radical prostatectomy: 84%	The DA significantly improved qualitative knowledge about impotence after radical prostatectomy, p<0.05
knowledge		About impotence after RT: 38%	About impotence after RT: 72%	The DA significantly improved quantitative knowledge about impotence after RT, p<0.05
knowledge		About serious bowel or bladder injury rate: 44%	About serious bowel or bladder injury rate: 56%	The DA significantly improved quantitative knowledge about serious bowel or bladder injury rate after RT, p<0.05
knowledge		About awareness of treatment for complications to do with incontinence: 53%	About awareness of treatment for complications to do with incontinence: 88%	The DA significantly improved awareness of treatment for complications to do with incontinence, p<0.05
knowledge		About awareness of treatment for complications to do with impotence: 63%	About awareness of treatment for complications to do with impotence: 96%	The DA significantly improved awareness of treatment for complications to

			do with impotence, p<0.05
knowledge	indication for watchful waiting: 28%	indication for watchful waiting: 88%	The DA significantly improved knowledge about indications for watchful waiting, p<0.05
knowledge	about relative efficacy of radiation and surgery: 44%	about relative efficacy of radiation and surgery: 75%	The DA significantly improved knowledge about the relative efficacy of radiation and surgery , p<0.05
decision making process	28% would defer the decision making process to the physician	16% would defer the decision making process to the physician	After viewing the video DA, a 12% reduction was observed in the number of men who would defer the decision making process to the physician. Statistical significance not evaluated.
decision making process	9% would pursue behaviours of info seeking	31% would pursue behaviours of info seeking	After viewing the video DA, the number of men who would pursue behaviours of info seeking increased by 22%. Statistical significance not evaluated.
decision making process	3% would participate in joint decision-making with the physician	22% would participate in joint decision-making with the physician	After viewing the video DA, the number of men who would participate in joint decision-making with the physician increased by 19%. Statistical significance not evaluated.
decision making process	3% would consider the treatment side effects	19% would consider the treatment side effects	After viewing the video DA, the number of men who would consider treatment side effects increased by 16%. Statistical significance not evaluated.

General comments

An important limitation of this study was that the subjects used in the evaluation of the video-tape did not actually have prostate cancer. This may have had an impact on the uptake of knowledge. The pre-test may have influenced the men and there knowledge and awareness of issues and thereby influencing the results of the post test. An RCT would provide an unbiased analysis. An underestimation the effectiveness of the DA may have occurred.

No follow-up analysis was conducted; limiting the long term effects of the DA, i.e. knowledge of men some months after the DA was used.

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.

Reference List

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1.3 Specific problems

What are the information/communication needs of the wives, partners, carers, and family of men with prostate cancer about treatment options?

Clinical question

What are the information/communication needs of partners, wives, carers or family of men considering treatment options for prostate cancer?

Evidence Summary

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

There was some overlap with the outcomes measure in the studies including stress and well being variables (include in the FACT-P). Both studies did report a partial effectiveness of the interventions in terms of these outcomes.

Evidence Tables

(Manne *et al.* 2004)
Design: Randomized controlled trial (therapy), evidence level: 1- Country: , setting: Secondary care **Inclusion criteria** Criteria for inclusion in the study were: (a) partner 18 years of age or older; (b) patient married or living with partner; (c) patient diagnosed with any stage of prostate cancer, (d) Wife able to provide informed consent. **Exclusion criteria** – **Population** – Mean Age = 59.63 84% had greater than high school education 84% were white Americans Sample size = 60

Interventions

The intervention was a closed, structured group intervention.

Groups met on six consecutive weeks for 1 hour.

The following topics were covered:

Session 1: Medical information about prostate cancer and Treatment (led by a radiation oncologist);

Session 2: Maintaining good nutrition during and after treatment (led by a nutritionist);

Session 3: Stress management and coping skills training (led by a psychologist);

Session 4: Maintaining good communication and how to better get support needs met (led by a psychologist); Session 5: Maintaining intimacy and dealing with sexual concerns (led by a psychologist);

Session 6: Survivorship issues (common post treatment concerns and ways of coping) (led by a social worker).

Didactic presentations were combined with group contribution (e.g. input about what constitutes non-supportive reactions) and in session exercises. Home practice assignments were given after Session 3 (practice relaxation) and Session 4 (disclose feelings, ask for support).

Sessions were delivered by Two psychologists, a nutritionist specialised in cancer nutrition, a social worker.

Control group.

Standard psychosocial care available at the hospital was available to these participants. This care consisted of support from a social worker and referral to a community mental health professional.

Outcomes

- Demographics and mental health service utilization.
- General psychological distress.
- Cancer-specific distress.
- Coping.
- Post-traumatic growth inventory: assesses positive changes that occurred as a result of a stressful life event
- Cancer-specific marital interactions.

Results

The final sample size was 60,

29 intervention group participants

31 control group participants.

Four wives assigned to the intervention group and three wives assigned to the control group dropped out.

The study participation rate was 57%.

Study completion rate was 88% (completed both baseline and post-test surveys).

Participants completed a questionnaire prior to being assigned to study condition (baseline) and 1 month after completion of the intervention (post-test).

Control group participants were sent the post-test survey at the same time point.

The intervention and control groups were compared on baseline demographic and patient medical variables. There were no differences between study conditions.

Distress:

Comparisons of baseline distress did not suggest significant differences for general (p=0.80) or cancer-specific (p=0.34) distress.

Post-test comparisons with all study participants revealed that there were no significant differences between groups in either general or cancer-specific distress. An examination of group means suggested that general psychological distress declined over the course of the study in both groups.

IES scores declined in the intervention while remaining somewhat stable in the control group; however, the Mann-Whitney tests showed that post-test IES scores did not differ significantly between the two groups.

Coping and post-traumatic growth:

Results suggested differences between groups on two of the five coping scales: positive reappraisal and growth and denial coping. Positive reappraisal and growth was significantly higher among the group of wives who participated in the group intervention.

Denial was significantly lower among the group of wives who participated in the intervention. These findings remained significant when wives who attended fewer than half the groups were excluded from analyses.

Post-traumatic growth inventory: (PTGI)

Mann-Whitney tests indicated differences between groups for specific components of the PTGI (Relate to others, personal strength, Spiritual growth, Appreciation for life) variables. Scores for PTGI scales were higher among wives in the Intervention group.

Cancer-specific marital communication:

Mann-Whitney tests did not indicate differences between groups on for any of the marital communication variables.

In general, the results of this study suggested that the psycho educational group intervention did not reduce psychological distress.

General comments

The limitations of this study outlined below will reduce the reliability and validity of the findings reported.

No Blinding was described and small numbers included in the study limit the reliability to which the effect of the intervention.

The study was not representative of wives of men with prostate cancer and may have biased the study findings. That is, it is possible that the most distressed wives did not participate in the study. This biasing would result in lower distressed levels and potentially contribute to our lack of impact on distress, as those most in need of intervention may not have participated.

The sample composition was not well represented with ethnic minorities, limiting the application to wider UK populations.

The age of the population was relatively young given the general population of men affected by PCa.

Overall, the effects of this intervention were modest and psychological distress was not impacted.

(Thornton *et al.* 2004)

Design: RCT, evidence level: 1-

Country: United States, setting: Other

Inclusion criteria

Study participants were partnered men who underwent a radical prostatectomy for prostate cancer at Norris Comprehensive Cancer Centre (NCCC) between 01/01/1997 and 05/31/1999, and their partners.

Specific inclusion criteria and study participant numbers:

1) patient is partnered (n = 50);

2) patient's partner plans to attend the presurgical appointment (n = 31);

3) patient's surgery is scheduled to allow sufficient time for the study team to contact him (i.e., there are at least 4 days between receipt of patient's contact information by the researchers and the date of the patient's presurgical appointment (n = 96);

4) patient's presurgical appointment is scheduled at NCCC (n = 12);

5) patient and partner are fluent in written and spoken English (n = 15);

6) patient has no other active cancers and is not undergoing salvage prostatectomy (n = 4);

7) both patient and partner are aware of the cancer diagnosis (n = 5, of these, two patients denied having prostate cancer themselves);

8) Patient has no co morbid psychiatric diagnosis (n = 1).

Exclusion criteria -

Population –

Mean age = 61.16 years (41-78, SD 7.22)

Highly educated Caucasian men and wives.

Interventions

The aim of this study was to determine the effectiveness of a brief, presurgical, couple-based communication-enhancement intervention (for only partnered prostatectomy patients).

All patients received NCCC standard care, which also served as the control condition for this study. As part of standard care practices, patients had an appointment at NCCC on the day before surgery. During this appointment, they underwent several procedures in preparation for surgery the following day and met with a nurse who provided them with basic information related to their surgery.

The intervention comprised of two parts:

Part 1. The counsellor helped patients and partners identify questions they had for the medical team and ways they could meet their information needs.

Part 2. The counsellor focused on helping the patient and partner identify and discuss their support needs.

Outcomes

Patient and partner quality of life and psychosocial outcomes before surgery and at 3 weeks, and 1 year post surgery were measured.

Standardized questionnaires assessing general and disease-specific (patients only) quality of life, affect, stress, and relationship quality were compiled into separate patient and partner questionnaire packets.

The Rand 36-Item Health Survey was used to assess patient and partner general health-related quality of life. This instrument quantifies quality of life in eight areas :

- physical functioning
- role limitations due to physical health
- pain
- general health perception
- emotional wellbeing
- role limitations due
- to emotional problems
- energy
- social functioning

Individual scale items are transformed to a 0-100-point scale with higher scores indicating better quality of life.

Patient disease specific quality of life with the Functional Assessment of Cancer Treatment-Prostate version (FACT-P). The FACT-P evaluates patient quality of life in six areas: physical wellbeing, functional wellbeing, prostate-specific functioning (the prostate cancer subscale or PCS), social/family wellbeing, emotional wellbeing, and relationship with physician.

Patients indicate their agreement with 47 items via Likert-type scale. Where 0 (not at all) to 4 (very much) and higher scores indicate better functioning.

A modified version of the 4-item Urinary Incontinence scale to assess the patient's urinary functioning at pre-surgery and 1 year post-surgery was included. Patients also were asked to report on their typical level of erection during sexual activity with a partner using a 5-point scale ranging from 1 (totally soft) to 5 (rigid and un-bendable). For both measures, higher scores indicate better functioning.

Patient and partner affect was assessed with the Positive and Negative Affect Schedule (PANAS). Two 10 item subscales measure positive and negative affect. Respondents use a 1 (very slightly or not at all) to 5 (extremely) scale to indicate the extent to which they believe that each of a series of 20 adjectives applies to them.

The Impact of Event Scale (IES) was used to measure stress symptoms specific to the cancer experience. Respondents use a 4-point scale ranging from 1 (not at all) to 4 (often), to rate

15 items that measure symptoms of intrusion or avoidance, with higher scores indicating more stress.

General stress was assessed with the Perceived Stress Scale (PSS); it assesses the extent to which participants appraise situations in their lives as being stressful, out of control, and difficult to manage. Respondents rate each of 14 items on a 5-point scale ranging from 0 (never) to 4 (very often), and higher scores indicate greater stress.

The overall quality of the couple's relationship with the Dyadic Adjustment Scale (DAS) was measured; it is a 32-item measure that assesses total relationship quality. Respondents indi-

cate the frequency with which they engage in specific behaviours with their partner as well as the extent of agreement on relationship issues.

Follow up

Patient and partner quality of life and psychosocial outcomes were assessed 1 year post surgery.

Results

207 patients and partners were eligible, only 106 participants were recruited. Selection of patients for this study was drawn from a list of patients who were scheduled for upcoming surgery.

An assessment of patient and partner quality of life and psychosocial outcomes before surgery, and at 3 weeks, 6 months, and 1 year post surgery was conducted.

80 patients returned questionnaires corresponding to pre-surgery-, 3 weeks post-surgery, and 1 year post-surgery and comprised our final sample and completed all surveys.

Of the 106 consenting patients:

93 completed the 3 week post-surgery follow-up questionnaire. (18 of these patients did not complete the 6 month follow-up questionnaire, and 13 did not complete the 1 year follow-up questionnaire.)

To maximize the sample size and power to detect effects, the 80 patients who returned questionnaires corresponding to pre-surgery, 3 weeks post-surgery, and 1 year post-surgery comprised the final sample.

Partner data at these three time points were available for 65 of these patients' partners.

The authors describe that although the final sample of patients was largely comparable to no completing patients, several differences between completing and non-completing partners did exist suggesting that partners who were better adjusted and who were married to patients who were better adjusted were more likely to complete the study.

At the patient's presurgical appointment a presurgical questionnaires was completed.

Consenting couples were randomized to the communication enhancement intervention or control condition. (They were told their condition assignment)

The couple received a second questionnaire packet timed to at the patient's 3 week post surgery appointment, (with instructions not to complete the questionnaires until after that appointment.)

The follow-up packet was similar to the one sent prior to surgery.

The differences between participant’s variables and within participant variables were measured for each group (intervention of control) at 3 different time points.

For patients, the effect of time remained significant within each FACT-P variable, with both standard care and intervention groups indicating poorer social wellbeing at 1 year post surgery compared to 3 weeks post surgery and 1 year post surgery compared to pre-surgery

for the intervention group,

$F[1, 40] = 37:92$, $p < 0.001$, (1 year post surgery compared to 3 weeks post surgery)

and $F[1, 40]=17:43$, $p < 0.001$ (1 year post surgery compared to pre-surgery)

for the control group,

$F[1, 38] = 6:90$, $p = 0.01$ (1 year post surgery compared to 3 weeks post surgery) and

F [1, 38] = 10:93, p =0.002, (1 year post surgery compared to pre-surgery).

Patients showed a trend towards improved social/family well being at 3 weeks that resulted in better functioning compared to control patients at this time only, t(78) = -2.62, p =0.01.

For partners, the intervention had a significant impact on general stress.

Partners in the intervention reported less stress at 3 weeks post surgery compared to pre-surgery, F(1, 32) = 5:51, p =0.03;

at 1 year post surgery compared to 3 weeks post surgery, F(1, 32) = 5:34, p =0.03; and at 1 year post surgery compared to pre-surgery, F (1, 33) = 8:99, p =0.005.

Intervention partners indicated lower levels of general stress compared to standard care partners at 1 year post surgery, t(63) = 1.97, p=0.05.

General comments

Patients who participated in the intervention reported better social/family wellbeing 3 weeks after surgery compared to those who received standard care.

Additionally the intervention indicated that general stress scores for partners decreased over time for those who participated in the communication intervention only. Authors note that change on this variable seems especially relevant to this group given that partners reported more general stress than patients at pre-surgery and 3 weeks post surgery.

Limits to this study:

Nearly half of the patients who were eligible for entry into the study declined participation, this selection bias will impact on the effect of the intervention. As it turns out, the population included in the study were well adjusted as observed by the initial Quality of life questionnaire.

As the authors point out and which is highly relevant, that type one error may exist for this study. This means you report an effect of the intervention when actually there is no effect probably due to the selection boas of the included population.

This study did not describe blinding, allocation concealment or intention to treat analysis. All these mentioned factors seriously affect the validity of this study and the confidence we can assume that the intervention evaluated made any difference to the men's or partners quality of life.

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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Thornton, A. A., Perez, M. A. & Meyerowitz, B. E. (2004) Patient and partner quality of life and psychosocial adjustment following radical prostatectomy. *Journal of Clinical Psychology in Medical Settings,* 11: 15-30.

2 Diagnosis and Staging of Prostate Cancer

2.1 When to biopsy

Should men who have a raised PSA level automatically be referred for biopsy to determine if they have prostate cancer?

Short summary

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

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOMES
Men who have a raised PSA and have been referred for investigation.	Immediate biopsy	Delayed biopsy with biochemical monitoring.	▪ Morbidity of biopsy ▪ Mortality of biopsy ▪ Probability of detection of 'significant' prostate cancer on biopsy ▪ Probability of detection of 'irrelevant' prostate cancer on biopsy ▪ Probability of subsequent biopsy if initially observed ▪ Biochemical-PFS ▪ Overall survival ▪ Psychological health of 'coping' with measuring continuously suspect PSA levels

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

Evidence Summary

The literature search found no directly relevant studies comparing immediate and delayed biopsy in men with raised PSA.

Decision Aids

The literature search for the question about decision aids (see chapter two) showed that most research was about treatment decisions for men with histologically established prostate cancer. Although some studies reported decisions aids for screening tests, there was a lack of work on decision aids for men with suspected prostate cancer who are contemplating biopsy.

Morbidity due to biopsy

A good quality 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.

Morbidity due to over treatment of insignificant cancer could also be considered an adverse effect of biopsy. Evidence about outcomes after radical therapies in men with local prostate cancer suggests that although some men will benefit from the diagnosis of their prostate cancer, many will not. Some may experience greater harm than if their cancer had gone undiagnosed, due to treatment toxicity. Factors associated with benefit from radical treatment include high grade disease and greater life expectancy (see treatment of clinically localised disease, chapter four).

Predicting high grade prostate cancer on biopsy

A number studies reported models to predict the outcome of prostate biopsy (see tables 3.6.1 to 3.6.4 below). The most relevant are the five studies with models to predict high grade cancer on prostate biopsy (Borden *et al.* 2006; Garzotto *et al.* 2005; Krejcarek *et al.* 2007; Nam *et al.* 2006; Thompson *et al.* 2006), since men with high grade disease more likely to benefit from diagnosis and treatment.

There is evidence that a number of variables are associated with the risk of high grade prostate cancer in men undergoing sextant prostate biopsy (see Table 1 below). The odds of high-grade cancer were related to age, PSA, DRE result, prior negative biopsy, black ethnicity and prostate volume. The effect of LUTS and black ethnicity, however, were of borderline statistical significance in some of the studies.

Two of these studies presented nomograms for the prediction of high grade disease (Garzotto *et al.* 2005; Nam *et al.* 2006). Validation of the nomogram was internal in one study (Nam *et al.* 2006) and external in the other (Garzotto *et al.* 2005), with reported area under the ROC curve values of 0.77 and 0.74 respectively

Table 1. Characteristics of studies that developed models to predict prostate cancer on biopsy

Study	Country	No. of patients	No. with prostate cancer detected on biopsy (%)	Patient inclusion criteria	Study design	Biopsy technique
(Karakiewicz *et al.* 2005)	USA	4193	1477 (35)	PSA ≤ 50 ng/ml and referred for biopsy	Retrospective case series	Sextant
(Borden *et al.* 2006)	USA	790	320 (41)	Raised PSA (not defined) or abnormal DRE, referred for biopsy.	Prospective case series	5 or more cores

Study	Country	No. of patients	No. with prostate cancer detected on biopsy (%)	Patient inclusion criteria	Study design	Biopsy technique
(Eastham *et al.* 1999)	USA	700	65 (9)	PSA ≤ 4 ng/ml, suspicious DRE and referred for biopsy	Retrospective case series	Sextant + lesion directed biopsies
(Finne *et al.* 2002)	Finland	758	200 (26)	PSA 4–20 ng/ml, age 55–67, population based screening	Prospective, cancer screening trial	Sextant + lesion directed biopsies
(Nam *et al.* 2006)	Canada	2637	1282 (49)	PSA > 2.5 ng/ml or abnormal DRE and referred for biopsy	Retrospective case series	6 to 15 cores (median 8)
(Roobol *et al.* 2007) (men with NO previous biopsy)	Europe	2483	665 (27)	PSA ≥ 4 ng/ml, in a screening trial, no previous prostate biopsy	Prospective, cancer screening trial	Mostly sextant, a few had 10 – 12 cores
(Roobol *et al.* 2007)(men with previous biopsy)	Europe	988	197 (20)	PSA ≥ 4 ng/ml, in a screening trial, previous prostate biopsy negative for cancer	Prospective, cancer screening trial	Mostly sextant, a few had 10 – 12 cores
(Al-Azab *et al.* 2007)	Canada	1796	771 (43)	PSA 2–9 ng/ml referred for first biopsy	Retrospective case series	Sextant + lesion directed biopsies
(Thompson *et al.* 2006)	USA	5519	1211 (22)	Age ≤55, PSA <3ng/ml and normal DRE at time of entry into the placebo group of a prostate cancer prevention trial.	Prospective, single arm of randomised trial	Sextant
(Kranse *et al.* 1999)	Netherlands	1923	425 (22)	PSA ≥ 4ng/ml and/or abnormal DRE and/or abnormal TRUS, age 55–74 years, population based screening	Prospective, cancer screening trial	Sextant

Study	Country	No. of patients	No. with prostate cancer detected on biopsy (%)	Patient inclusion criteria	Study design	Biopsy technique
(Finne *et al.* 2004)	Finland Netherlands Sweden	1183	253 (21)	PSA 4–10 ng/ml, age 55–67yrs, population based screening	Prospective, cancer screening trial	Sextant + lesion directed biopsies
(Loeb *et al.* 2007)	USA	6844	346 (5)	Age between 40 and 60 years, abnormal DRE or PSA more than 4 ng/ml (pre 1995) or 2.5 ng/ml (1995 onwards)	Prospective, cancer screening trial	At least quadrant (pre 1995) or sextant (1995 on)
(Yanke *et al* 2006)	USA	9473	1895 (20)	Men referred for biopsy due to elevated PSA or abnormal DRE.	Retrospective case series	Varied: median number of cores >6.

Table 2. Characteristics of studies that developed models to predict high grade prostate cancer on biopsy

Study	Country	No. of patients	No. with high grade prostate cancer detected on biopsy (%)	Patient inclusion criteria	Study design	Biopsy technique
(Borden *et al.* 2006)	USA	790	144 (18)	Raised PSA (not defined) or abnormal DRE, referred for biopsy.	Prospective case series	Sextant
(Garzotto *et al.* 2005)	USA	1699	157 (9)	PSA ≤ 10 ng/ml and referred for biopsy	Prospective case series	5 or more cores

(Nam *et al.* 2006)	Canada	2637	762 (29)	PSA > 2.5 ng/ml or abnormal DRE and referred for biopsy	Retrospective case series	Sextant + lesion directed biopsies
(Krejcarek *et al.* 2007)	USA	358	73 (20)	Men treated with EBRT for prostate cancer at a single institution	Retrospective case series	Mean and median 6 cores
(Thompson *et al.* 2006)	USA	5519	257 (5)	Age ≤55, PSA <3ng/ml and normal DRE at time of entry into the placebo group of a prostate cancer prevention trial.	Prospective, single arm of randomised trial	Sextant + lesion directed biopsies

Table 3. Variables included in models for the prediction of prostate cancer on biopsy. Figures are odds ratios [95% confidence intervals] of prostate cancer.

Study	Age (years)	Serum PSA (ng/ml)	%fPSA	PSAV	DRE[2]	TRUS	Ethnicity[1]	Prostate volume (ml)	LUTS	Previous negative biopsy	Family History[3]	Other variables
(Karakiewicz *et al.* 2005)	1.025	1.029	0.917	–	Suspicious 6.182	–	–	–	–	–	–	
(Borden *et al.* 2006))	1.05 [1.01–1.07]	*<4ng/ml* 0.45 [0.29–0.70] *4.0–9.9 ng/ml* 1.00 *>10 ng/ml* 2.74 [1.75–4.31]	–	–	Abnormal 2.18 [1.53–3.10]	–	Black 1.00 [0.55–1.82]	0.98 [0.97–0.99]	–	–	–	Year of biopsy, number of cores,
(Eastham *et al.* 1999)	1.30 [0.87–1.94]	3.78 [2.48–5.75]	–	–	–	–	Black 1.03 [0.59–1.78]	–	–	–	–	
(Finne *et al.* 2002)	–	ln(PSA) 2.223 [1.371–3.611]	0.908 [0.871–0.948]	–	Suspicious 2.801 [1.831–4.286]	–	–	≥ 37 ml 0.533 [0.356–0.796]	–	–	–	
(Nam *et al.* 2006)	1.05 [1.03–1.05]	1.07 [1.05–1.08]	–	–	Nodule present 1.48 [1.2–1.8]	–	Black 1.51 [1.1–2.0] Asian 0.40 [0.3–0.6]	0.98 [0.97–0.99]	0.86 [0.7–1.0]	0.45 [0.4–0.6]	1.41 [1.1–1.8]	
(Roobol *et al.* 2007) (men with NO previous biopsy)	1.003 [0.96–1.030]	log(PSA) 8.90 [2.08–38.05]	–	0.851 [0.69–1.05]	1.74 [1.26–2.42]	Positive 1.633 [1.16–2.30]	–	log(vol.) 0.02 [0.01–0.05]	–	–	–	
(Roobol *et al.* 2007) (men with previous biopsy)	1.006 [0.97–1.05]	log(PSA) 3.47 [0.86–14.01]	–	1.11 [0.85–1.43]	1.28 [0.82–2.01]	Positive 1.13 [0.70–1.83]	–	log(vol.) 0.04 [0.02–0.12]	–	–	–	
(Al-Azab *et al.* 2007)	1.05 [1.04–1.07]	log(PSA) 3.20 [2.54–4.54]	–		–	Positive 2.42 [1.96–2.99]	–	log(volume) 0.12 [0.09–0.16]	–	–	–	

Study	Age (years)	Serum PSA (ng/ml)	%fPSA	PSAV	DRE[2]	TRUS	Ethnicity[1]	Prostate volume (ml)	LUTS	Previous negative biopsy	Family History[3]	Other variables
(Thompson *et al.* 2006))	–	log(PSA) 2.34 [2.13–2.56]	–	–	2.47 [2.03–3.01]	–	–		–	0.64 [0.53–0.78]	1.31 [1.11–1.55]	no. of PSA screens
(Kranse *et al.* 1999)[4]	–	log(PSA) 56.261 [35.163–90.017]	–	–	Suspicious 2.915 [2.270–3.743]	Suspicious 0.91 [0.66–1.16]	–	log(volume) 0.017 [0.008–0.038]	–	–	–	
(Finne *et al.* 2004)	–	Transformed[3] 2.10 [1.37–3.22]	0.91 [0.88–0.93]	–	Suspicious 3.61 [2.52–5.18]	–	–	ln(volume) 0.28 [0.17–0.45]	–	–	–	
(Yanke *et al* 2006)	Groups not reported 1.30 [1.22–1.39]	1.47 [1.42–1.52]	–	–	1.75 [1.57–1.95]	–	Black 1.35 [1.20–1.49]	–	–	–	–	Year of biopsy, no. of cores.
(Loeb *et al.* 2007)	50-59 vs. 40-49, 1.9 [0.9–4.0]	1.1 [1.07–1.16]		>0.4ng/ml/yr 6.7 [5.2–8.7]			1.7 [1.2–2.5]				1.2 [0.9–1.6]	

Abbreviations: PCa, prostate cancer; PSA, prostate-specific antigen; PSAV, prostate-specific antigen velocity; %fPSA, percent free prostate-specific antigen; DRE, digital rectal examination; TRUS, transrectal ultrasound; LUTS, lower urinary tract symptoms.

Footnotes
1. Compared with white
2. Compared with normal DRE
3. PSA was transformed using: exp [(PSA-6.5)×2] / (exp [(PSA-6.5)×2] +1)
4. Odds ratios for PSA and volume differ by an order of magnitude to the other studies, suggesting calculation error.
5. Other risk factors analysed by the study, but not included in this table

Variables associated with increased probability of prostate cancer detection:

Age.

In studies that treated age as a continuous variable, the odds of prostate cancer on biopsy increased with age by a factor of around 1.05 with each additional year. Loeb et al (2007) dichotomised age into 40–49 vs. 50–59 year old groups, and found that the difference in the odds of prostate cancer was not significant.

PSA

Increased serum PSA level was always associated with increased odds of prostate cancer at biopsy in all studies. It is difficult to judge the size of the effect of serum PSA, due to the different transformations of the PSA scale used in different studies. All but two of the studies used selection criteria involving serum PSA thresholds, restricting the range of possible PSA levels. In studies using the log transform, the odds of detecting prostate cancer increased by a factor of between 2.3 to 8.9 with each unit increase of log (PSA). In men who had been previously biopsied however, log (PSA) was not significantly associated with increased odds of prostate cancer (Roobol *et al.* 2007).

Positive family history

Risk of prostate cancer on biopsy was greater in men with a family history of prostate cancer. The odds of prostate cancer were increased by a factor of 1.41 in one study and 1.31 in another, if a first or second degree relative had prostate cancer. The effect of family history was not significant in the Loeb study ((Loeb *et al.* 2007).

Abnormal or suspicious DRE

Studies reporting DRE noted an approximately threefold increase in the odds of prostate cancer when DRE was abnormal or suspicious for cancer. Studies often used abnormal DRE as a criterion for prostate biopsy.

Variables associated with decreased probability of prostate cancer detection:

%fPSA

There was good consistency in the three studies reporting %fPSA. With each percentage point increase in %fPSA, the odds of detecting prostate cancer decreased by a factor of 0.91.

Previous prostate biopsy negative for cancer

Risk of prostate cancer on biopsy decreases with: previous negative biopsy, prostate volume, and %fPSA.

Increased prostate volume was associated with a decreased risk of prostate cancer. A previous negative biopsy decreased the odds of detecting prostate cancer by about a half.

Prostate volume

All studies that considered prostate volume (or the log of prostate volume) noted that the odds of prostate cancer decreased with increasing prostate volume.

Variables where the relationship with prostate cancer was inconsistent

TRUS findings

There was inconsistent evidence about the effect of transrectal ultrasound. Two studies reported that a positive TRUS was associated with significantly increased odds of prostate cancer, whereas another two studies did not find a significant association. One of the studies noted that TRUS was only associated with increased likelihood of prostate cancer on the first biopsy (Roobol *et al.* 2007).

Black race

There was inconsistent evidence about the effect of black race. Three studies noted an increase in the odds of prostate cancer in black men, when compared to whites, whereas another two studies did not report a significant increase.

LUTS

One study (Nam *et al.* 2006) looked at lower urinary tract symptoms (LUTS), and reported that LUTS were associated with reduced odds of prostate cancer, of borderline statistical significance.

PSAV

When PSAV was treated as a continuous variable, there was no significant association with the odds of prostate cancer. One study (Loeb *et al.* 2007) used a cut-off threshold of 0.4 ng/ml/yr to categorise men, and found that the higher PSAV group had a greatly increased odds of prostate cancer. The cut-off value, however, was chosen from the data to give the greatest discrimination between cancer and non-cancer cases.

Table 4. Variables included in models for the prediction of high grade (Gleason 7 or more) prostate cancer on biopsy. Figures are odds ratios [95% confidence intervals] of high grade prostate cancer.

Study	Age (years)	PSA (ng/ml)	PSAV	DRE[2]	Ethnicity[1]	Prostate volume (ml)	LUTS	Previous negative biopsy	Family History[3]	Other variables
(Borden *et al.* 2006)	1.07 [1.04–1.10]	*<4ng/ml* 0.30 [0.15–0.58] *4.0–9.9 ng/ml* 1.00 *>10 ng/ml* 3.84 [2.28–6.50]	–	Abnormal 3.39 [2.07–5.53]	Black 1.05 [0.47–2.32]	0.97 [0.96–0.98]	–	–	–	Year of biopsy, number of cores
(Garzotto *et al.* 2005)	70 or more 1.580 [95%CI 1.010 to 2.409]	*0.07 ≤ PSAD ≤0.12* 6.489 [1.811–22.232] *0.12 ≤ PSAD ≤0.18* 7.633 [2.244–25.955] 0.18 ≤ PSAD 24.602 [7.537–80.308]	–	Suspicious 2.52 [1.451–3.495] Cancer likely 9.747 [4.421–21.492]	–	–	–	–	–	
(Nam *et al.* 2006)	1.06 [1.05–1.08]	1.08 [1.07–1.08]	–	Nodule present 2.11 [1.7–2.7]	Black 1.48 [1.0–2.1] Asian 0.40 [0.3–0.6]	0.97 [0.97–0.99]	0.86 [0.7–1.0]	0.26 [0.18–0.38]	1.16 [0.8–1.6]	
(Krejcarek *et al.* 2007)	1.07 [1.02–1.13]		1.06 [1.02–1.10]	Clinical T stage 2.17 [1.21–3.92]	–	–	–	–	–	
(Thompson *et al.* 2006)	1.03 [1.01–1.06]	log(PSA) 3.64 [3.04–4.37]	PSAV[4] 0.82 [0.44–1.53]	2.72 [1.96–3.77]	Black 2.61 [1.55–4.41]	–	–	0.70 [0.49–0.99]	N.S.	no. of PSA screens

Abbreviations: HG PCa, high grade prostate cancer; PSA, prostate-specific antigen; PSAV, PSA velocity; PSAD, PSA density; DRE, digital rectal examination; N.S., not statistically significant;

Footnotes

1. Compared with white
2. Compared with normal DRE
3. At least one first or second degree relative with prostate cancer
4. PSA velocity was defined as the slope of log (PSA) obtained by linear regression using all PSA values obtained in the previous 3 years.

Variables associated with increased probability of high grade prostate cancer detection:

Risk of high grade prostate cancer on biopsy increases with:

Age

The three studies that treated age as a continuous variable (Nam *et al.* 2006; Thompson *et al.* 2006) (Krejcarek *et al.* 2007) found that odds of high grade disease increased by a factor of around 1.05 with each year in age. Garzotto et al (Garzotto *et al.* 2005), treated age as a dichotomous variable and in a group of men with PSA <10 referred for biopsy, found that those older than 70 had a greater odds of high grade disease than those younger than 70.

PSA level,

The odds of high grade cancer increased with serum PSA level. One study noted a significant relationship between PSA density and risk of high grade disease, when men were classified into one of three PSA density categories.

abnormal DRE

An abnormal DRE increased the odds of prostate cancer by a factor of between 2.1 and 3.4. One study considered cases were DRE findings meant cancer was likely, and the odds of high grade disease were increased by a factor of 9.7 in these cases.

Clinical T stage

In a series of men treated with radiotherapy for prostate cancer, retrospective analysis showed pre-diagnosis clinical T stage was significantly associated with the odds of high grade disease on biopsy. Men with clinical T3 or T4 disease had more than twice the odds of high grade disease of those with clinical T stage T1 or T2.

Variables associated with decreased probability of high grade prostate cancer detection:

Risk of high grade prostate cancer on biopsy decreased with:

previous negative biopsy

The odds of high grade cancer were decreased if a man had a prior negative biopsy.

prostate volume

Odds of high grade cancer decreased by a factor of 0.97 with each additional cubic centimetre.

Variables where the evidence was inconsistent or no significant relationship was found

black ethnicity

Black ethnicity was associated with increased odds of high grade disease in the three studies that considered it, although this increase was not statistically significant in one of these studies (Borden *et al.* 2006) and of borderline significance in another (Nam *et al.* 2006).

LUTS

One study considered LUTS (Nam *et al.* 2006) and found that the odds of high grade cancer were lower in men with LUTS, but the difference was of borderline statistical significance.

Rate of change of PSA

PSAV was not significantly associated with the odds of high grade disease in the prostate cancer prevention trial (Thompson *et al.* 2006). In a series of men with established prostate cancer (Krejcarek *et al.* 2007), however, pre-diagnostic PSAV was significantly associated with high grade disease.

family history

A family history of prostate cancer was not significantly associated with a significantly higher risk of high grade disease in the two studies that examined this variable.

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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In men presenting with bone metastases and unknown primary cancer, at what level of PSA does a biopsy become unnecessary?

Short Summary

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

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Men with positive bone scan, but histologically unconfirmed primary neoplasm	Diagnosis of prostate cancer based on PSA level (without biopsy)	Diagnosis of prostate cancer using biopsy	• Accuracy of diagnosis (compared to gold standard) • Morbidity due to biopsy • Morbidity due to misdiagnosis

Evidence Summary

There was very limited evidence about the prevalence of prostate cancer in men presenting with bone metastases and unknown primary tumour, but two case series suggest the figure is about 30% (Vandecandelaere *et al.* 2004; Katagiri *et al.* 1999).

A number of case series reported PSA concentration and bone scan results in men with untreated newly diagnosed prostate cancer (Wymenga *et al.* 2001; Gleave *et al.* 1996; O'Sullivan *et al.* 2003; Lin *et al.* 1999; Oesterling 1993). These series allow estimation of the sensitivity of PSA concentration in the diagnosis of prostate cancer in men with positive bone scans (see table below).

There was no evidence about the specificity of PSA concentration in people with bone metastases and undiagnosed primary tumour. The values for specificity in the table come from population based PSA screening studies (Hakama *et al.* 2001; Donovan *et al.* 2003; Oesterling 1993). It was only possible to estimate specificity for the >10 ng/ml PSA cut-off; the specificity for the 20 and 50 ng/ml thresholds will be greater.

Serum PSA cut-off (ng/ml)	Sensitivity for Prostate Cancer	Specificity for Prostate Cancer
>10	87% to 100%	97.5% to 99.5%
>20	78% to 86%	>97.5% to 99.5%
>50	53% to 73%	>97.5% to 99.5%

The systematic review of prostate biopsy techniques (Eichler *et al.* 2006) found a single diagnostic accuracy study (Terris 1999). This study estimated the sensitivity and specificity of sex-

tant biopsy for the diagnosis of prostate cancer (> 2cc in volume) as 83.3% and 97.3% respectively.

The 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. There was no evidence about the emotional distress of biopsy.

The search did not find evidence about the harms of misdiagnosis of metastatic prostate cancer in men presenting with bone metastases.

Evidence tables

Systematic reviews of cohort studies

Eichler, Wilby, Hempel, Myers & Kleijnen. Diagnostic value of systematic prostate biopsy methods in the investigation for prostate cancer. A systematic review. 2005.

Design: Systematic review of cohort studies (diagnosis, screening), evidence level: 2++

County: International, setting: Secondary care

Inclusion criteria Studies comparing systematic prostate biopsy methods. 87 studies met the inclusion criteria for the review.

Exclusion criteria Retrospective studies, non-comparative studies. Studies where the main topic was not biopsy method.

Population -

Interventions Systematic prostate biopsy schemes, ranging from 6 to 18 core schemes.

Outcomes Adverse effects due to prostate biopsy

Follow up The authors note that the length of follow up was often not reported or not long enough to discover delayed events.

Results 44/87 studies in the review mentioned adverse effects and 36/87 studies included data about adverse effects

Numeric results

Morbidity due to biopsy		
	Minimum (%)	Maximum (%)
Outcome: Major infection	0.0	1.8
	Minimum (%)	Maximum (%)
Outcome: Minor infection	0.0	6.9
	Minimum (%)	Maximum (%)

Outcome: Prostatitis	0.0	1.25
	Minimum (%)	Maximum (%)
Outcome: Urinary tract infection	0.0	2.5
	Minimum (%)	Maximum (%)
Outcome: Voiding difficulties	0.0	10.5
	Minimum (%)	Maximum (%)
Outcome: Major bleeding	0.0	0.6
	Minimum (%)	Maximum (%)
Outcome: Haematuria (minor)	0.8	95
	Minimum (%)	Maximum (%)
Outcome: Haematospermia (minor)	2.0	95
	Minimum (%)	Maximum (%)
Outcome: Rectal bleeding (minor)	0.7	95
	Minimum (%)	Maximum (%)
Outcome: Pain	6	64.8

General comments Emotional distress due to biopsy is not reported.

Prospective cohort studies

Donovan, Hamdy, Neal, Peters, Oliver, Brindle, Jewell, Powell, Gillatt, Dedman, Mills, Smith, Noble & Lane. Prostate Testing for Cancer and Treatment (ProtecT) feasibility study. Health Technol. Assess. 7[14]. 2003.

Design: Prospective cohort study (diagnosis, screening), evidence level: 2+

County: United Kingdom, setting: Community

Inclusion criteria Men aged 50 to 69, from 18 primary care areas, were invited to attend prostate check clinics. This led to 7383 men having a PSA test.

Exclusion criteria Men considered by their GP to be unfit for any of the potential treatments for prostate cancer.

Population number of patients = 7383.

Interventions Prostate check clinic, including PSA test

Outcomes Positive predictive value of PSA level at various thresholds

Follow up Patients with raised PSA were offered biopsy

Results The detection rate of prostate cancer was 165/7383 clinic attendees.

Numeric results

Specificity of PSA >10 ng/mL for prostate cancer
Outcome: Specificity of PSA >10 ng/ml for prostate cancer 99.5%

General comments This was a feasibility exercise for the ProtecT study of population screening for prostate cancer. Specificity at PSA thresholds greater than 10 ng/ml was not reported

Oesterling, Jacobsen, Chute, Guess, Girman, Panser & Lieber. Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. JAMA 270[7]. 1993.

Design: Prospective cohort study (diagnosis, screening), evidence level: 2+

County: United States, setting: Community

Inclusion criteria White men aged 40-79 years were randomly invited from a population based register (Olmsted County, Minnesota), 51% agreed to participate and 537 of these were chosen for detailed clinical examination.

Exclusion criteria History of prostate cancer, prostatectomy or other conditions that would interfere with voiding function.

Population number of patients = 537, age range 40 to 79 years, mean age = 56 years.

Interventions PSA test (Tandem-R PSA assay), DRE and TRUS. On the basis of these tests 52 men underwent TRUS biopsy, 5 were found to have prostate cancer and excluded from the study.

Outcomes Serum PSA concentration, prostatic volume. Both variables were summarised within decade age ranges.

Results The 97.5th percentile of the normal range of PSA ranged from 2.6 ng/ml in 40 year olds to 9.4 ng/ml in 80 year olds. Thus, the specificity of a PSA cut-off of 10 ng/ml for prostate cancer was at least 97.5% in this group.

Numeric results

Specificity of PSA >10 ng/mL for prostate cancer
Outcome: Specificity of PSA >10 ng/ml for prostate cancer >97.5%

General comments Only a subset had biopsy, possibility of undetected prostate cancer.

Retrospective cohort studies

Hakama, Stenman, Aromaa, Leinonen, Hakulinen & Knekt . Validity of the prostate specific antigen test for prostate cancer screening: followup study with a bank of 21,000 sera in Finland. J Urol. 166[6]. 2001.

Design: Retrospective cohort study (diagnosis, screening), evidence level: 2+

County: Finland, setting: Primary care

Inclusion criteria A population based sample of men >15 years were invited to enrol in the study (1966 to 1972). Serum samples, taken between 1966 and 1976, from this cohort were analysed for PSA levels. This sample was linked to the Finnish cancer registry to establish the prevalence of prostate cancer in 1993.

Exclusion criteria -

Population number of patients = 21387.

Interventions Measurement of PSA

Outcomes Sensitivity and specificity of PSA level (with thresholds at 2.5 and 4 ng/ml) for clinically detected prostate cancer.

Results The prevalence of clinically detected prostate cancer in the group was 108/21387.

Numeric results

Specificity of PSA >10 ng/mL for prostate cancer	
Outcome: Specificity of PSA >10 ng/ml for prostate cancer	98.5%

General comments Specificity of PSA thresholds at 20 or 50 ng/ml is not reported.

Serum was stored at -20C; the authors comment that part of the PSA may have been lost in these conditions. It is unclear how the 10 ng/ml threshold in frozen samples compares to fresh samples.

Prospective comparative studies

Terris. Sensitivity and specificity of sextant biopsies in the detection of prostate cancer: preliminary report. Urology 54[3]. 1999.

Design: Prospective comparative study (diagnosis, screening), evidence level: 2+

County: United States, setting: Tertiary care

Inclusion criteria Men scheduled for radical cystoprostatectomy for transitional cell carcinoma of the bladder.

Exclusion criteria Prior prostate needle biopsy, neoadjuvant radiotherapy, chemotherapy or androgen therapy

Population number of patients = 43, age range 40 to 80 years.

Interventions Sextant prostate biopsy and prostatectomy

Outcomes The concordance of histological diagnosis of prostate cancer based on biopsy and prostatectomy specimens (the sensitivity and specificity of biopsy).

Results 10/43 patients (23.3%) were found to have prostate cancer in the prostatectomy specimen. The volume of the primary tumours ranged from 0.05 to 6.5 cc (mean 2.4cc).

Numeric results

Sensitivity and specificity of prostate biopsy for prostate cancer		
	All cancers	Cancers >2cc
Outcome: Sensitivity (%)	value = 60 (total N = 43)	value = 83.3 (total N = 43)
	All cancers	Cancers >2cc
Outcome: Specificity (%)	value = 100 (total N = 43)	value = 97.3 (total N = 43)

General comments Unusual study in that all men had prostatectomy, regardless of their biopsy result. Gives the sensitivity and specificity of sextant biopsy to detect prostate cancer in men with normal DRE and bladder cancer, limited applicability to men referred for prostate biopsy. Sextant biopsy is no longer the standard; the current sensitivity of prostate biopsy is likely to be greater than in this study.

Retrospective case series

Gleave, Coupland, Drachenberg, Cohen, Kwong, Goldenberg & Sullivan. Ability of serum prostate-specific antigen levels to predict normal bone scans in patients with newly diagnosed prostate cancer. Urology 47[5]. 1996.

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

County: Canada (federal state, Commonwealth Realm), setting: Tertiary care

Inclusion criteria Patients referred for bone scans for the staging of prostate cancer at a single institution.

Exclusion criteria prior therapy or serum PSA obtained more than 3 months before the bone scan.

Population number of patients = 490, age range 39 to 100 years, mean age = 69 years, median age = 69 years.

Interventions Serum PSA concentration was determined using either IMX or Tandem-R assays.

Outcomes Bone metastases on Technetium bone scan.

Results 28 men had a positive bone scan and 462 a negative bone scan. Prevalence of bone metastases in this series was 6%.

Numeric results

Serum PSA levels in men with prostate cancer and positive bone scan	
Outcome: Proportion with serum PSA < 10 ng/mL	0/28
Outcome: Proportion with serum PSA < 20 ng/mL	4/28
Outcome: Proportion with serum PSA < 50 ng/mL	9/28
Outcome: Proportion with serum PSA > 50 ng/mL	19/28

General comments 2 physicians interpreted the bone scans, blind to the PSA test results. A third decided equivocal cases.

Katagiri, Takahashi, Inagaki, Sugiura, Ito & Iwata. Determining the site of the primary cancer in patients with skeletal metastasis of unknown origin: a retrospective study. Cancer 86[3]. 1999.

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

County: Japan, setting: Tertiary care

Inclusion criteria Patients whose first symptom of malignancy was bony metastasis.

Exclusion criteria History of malignant disease, multiple myeloma, malignant lymphoma of bone.

Population number of patients = 64, age range 21 to 88 years, mean age = 62 years.

Interventions Clinical examination, complete blood count and blood chemistry analysis, lab tests for tumour markers (in selected patients), X-ray of chest and affected bones, technetium bone scan. In some patients, there was gastroscopic, colonoscopic examination and biopsy of the skeletal lesion or other tissues.

Outcomes Location of primary tumour

Results The proportion of males and females with each tumour type was not reported so only the range of prostate cancer prevalence can be estimated.

Numeric results

Prevalence of prostate cancer in men presenting with bone metastases		
	Minimum	Maximum
Outcome: Prevalence	26%	30%

General comments In 5/64 patients the primary was still unknown after all investigations.

Lin, Szabo, Chin & Civelek. The value of a baseline bone scan in patients with newly diagnosed prostate cancer. Clin Nucl Med 24[8]. 1999.

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

County: United States, setting: Tertiary care

Inclusion criteria Men with untreated histologically confirmed prostate cancer referred for a staging bone scan at a single institution (1995 to 1997).

Population number of patients = 270.

Interventions Measurement of serum PSA level

Outcomes Presence of bone metastases on technetium-99 bone scan.

Results 24/270 scans were positive for metastatic disease (prevalence 8.8%).

Numeric results

Serum PSA levels in men with prostate cancer and positive bone scan	
Outcome: Proportion with serum PSA < 10 ng/mL	3/24
Outcome: Proportion with serum PSA < 20 ng/mL	5/24
Outcome: Proportion with serum PSA < 50 ng/mL	8/24
Outcome: Proportion with serum PSA > 50 ng/mL	16/24

General comments -

O'Sullivan, Norman, Cook, Fisher & Dearnaley. Broadening the criteria for avoiding staging bone scans in prostate cancer: a retrospective study of patients at the Royal Marsden Hospital. BJU Int 92[7]. 2003.

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

County: United Kingdom, setting: Tertiary care

Inclusion criteria Patients with untreated histologically confirmed prostate cancer, referred for a staging isotope bone scan between 1995 and 2000 at a single institution. PSA had to be measured within 30 days of the date of the scan.

Exclusion criteria Hormonal therapy, histology not reviewed at the Royal Marsden.

Population number of patients = 420, median age = 68 years.

Interventions PSA level

Outcomes Presence of bone metastases on isotope bone scan.

Results 67/420 patients had bone scans which indicated metastatic disease; prevalence of bone metastases was 16%.

Numeric results

Serum PSA levels in men with prostate cancer and positive bone scan	
Outcome: Proportion with serum PSA < 10 ng/mL	5/67
Outcome: Proportion with serum PSA < 20 ng/mL	15/67

Outcome: Proportion with serum PSA < 50 ng/mL	31/67
Outcome: Proportion with serum PSA > 50 ng/mL	36/67

General comments It was the practice of the institution perform an isotope staging scan in all patients with prostate cancer.

Oesterling, Martin, Bergstralh & Lowe . The use of prostate-specific antigen in staging patients with newly diagnosed prostate cancer.[see comment]. JAMA 269[1]. 1993.

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

County: United States, setting: Tertiary care

Inclusion criteria Men with newly diagnosed, untreated, histologically confirmed prostate cancer, with a serum PSA of less than 20 ng/ml.

Exclusion criteria Prior treatment, PSA > 20 ng/ml

Population number of patients = 852.

Interventions Serum PSA concentration was measured using the Tandem-R PSA assay. Radionuclide bone scan. Both tests were completed within 31 days of each other.

Outcomes Result of bone scan: normal, abnormal or indeterminate.

Results 10/842 patients had abnormal or indeterminate bone scan results.

Numeric results

Serum PSA levels in men with prostate cancer and positive bone scan	
Outcome: Proportion with serum PSA < 4 ng/mL	0/10
Outcome: Proportion with serum PSA < 10 ng/mL	4/10
Outcome: Proportion with serum PSA < 20 ng/mL	10/10

General comments The 20 ng/ml cut-off limits the usefulness of the results for this question. The radiologists interpreted the bone scans without knowledge of the PSA test results.

Vandecandelaere, Flipo, Cortet, Catanzariti, Duquesnoy & Delcambre . Bone metastases revealing primary tumors. Comparison of two series separated by 30 years. Joint Bone Spine 71[3]. 2004.

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

County: France, setting: Tertiary care

Inclusion criteria Patients presenting with bone metastases and unknown primary tumour to a single rheumatology department.

Exclusion criteria Patients with known primaries (this group is reported separately in the paper)

Population number of patients = 100, age range 37 to 87 years, mean age = 63 years.

Interventions The primary tumour was identified on the basis of clinical, biological and radiological findings.

Outcomes Location of primary tumour

Results The number of males and females with each type of tumour is not reported, so only the range of prevalence can be estimated. The primary tumour was still unknown after all investigations in 36/100 patients.

Numeric results

Prevalence of prostate cancer in men presenting with bone metastases		
	Minimum	Maximum
Outcome: Prevalence	19%	36%

General comments The paper cites 5 other French case series with estimates of prevalence of prostate cancer in patients presenting with bone metastases ranging from 20% to 28%.

Histological confirmation of the diagnosis is not reported, it is likely that the diagnosis of prostate cancer was based on clinical examination and PSA test.

Wymenga, Boomsma, Groenier, Piers & Mensink . Routine bone scans in patients with prostate cancer related to serum prostate-specific antigen and alkaline phosphatase. BJU Int 88[3]. 2001.

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

County: Netherlands, the, setting: Tertiary care

Inclusion criteria Men with newly diagnosed prostate cancer referred for a bone scan at a single institution (1989-1997).

Exclusion criteria Previous therapy for prostatic disease; abnormal liver disease

Population number of patients = 363, age range 48 to 97 years, median age = 72 years.

Interventions Serum PSA concentration, measured using equimolar immunoassay (IMx PSA kit, 1989 to 1995; Immulite PSA kit, 1995 to 1997).

Outcomes Presence of bone metastases on technetium bone scintigraphy

Results Bone scan was positive in 111/363, giving a prevalence of bone metastases of 30.6% in men referred for bone scans.

Numeric results

Serum PSA levels in men with prostate cancer and positive bone scan	
Outcome: Proportion with serum PSA < 10 ng/mL	14/111
Outcome: Proportion with serum PSA < 20 ng/mL	19/111
Outcome: Proportion with serum PSA < 50 ng/mL	30/111
Outcome: Proportion with serum PSA > 50 ng/mL	81/111

General comments -

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.

Reference List

Donovan, J., Hamdy, F., Neal, D., Peters, T., Oliver, S., Brindle, L., Jewell, D., Powell, P., Gillatt, D., Dedman, D., Mills, N., Smith, M., Noble, S. & Lane, A. (2003) Prostate Testing for Cancer and Treatment (ProtecT) feasibility study. *Health Technol. Assess.,* 7: 1-88.

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

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

Hakama, M., Stenman, U. H., Aromaa, A., Leinonen, J., Hakulinen, T. & Knekt, P. (2001) Validity of the prostate specific antigen test for prostate cancer screening: followup study with a bank of 21,000 sera in Finland. *J Urol,* 166: 2189-2191.

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

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

O'Sullivan, J. M., Norman, A. R., Cook, G. J., Fisher, C. & Dearnaley, D. P. (2003) Broadening the criteria for avoiding staging bone scans in prostate cancer: a retrospective study of patients at the Royal Marsden Hospital. *BJU Int,* 92: 685-689.

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

Terris, M. K. (1999) Sensitivity and specificity of sextant biopsies in the detection of prostate cancer: preliminary report. *Urology,* 54: 486-489.

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

Wymenga, L. F., Boomsma, J. H., Groenier, K., Piers, D. A. & Mensink, H. J. (2001) Routine bone scans in patients with prostate cancer related to serum prostate-specific antigen and alkaline phosphatase. *BJU Int,* 88: 226-230.

2.2 Histological diagnosis

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

Rationale

TRUS is excellent at showing the prostate and its zonal anatomy but cannot highlight small foci of tumour. Most cancers (>50%) are invisible, and TRUS is particularly poor for anterior, apical and central lesions. TRUS guided biopsies are therefore limited: the biopsies are guided to zones within the gland, but generally not to a suspicious lesion. The false negative rate is 30-40% in patients with a PSA <10, with detection rates 29% (first biopsy), 19% (2nd biopsy) and 19% (3rd biopsy). Therefore, when biopsy is negative, and an interval rise in PSA justifies further investigation, MRI should be used before further TRUS guided biopsy undertaken in an effort to detect prostate cancer suspected but not detected by TRUS.

Presumed evidence

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

Expected recommendation

The combination of T2WI, DCE and DWI seems currently to be the most accurate and applicable technique for tumour detection and eventually assessment of tumour aggressiveness (Gleason grade). Lesion aggressiveness in terms of predicting underlying Gleason score is better assessed by DWI and ^{1}H-MRSI compared to T2W-MRI and DCE-MRI

MRI derived parameters may have a prognostic role with regard to potential metastatic activity and tumour aggressiveness (correlation with Gleason score).

PICO question

Population	Target condition	Diagnostic test	Outcomes
Men referred for initial investigation of possible new prostate cancer, in line with 'Referral guidelines for suspected cancer'	Prostate cancer	• TRUS biopsy alone • Multiparametric MRI + TRUS biopsy	• Diagnostic yield • Diagnosis-related morbidity • Diagnosis-related mortality • Health-related quality of life

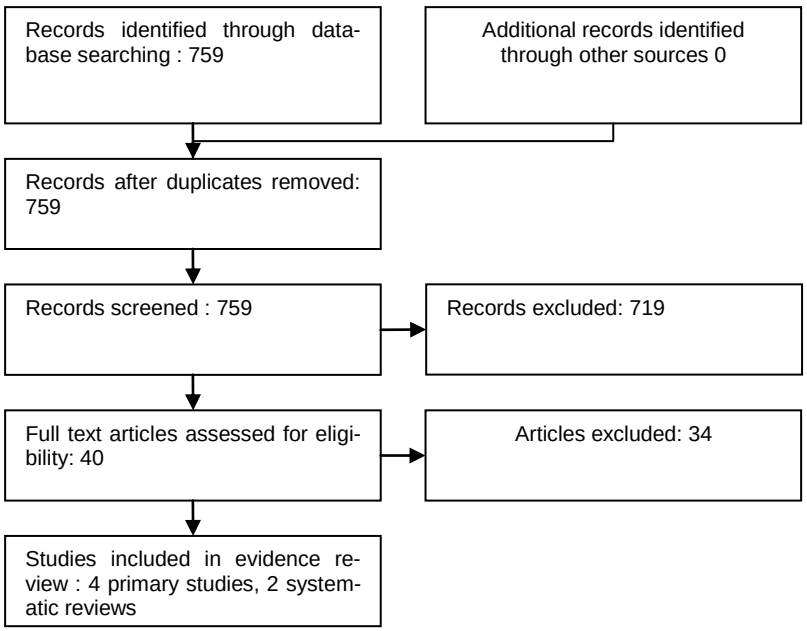
How the information will be searched

Sources to be searched	
Can we apply date limits to the search	This topic is not in the 2008 guideline. Can we specify the date when multiparametric / functional MRI was introduced?
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	We will not use study design filters as evidence will come from case series or cohort studies.
List useful search terms.	

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results?	We will use the evidence table for diagnostic studies (NICE guidelines manual appendix J). Diagnostic yield will be defined as the proportion of positive initial prostate biopsies. We will use the studies' definitions of diagnosis-related morbidity, diagnosis-related mortality.
Which quality checklist will we use for appraisal?	The QUADAS-2 quality checklist will be used (NICE guidelines manual appendix F).
List subgroups here and planned statistical analyses	Subgroup analysis could compare the component techniques of functional MRI.

Results of the search



Evidence Summary

Study quality

Low quality evidence about diagnostic yield came from four studies (Haffner et al 2011, Park et al 2011, Belas et al 2012 and Delongchamps et al 2013). The men in these studies all received both anatomic and functional magnetic resonance imaging (MRI) before their initial trans-rectal ultra sound (TRUS) guided biopsy for suspected prostate cancer.

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

The studies were not typical diagnostic accuracy studies: because there was no reference standard test it was only possible to compare the prostate cancer detection rates of the various

strategies. Men without lesions on MRI received fewer biopsy cores than those with lesions seen on MRI – which could confound estimates of the effectiveness of MRI targeted plus systematic biopsy. Systematic biopsies were not done blind to the results of the MRI and this could increase the detection rate of systematic biopsy. The delay between the pre-biopsy MRI and the prostate biopsy was not reported in the included studies.

Evidence about harms associated with TRUS biopsy came from a systemic review by Eichler et al (2006; see Table 7).

Evidence Statements

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

Evidence from observational studies indicates that cognitively targeting TRUS biopsies using pre-biopsy multi parametric MR (mp-MRI) increase the prostate cancer detection rate by around 2% (see Table 5). This suggests that for every 100 men using a mp-MRI targeted biopsy in addition to systematic TRUS biopsy instead of systematic TRUS biopsy alone we could expect to detect an additional two cases of prostate cancer. These studies suggest that the extra cases identified by mp-MRI targeted biopsies are not micro focal prostate cancers (see Table 6).

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

Morbidity due to biopsy

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

Harms due diagnosis of clinically insignificant disease or MRI procedure

Harms could be associated with under or over-diagnosis of clinically insignificant disease and with the MRI procedure itself, but there was no evidence on these outcomes in the included studies.

Table 5. Prostate cancer detection rate (diagnostic yield)

				Prostate cancer detection rate (diagnostic yield) per patient			
Study	**MRI sequence**	**Navigational system for biopsy**	**Proportion with lesions on MRI**	**MRI targeted cores**	**Standard systematic cores**	**Combined MRI targeted plus systematic cores**	**Absolute difference (combined – standard)**
Haffner 2011	T2/DCE	US (cognitive)	351/555 (63.2%)	236/555 (42.5%)	290/555 (52.3%)	302/255 (54.4%)	2.1%
Park 2011	T2/DCE/DWI	US (cognitive)	23/44 (52.3%)	9/44 (20.5%)	12/44 (27.3%)	13/44 (29.5%)	2.2%
Belas 2012	T2/DCE/DWI	US (cognitive)	37/71 (52.1%)	24/71 (33.8%)	35/71 (49.3%)	38/71 (53.5%)	4.2%
Delongchamps 2012	T2/DCE/DWI	US (cognitive)	54/127 (42.5%)	40/127 (31.5%)	55/127 (43.3%)	58/127 (45.7%)	2.4%
Delongchamps 2012	T2/DCE/DWI	Rigid MRI-TRUS image registration	78/131 (59.5%)	64/131 (48.9%)	60/131 (45.8%)	78/131 (59.5%)	13.7%
Delongchamps 2012	T2/DCE/DWI	Elastic MRI-TRUS image registration	82/133 (61.6%)	62/133 (46.7%)	44/133 (33%)	71/133 (53.4%)	20.4%

Table 6. Clinically significant prostate cancer detection rate (diagnostic yield)

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

2012		TRUS image registration	(single core, < 5mm Gleason 3+3)	(59.5%)	(44.3%)	(34.4%)	(45.8%)	
Delongchamps 2012	T2/DCE/DWI	Elastic MRI-TRUS image registration	NOT micro focal cancer (single core, < 5mm Gleason 3+3)	82/133 (61.6%)	58/133 (43.4%)	35/133 (26.3%)	60/133 (45.1%)	18.8%

Table 7. Adverse events according to number of cores in TRUS biopsy, from Eichler et al (2006)

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

Abbreviations: NR, not reported.

Table 8. Study characteristics of MRI targeted biopsy in biopsy naive men

		MRI				Biopsy				
Reference, country	**N**	**Machine**	**Mean no. lesions (range)**	**Sequence used**	**Endorectal coil?**	**Navigational system for biopsy**	**Analgesia**	**Standard cores taken blind to location of lesions?**	**Targeted cores per lesion (mean per patient)**	**Total cores taken**
Haffner et al (2010) France	555	1.5T Philips Gyroscan Intera	1.9 (NR)	T2/ DCE	Pelvic coils	US (cognitive)	Local anaesthetic	No	2 (3.8)	10 systematic cores + average of 4 targeted cores in patients with lesions on MRI
Park et al (2011) Korea	85 (44 had MRI)	3.0T Philips Achieva	NR (NR)	T2/ DCE/ DWI	No	US (cognitive)	NR	No	0-3 per patient	10-12 systematic cores + up to 3 targeted
Delongchamps et al (2012)	391	1.5T	214 lesions in 391 patients	T2/ DCE/ DWI	Pelvic coils	US (cognitive): N=127 Rigid MRI-TRUS registration: N=131 Elastic MRI-TRUS registration: N=133	NR	No	Median 3-4 per patient depending on navigational system used.	10-12 systematic cores + a median of 3-4 targeted cores in patients with lesions on MRI
Belas et al (2012)	71	1.5T Siemens Avanto	44 lesions in 37 patients	T2/ DCE/ DWI	Pelvic coils	US (cognitive)	Local anaesthetic	No	3 to 5 per patient	12 systematic cores plus up to 5 targeted

Abbreviations: DCE, dynamic contrast enhancement; DWI, diffusion weighted imaging; NR, not reported; MRI, magnetic resonance imaging; US, ultrasound.

References

Included studies

Systematic reviews

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

Primary studies

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N. B. Delongchamps, M. Peyromaure, A. Schull, F. Beuvon, N. Bouazza, T. Flam, M. Zerbib, N. Muradyan, P. Legman, and F. Cornud. Prebiopsy Magnetic Resonance Imaging and Prostate Cancer Detection: Comparison of Random and Targeted Biopsies. *J.Urol.* 189 (2):493-499, 2013.

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Park, B. K., Park, J. W., Park, S. Y., Kim, C. K., Lee, H. M., Jeon, S. S. et al. (2011). Prospective evaluation of 3-T MRI performed before initial transrectal ultrasound-guided prostate biopsy in patients with high prostate-specific antigen and no previous biopsy. AJR.American Journal of Roentgenology, 197, W876-W881

Excluded studies

Reason: MRI not done before the initial biopsy

H. A. Vargas, O. Akin, A. Shukla-Dave, J. B. Zhang, K. L. Zakian, J. T. Zheng, K. Kanao, D. A. Goldman, C. S. Moskowitz, V. E. Reuter, J. A. Eastham, P. T. Scardino, and H. Hricak. Performance Characteristics of MR Imaging in the Evaluation of Clinically Low-Risk Prostate Cancer: A Prospective Study. *Radiology* 265 (2):478-487, 2012.0

Arsov, C., Blondin, D., Rabenalt, R., Antoch, G., Albers, P., & Quentin, M. (2012). [Standardised scoring of a multi-parametric 3-T MRI for a targeted MRI-guided prostate biopsy]. [German]. Urologe (Ausg.A), 51, 848-856.

E. Rud, E. Baco, and H. B. Eggesbo. MRI and ultrasound-guided prostate biopsy using soft image fusion. *Anticancer Res.* 32 (8):3383-3389, 2012.

Pepe, P et al. Prostate cancer detection at repeat biopsy: can pelvic phased-array multiparametric MRI replace saturation biopsy? *Anticancer Research* 2013; 33(3): 1195-1199.

Reason: Transperineal biopsy

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Reason: MRI targeted cores were not reported

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In men who have been referred with suspected prostate cancer, what are the prognostic factors that determine the need for further investigation following a prior negative biopsy(s)?

Rationale:

One negative prostate biopsy does not give any guarantee that there is not a focus of cancer hiding in the gland which has not been picked up on biopsy. The pathologist can only comment on the tissue sent. This presents a dilemma with regard to further investigation of men who have had only one negative biopsy yet still have a suspicion of prostate cancer based on a raised PSA and/or abnormal DRE.

There are multiple variables that have been proposed to inform the debate, yet practice continues to differ throughout the country. Variables include examples such as an association between PSA doubling time (PSAdt), PSA density, and high-grade pin, with high-grade pin also considered as independent factor.

If a low risk group could be identified, this could be used to inform guidance on what to do with this group of patients.

PICO question

Population	Prognostic factors	Outcomes
Men whose initial biopsy proved negative for prostate cancer	• PSA velocity • PSA level • PSA density • Free-to-total PSA • Clinical stage • Family history • Ethnicity • Pathological features on biopsy (ASAP, PIN) • Biomarkers • Age	Diagnostic accuracy

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science and Biomed Central. Consideration will be given to subject-specific databases and used as appropriate.
Can we apply date limits to the search	Should we only consider studies using modern era biopsy techniques?
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	We will not use study design filters as evidence will come from case series or cohort studies.
List useful search terms.	

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? List subgroups here and planned statistical analyses	We will use the evidence table for diagnostic studies –this is not really a prognostic question (NICE guidelines manual appendix J). Diagnostic yield will be defined as the proportion of positive initial prostate biopsies. The QUADAS-2 quality checklist will be used (NICE guidelines manual appendix F).

Note any changes to the protocol (with dates) or other considerations below

1/1/2013 - Date limit of 2000 onwards will be used for the search, and only studies which used an initial biopsy of at least ten cores will be included. Papers published before 2005 are unlikely to include a ten core or greater initial biopsy – for this reason papers published before 2005 which do not mention in the abstract or title the number of cores in the initial biopsy will not be ordered.

Methods

Search strategy

The full strategy will be available in the full guideline. Only studies which used an initial 10-core biopsy were of interest. Therefore the search was restricted to studies published since 2000. The results of the topic 2 search were also screened for any relevant papers.

Selection of studies

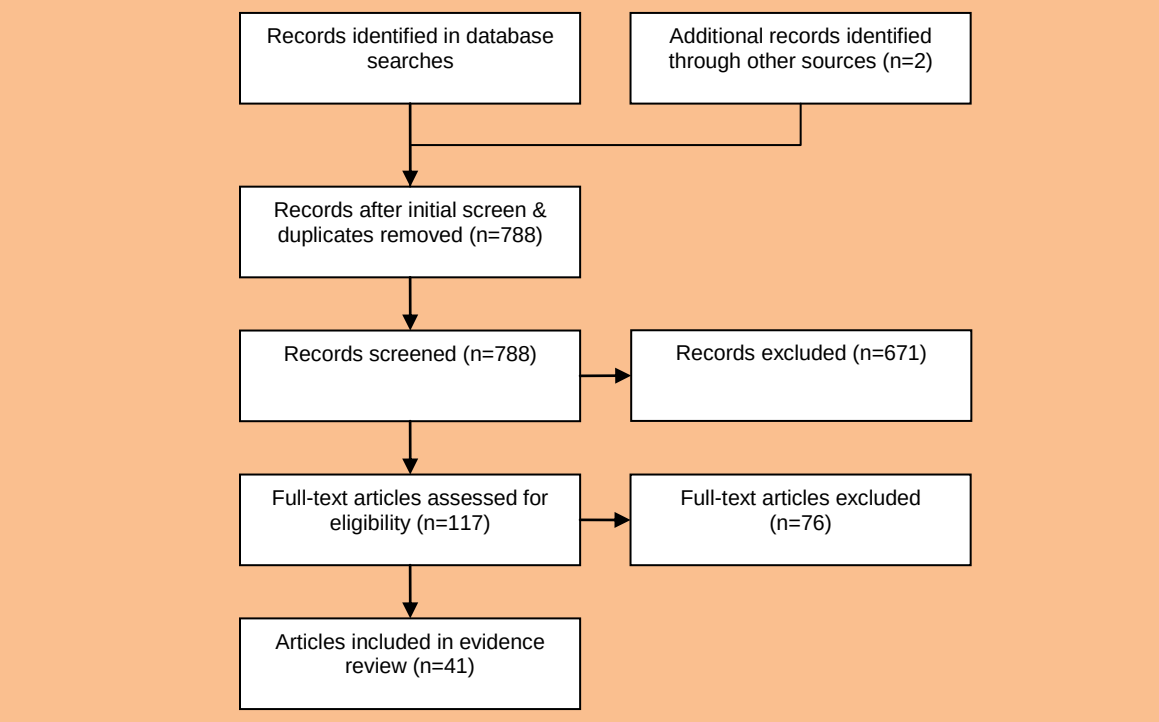
The information specialist undertook the first screen of the literature search results. One reviewer then selected potentially eligible studies by comparing their title and abstract to the inclusion criteria in the PICO question. Studies published prior to 2005 which did not specify the number of cores used in the initial biopsy to be 10 or more in the title or abstract were excluded. A second reviewer checked the included studies. The full articles were then obtained and studies were checked against the inclusion criteria.

Analysis

Odds ratios, confidence intervals and p-values were extracted and reported for univariate and multivariate models assessing a prognostic factor of interest. Where available, variables included in the multivariate models were recorded. Diagnostic accuracy outcomes which were extracted and reported included sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. Where the number of patients with and without malignancy at rebiopsy was available for those with and/or without the prognostic factor, the diagnostic accuracy outcomes were calculated (if not already available). Quality appraisal was conducted using relevant questions from both the QUADAS tool for diagnostic studies and the NICE checklist for prognostic studies.

Results

Results of the literature searches



The literature searches identified 788 potentially relevant articles of which 117 were ordered in full text. Forty-one publications referring to 38 studies were included.

Evidence Summary

Quality appraisal

The quality of studies was appraised using appropriate questions selected from both the QUADAS tool for studies on diagnostic test accuracy and the NICE methodology checklist for prognostic studies.

The quality of six studies (16%) was marked down due to differences between the study population and patients who would be likely to be tested in practice. Five studies (13%) were also marked down for not providing a clear description of their inclusion criteria. One study (3%) was marked down for limitations in the ability of the re-biopsy to identify a malignancy due to the collection of only 2-6 cores per patient.

Only ten (26%) of the studies reported the mean or median duration between biopsies; five of these were marked down for a period of greater than 1 year, during which new malignancies may have developed. Twenty-five (66%) of the studies were marked down due to the influence of the prognostic factor on whether they underwent re-biopsy, potentially introducing bias. Six (16%) of the remaining studies did not report the indications for re-biopsy.

Twelve studies (32%) were marked down for failure to include any important potential confounders in their statistical model, such as age, free-to-total PSA, or prostate volume. Twenty-six studies (68%) were marked down for lack of clarity in three or more areas where bias could potentially be introduced, such as whether the re-biopsy results were interpreted without prior knowledge of the prognostic factors or whether uninterpretable or indeterminate results were reported.

Evidence statements

Age

Twenty-three studies of very low quality assessed age as a (continuous) predictive factor for prostate cancer at re-biopsy (see Table 9). Six (33%) of 18 studies found age to be a significant predictor in a univariate model, two of which reported an odds ratio ranging from 1.04 to 1.08. Three (21%) of 14 studies found age to be a significant predictor in a multivariate model once other potentially confounding variables had been taken into account, the odds ratios ranged from 1.01 to 1.09. Studies varied over which variables had been taken into account in the model. Of the three studies reporting age to be a significant predictor, all accounted for the confounding effects of PSA level at initial biopsy, two for prostate volume, and one for DRE findings, free-to-total PSA (ftPSA), number of prior biopsies, and prostate weight.

Two low quality studies treated age as a categorical variable; Singh et al. (2004) found those aged > 64 and > 69 years to be significantly more likely to have prostate cancer at re-biopsy in univariate and multivariate models respectively (OR 3.24). While Campos-Fernandez (2009) found no significant difference between those aged ≤ 60 and > 60 years in univariate or multivariate models.

PSA level at first biopsy

Twenty-three studies of very low quality assessed PSA level at initial biopsy as a (continuous) predictive factor for prostate cancer at re-biopsy. Six (33%) of 18 studies found PSA level to be a significant predictor in a univariate model, where reported (two studies) the odds ratio ranged from 1.01 to 1.04. Three (21%) of 14 multivariate models found PSA level to be a significant predictor once other confounding variables had been taken into account, where reported (three studies) the odds ratio ranged from 1.02 to 1.04. Studies again varied over which variables had been taken into account in the model. Of the three studies reporting PSA level to be a significant predictor, two reported taking account of between six and 12 different potentially confounding variables.

Two low quality studies treated PSA level as a categorical variable; Bollito et al. (2012) found those with PSA 4-10 ng/ml compared to PSA < 4 ng/ml were not significantly more likely to have prostate cancer at re-biopsy in univariate or multivariate models. Those with PSA > 10 ng/ml were significantly more likely in a multivariate model when using a PCA3 cut-off of 39 but not of 50 (also taking into account ftPSA). While Campos-Fernandez (2009) found that PSA > 4 ng/ml was a significant predictor in a univariate model but PSA > 10 ng/ml was not a predictor in either univariate or multivariate models.

Six very low quality studies reported diagnostic accuracy for various PSA level cut-off points. Both sensitivity and specificity were not consistent for similar PSA levels between studies and showed no clear trend with increasing cut-off level (see Table 10). The plotted ROC curve demonstrates the low overall diagnostic accuracy of PSA level, being close to the line that would be expected by chance (see Figure 1).

Free-to-total PSA at first biopsy

Sixteen studies of low quality assessed the free-to-total PSA (ftPSA) ratio at initial biopsy as a (continuous) predictive factor for prostate cancer at re-biopsy. Seven (50%) of 14 studies found PSA level to be a significant predictor in a univariate model, where reported (three studies) the odds ratio ranged from 0.91 to 0.97. Four (44%) of nine multivariate models found ftPSA to be a significant predictor once other confounding variables had been taken into account, where reported (three studies) the odds ratio ranged from 0.87 to 1.40. Studies again varied over which variables had been taken into account in the model. The four studies reporting ftPSA to be a significant predictor took into account between six and nine different potentially confounding variables.

Three low quality studies treated ftPSA at initial biopsy as a categorical variable; Ploussard et al. (2010) found there to be a significant difference in risk of prostate cancer at re-biopsy between those with a ftPSA > 2.0 and those with a ftPSA ≤ 1.0, but not with those with a ftPSA 1.0-2.0. In a multivariate model ftPSA ≤ 0.1 was not a significant predictor. Bollito et al. (2012) found a ftPSA > 0.2 to be significantly more likely to result in malignancy at re-biopsy than ftPSA < 0.1 in a univariate model but not once PSA and PCA3 were taken into account in a multivariate model. While Campos-Fernandez et al. (2009) found a ftPSA > 0.15 to be a significant predictor in a univariate model but not in a multivariate model.

Five very low quality studies reported diagnostic accuracy for various ftPSA cut-off points. Both sensitivity and specificity were not consistent for similar PSA levels between studies and showed no clear trend with increasing cut-off level. The plotted ROC curve demonstrates the low overall diagnostic accuracy of ftPSA being close to the line that would be expected by chance (see Figure 1).

PSA density at first biopsy

Eight studies of low quality assessed PSA density (PSAd) at initial biopsy as a (continuous) predictive factor for prostate cancer at re-biopsy. Five (71%) of seven studies found PSAd to be a significant predictor in a univariate model, though none reported an OR. Three (75%) of four multivariate models found PSAd to be a significant predictor once other confounding variables had been taken into account, where reported (three studies) the odds ratio ranged from 1.01 to 24.7. Studies again varied over which variables had been taken into account in the model but included between four and ten different potentially confounding variables.

Two studies treated PSAd as a categorical variable; both Campos-Fernandez et al. (2009) and Wu et al. (2012) provided low quality evidence that those with PSAd > 0.15 ng/ml/ml were significantly more likely to have prostate cancer at re-biopsy in a multivariate models (OR 2.3 in both studies).

PSA velocity at first biopsy

Eight studies of very low quality assessed PSA velocity (PSAv) at initial biopsy as a (continuous) predictive factor for prostate cancer at re-biopsy. Four (50%) of eight studies found PSAv to be a significant predictor in a univariate model. All three (100%) of the multivariate models found PSAv to be a significant predictor once other confounding variables had been taken into account, where reported (two studies) the OR ranged from 1.34 to 1.58. Studies again varied over which variables had been taken into account in the model but included between six and eight different potentially confounding variables.

Three low quality studies treated PSA velocity at initial biopsy as a categorical variable; both Campos-Fernandez et al. (2009) and Naya et al. (2004) did not find a PSAv ≥ 0.75 ng/ml/year to be a significant predictor in either univariate or multivariate models. Singh et al. (2004) did not find a PSAv > 0.93 ngml/year to be a significant predictor in a univariate model.

Four very low quality studies reported diagnostic accuracy for various PSAv cut-off points. Neither sensitivity nor specificity showed a clear trend with increasing cut-off level. The plotted ROC curve demonstrates the low overall diagnostic accuracy of PSAv, being close to the line that would be expected by chance (see Figure 1).

Abnormal DRE at first biopsy

Seventeen studies of very low quality assessed an abnormal DRE finding at initial biopsy as a predictive factor for prostate cancer at re-biopsy. Four (33%) of 12 studies found abnormal DRE to be a significant predictor in a univariate model, where reported (three studies) the OR ranged from 2.65 to 2.80. Five (38%) of 13 multivariate models found abnormal DRE to be a significant

predictor once other confounding variables had been taken into account, where reported (three studies) the OR ranged from 2.63 to 4.61. Studies again varied over which variables had been taken into account in the model. Of the six studies reporting abnormal DRE to be a significant predictor, five reported including between four and six different potentially confounding variables.

Eight very low quality studies reported diagnostic accuracy for abnormal DRE at initial biopsy. The plotted ROC curve demonstrates the low overall diagnostic accuracy of DRE, with most studies reporting low sensitivity but high specificity (see Figure 2).

Pathological features at first biopsy

PIN and HGPIN

Two studies of very low quality assessed the presence of prostatic intraepithelial neoplasia (PIN) at initial biopsy as a predictive factor for prostate cancer at re-biopsy, one (50%) of which found it to be a significant predictor.

Ten studies of very low quality assessed the presence of high grade prostatic intraepithelial neoplasia (HGPIN) at initial biopsy as a predictive factor for prostate cancer at re-biopsy. Two (23%) of seven studies found HGPIN to be a significant predictor in a univariate model, where reported (one study) the OR was 5.07. Four (50%) of eight multivariate models found HGPIN to be a significant predictor once other confounding variables had been taken into account, where reported (two studies) the OR ranged from 1.38 to 3.2. Studies again varied over which variables had been taken into account in the model but included between four and 12 different potentially confounding variables.

Five very low quality studies reported diagnostic accuracy for the presence of HGPIN at initial biopsy. The plotted ROC curve demonstrates the low overall diagnostic accuracy of HGPIN, being close to the line that would be expected by chance (see Figure 2).

ASAP and AGSC

Six studies of very low quality assessed the presence of atypical small acinar proliferation (ASAP) at initial biopsy as a predictive factor for prostate cancer at re-biopsy. Two (50%) of four studies found ASAP to be a significant predictor in a univariate model, with the OR ranging between 2.79 and 3.12. All four (100%) of the multivariate models found ASAP to be a significant predictor once other confounding variables had been taken into account, with the OR ranging between 2.97 and 3.65. Studies again varied over which variables had been taken into account in the model but included between four and 12 different potentially confounding variables.

Two low quality studies reported diagnostic accuracy for the presence of ASAP at initial biopsy, both suggesting low sensitivity but high specificity (see Figure 2).

One very low quality study assessed the presence of atypical glands suspicious for carcinoma (AGSC) at initial biopsy and found it to be a predictive factor of prostate cancer at re-biopsy in both a univariate and two multivariate models, with an OR of 20.71 reported by one model, taking account of seven different potential confounders.

PCA3 score at first biopsy

Four studies of very low quality assessed the biomarker PCA3 as a predictive factor for prostate cancer at re-biopsy. All of three studies (100%) found PCA3 to be a significant predictor in a univariate model and the only multivariate model found PCA3 to be a significant predictor when taking into account five potentially confounding variables, with an OR of 1.02.

Three low quality studies treated PCA3 score at initial biopsy as a categorical variable; all three found a significant difference in malignancy rates at re-biopsy in univariate models for various cut-off levels, ranging from 15 to 70. Two of the studies also assessed PCA3 score in multivari-

ate models and found it to remain significant once 2-6 other variables had been taken into account, for cut-off scores of 30, 39 and 50.

Twelve very low quality studies reported diagnostic accuracy for various PCA3 score cut-off points. Both sensitivity and specificity were not consistent for similar PSA levels between studies and showed no clear trend with increasing cut-off level (see Table 10). The plotted ROC curve demonstrates the low overall diagnostic accuracy of PCA3 score, being close to the line that would be expected by chance (see Figure 3). Two studies reported diagnostic accuracy of PCA3 cut-off for three subgroups with different ftPSA or PSA levels; these also demonstrated low diagnostic accuracy.

Family history of prostate cancer

Two very low quality studies assessed family history of prostate cancer as a predictive factor for prostate cancer at re-biopsy. Both (100%) found family history to be a significant predictor in multivariate models including more than five potential confounders, with one reporting an OR of 3.1.

Ethnicity

One very low quality study assessed ethnicity as a predictive factor for prostate cancer at re-biopsy. Lee et al. (2011) found no significant difference between those of Caucasian ethnic origin and those not in a multivariate model including nine potential confounders.

Clinical stage at diagnosis

One moderate quality study assessed clinical stage as a predictive factor for prostate cancer at re-biopsy. Campos-Fernandez et al. (2009) found no significant difference between those with T1 and those with T2 in either a univariate or a multivariate model.

Table 9. Results of uni- and multi-variate models from studies comparing prognostic factors and re-biopsy detection rates

Abbreviations: AGSC = atypical glands suspicious for carcinoma; ASAP = atypical small acinar proliferation; Bx = biopsy; cPSA = complexed PSA; DRE = digital rectal examination; ftPSA = free-to-total PSA; HGPIN = high grade prostatic intraepithelial neoplasia; NPV = negative predictive value; NS = not significant; PPV = positive predictive value; PSAd = PSA density; PSAv = PSA velocity

Prognostic factor	Study	Univariate analyses			Multivariate analyses			Variables include in multivariate model									
		OR	95% CI	p-value	OR	95% CI	p-value	Age	PSA	PSA	PSAd	PSAv	HG-PIN	ASAP	DRE	Volume	Other
Age (continuous)	Naya 2004	-	-	0.06		-	NS	✓	✓	✓	✓	✓	✓		✓		cPSA; no. cores HGPIN+; AGSC
	Mian 2002[1]	-	-	-		(0.94 – 1.12)	0.60	✓	✓	✓			✓		✓	✓	TRUS; AGSC
	San Francisco 2003	-	-	0.15		-	-	-	-	-	-	-	-	-	-	-	-
	Merrimen 2010	-	-	-		-	0.54	✓	✓	-	-	-	-	-	-	-	Pathologist
	Merrimen 2009[2]	-	-	-		-	**0.05**	✓	✓	-	-	-	-	-	-	-	Sampling extent; pathologist
	Xu 2011	-	-	0.57		-	-	-	-	-	-	-	-	-	-	-	-
	Singh 2004	-	-	**0.01**		-	-	-	-	-	-	-	-	-	-	-	-
	Shimbo 2009	-	-	**0.02**		-	-	-	-	-	-	-	-	-	-	-	-
	Scattoni 2011	1.04	(1.00 – 1.07)	**0.05**	-	-	-	-	-	-	-	-	-	-	-	-	-
	Rochester 2009	-	-	0.41	-	-	NS	✓	✓	✓		✓			✓	✓	
	Moussa 2010	-	-	-	-	-	0.27	✓	✓			✓	✓	✓	✓	✓	No. –ive cores; BMI; family history; months since prior Bx; months since initial Bx
	Mabjeesh 2012	-	-	**0.005**	1.08	(0.97 – 1.20)	0.16	✓	✓			✓			✓	✓	Free PSA; histology; no. prior Bx
	Lee 2011	-	-	-	1.1	(0.9 – 1.3)	NS	✓	✓	✓			✓	✓	✓		Ethnicity; family history; > 20 cores;
	Lazzeri 2012	-	-	0.55	1.01	(0.97 – 1.06)	0.52	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Kim 2012	-	-	**0.01**		-	-	-	-	-	-	-	-	-	-	-	-
	Engehausen 2012	-	-	0.69		-	-	-	-	-	-	-	-	-	-	-	-
	Chun 2007	1.01	-	0.50		-	**0.01**	✓	✓	✓					✓	✓	NR; no. prior Bx
	Campos-Fernandez 2009	-	-	0.15		-	-	-	-	-	-	-	-	-	-	-	-
	Benecchi 2008	-	-	-	-	-	NS	✓	✓	✓	✓	✓	✓		✓		
	Auprich 2011	-	-	0.38	-	-	-	-	-	-	-	-	-	-	-		-

Prognostic factor	Study	Univariate analyses			Multivariate analyses			Variables include in multivariate model									
		OR	95% CI	p-value	OR	95% CI	p-value	Age	PSA	PSA	PSAd	PSAv	HG-PIN	ASAP	DRE	Volume	Other
	Abdollah 2011	1.01	(0.97 – 1.05)	0.7	1.02	(0.98 – 1.07)	0.3	✓	✓				✓	✓	✓	✓	No. prior Bx
	Kravchick 2009	-	-	-	1.01	-	0.21	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Eskicorapci 2007	-	-	0.21	-	-	-	-	-	-	-	-	-	-	-	-	-
	Bollito 2012	1.47	(0.98 – 2.21)	0.06	-	-	-	-	-	-	-	-	-	-	-	-	-
	Bhojani 2013	1.08	-	**<0.001**	1.09	-	**<0.001**	✓	✓	-	-	-	-	-	-	✓	Weight of prostate
> 60 vs ≤ 60	Campos-Fernandez 2009	-	-	0.655	-	-	0.844	-	-	-	-	-	-	-	-	-	-
≤ 62 vs > 62	Singh 2004	3.24	(1.14 – 9.22)	**0.02**		-	-	-	-	-	-	-	-	-	-	-	-
PSA level at first biopsy																	
PSA level	Naya 2004	-	-	0.28		-	NS	✓	✓	✓	✓	✓	✓		✓		cPSA; no. cores HGPIN+; AGSC
	Mian 2002[1]	-	-	-		(0.94 – 1.15)	0.49	✓	✓	✓			✓		✓	✓	TRUS; AGSC
	San Francisco 2003	-	-	0.44		-	-	-	-	-	-	-	-	-	-	-	-
	Xu 2011	-	-	**0.02**		(1.00 – 1.04)	**0.04**		✓	✓	✓				✓	✓	Volume-to-Bx ratio
	Wu 2012	-	-	-	0.93	(0.86 – 1.01)	NS		✓		✓				✓		TRUS; PCA3
	Singh 2004	-	-	0.15		-	-	-	-	-	-	-	-	-	-	-	-
	Shimbo 2009	-	-	0.72		-	-	-	-	-	-	-	-	-	-	-	-
	Scattoni 2011	1.02	(0.99 – 1.05)	0.2	-	-	-	-	-	-	-	-	-	-	-	-	-
	Rochester 2009	-	-	0.74	-	-	NS	✓	✓	✓		✓			✓	✓	
	Ploussard 2010	-	-	-	-	-	0.26		✓	✓					✓	✓	PCA3; no. prior Bx
	Moussa 2010	-	-	-	-	-	**0.003**	✓	✓			✓	✓	✓	✓	✓	No. –ive cores; BMI; family history; months since prior Bx; months since initial Bx
	Mabjeesh 2012	-	-	0.06	0.96	(0.89 – 1.03)	0.25	✓	✓			✓			✓	✓	Free PSA; histology; no. prior Bx
	Lee 2011	-	-	-	1.0	(1.0 – 1.1)	NS	✓	✓	✓			✓	✓	✓		Ethnicity; family history; > 20 cores;
	Lazzeri 2012	-	-	0.66	1.02	(0.88 – 1.18)	0.81		✓	✓	✓				✓	✓	Free PSA

Prognostic factor	Study	Univariate analyses			Multivariate analyses			Variables include in multivariate model									
		OR	95% CI	p-value	OR	95% CI	p-value	Age	PSA	PSA	PSAd	PSAv	HG-PIN	ASAP	DRE	Volume	Other
	Kim 2012	-	-	0.71		-	-	-	-	-	-	-	-	-	-	-	-
	Grepl 2009	-	-	**0.002**		-	-	-	-	-	-	-	-	-	-	-	-
	Engehausen 2012	-	-	**0.004**		-	-	-	-	-	-	-	-	-	-	-	-
	Chun 2007	1.04	-	**0.001**		-	**0.03**	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Campos-Fernandez 2009	-	-	**<0.001**		-	-	-	-	-	-	-	-	-	-	-	-
	Benecchi 2008	-	-	-	-	-	NS	✓	✓	✓	✓	✓	✓		✓		
	Auprich 2011	-	-	0.21	-	-	-	-	-	-	-	-	-	-	-		-
	Abdollah 2011	0.98	(0.93 – 1.03)	0.3	1.04	(0.97 – 1.10)	0.2	✓	✓				✓	✓	✓	✓	No. prior Bx
	Eskicorapci 2007	-	-	**0.05**	-	-	-	-	-	-	-	-	-	-	-	-	-
	Bhojani 2013	1.01	-	0.1	1.02	-	0.14	✓	✓	-	-	-	-	-	-	✓	Weight of prostate
LogPSA	Merrimen 2010	-	-	-		-	0.25	✓	✓	-	-	-	-	-	-	-	Pathologist
	Merrimen 2009[2]	-	-	-		-	0.54	✓	✓								Sampling extent; pathologist
PSA: 4-10 vs < 4	Bollito 2012	1.55	(0.52 – 4.63)	0.44		(0.53 – 14.54)	0.22		✓	✓							PCA3 (39)
						(0.41 – 12.23)	0.35		✓	✓							PCA3 (50)
PSA: > 10 vs < 4	Bollito 2012	2.47	(0.80 – 7.67)	0.12		(1.03 – 32.59)	**0.05**		✓	✓							PCA3 (39)
						(0.82 – 27.76)	0.08		✓	✓							PCA3 (50)
PSA: > 10 vs ≤ 10	Campos-Fernandes 2009	1.57	-	0.027		-	0.705	✓	✓	✓	✓	✓	-	-	-	✓	T-stage
PSA: > 6 vs ≤ 6		2.08	-	**<0.001**		-	-	-	-	-	-	-	-	-	-	-	-
Free-to-total PSA at first biopsy																	
ftPSA (continuous)	Naya 2004	-	-	0.25	-	-	NS	✓	✓	✓	✓	✓	✓		✓		cPSA; no. cores HGPIN+; AGSC
	Mian 2002[1]	-	-	-	1.05	(0.94 – 1.17)	0.43	✓	✓	✓			✓		✓	✓	TRUS; AGSC
	Xu 2011	-	-	**< 0.001**		(0.78 – 0.96)	**0.01**		✓	✓	✓				✓	✓	Volume-to-Bx ratio
	Shimbo 2009	-	-	0.33		-	-	-	-	-	-	-	-	-	-	-	-
	Scattoni 2011	0.97	(0.93 – 1.00)	**0.05**	-	-	-	-	-	-	-	-	-	-	-	-	-
	Rochester 2009	-	-	0.13	-	-	NS	✓	✓	✓		✓			✓	✓	
	Ploussard 2010	-	-	0.07	-	-	0.10		✓	✓					✓	✓	PCA3; no. prior Bx

Prognostic factor	Study	Univariate analyses			Multivariate analyses			Variables include in multivariate model									
		OR	95% CI	p-value	OR	95% CI	p-value	Age	PSA	PSA	PSAd	PSAv	HG-PIN	ASAP	DRE	Volume	Other
	Mabjeesh 2012	-	-	0.50	-	-	-	-	-	-	-	-	-	-	-	-	-
	Lee 2011	-	-	-	1.4	(1.1 – 1.7)	**<0.05**	✓	✓	✓			✓	✓	✓		Ethnicity; family history; > 20 cores;
	Lazzeri 2012	-	-	**0.01**	1.00	(0.995 – 1.006)	0.87		✓	✓	✓				✓	✓	Free PSA
	Grepl 2009	-	-	**0.002**		-	-	-	-	-	-	-	-	-	-	-	-
	Engehausen 2012	-	-	**0.005**		-	-	-	-	-	-	-	-	-	-	-	-
	Chun 2007	0.91	-	**<0.001**		-	**<0.001**	✓	✓	✓					✓	✓	NR; no. prior Bx
	Benecchi 2008	-	-	-	-	-	**<0.05**	✓	✓	✓	✓	✓	✓		✓		
	Auprich 2011	-	-	**<0.001**	-	-	-	-	-	-	-	-	-	-	-	-	-
	Eskicorapci 2007	-	-	0.11	-	-	-	-	-	-	-	-	-	-	-	-	-
	Campos-Fernandez 2009	-	-	0.014	-	-	-	-	-	-	-	-	-	-	-	-	-
ftPSA ≤ 0.1 vs > 0.2	Ploussard 2010	-	-	**0.03**	-	-	-	-	-	-	-	-	-	-	-	-	-
ftPSA > 0.15 vs ≤ 0.15	Campos-Fernandez 2009	0.47	-	**0.003**	-	-	0.063	-	-	-	-	-	-	-	-	-	-
ftPSA > 0.2 vs < 0.1	Bollito 2012	0.42	(0.19 – 0.91)	**0.03**	0.46	(0.19 – 0.11)	0.08		✓	✓							PCA3 (39)
					0.50	(0.21 – 1.20)	0.12		✓	✓							PCA3 (50)
ftPSA 0.1-0.2 vs > 0.2	Ploussard 2010	-	-	NS	-	-	-	-	-	-	-	-	-	-	-	-	-
ftPSA 0.1-0.2 vs < 0.1	Bollito 2012	0.54	(0.28 – 1.07)	0.08	0.70	(0.32 – 1.53)	0.38		✓	✓							PCA3 (39)
					0.71	(0.32 – 1.54)	0.38		✓	✓							PCA3 (50)
ftPSA 0.1-0.2 vs ≤ 0.1	Ploussard 2010	-	-	NS	-	-	-	-	-	-	-	-	-	-	-	-	-
ftPSA ≤ 0.1 vs > 0.1	Ploussard 2010	-	-	-	1.80	(0.85 – 3.82)	0.13			✓							PCA3
PSA density at first biopsy (ng/ml/ml)																	
PSAd	Naya 2004	-	-	**0.03**	-	-	**0.002**	✓	✓	✓	✓	✓	✓		✓		cPSA; no. cores HGPIN+; AGSC
	Xu 2011	-	-	**0.003**	-	-	-	-	-	-	-	-	-	-	-		-
	Shimbo 2009	-	-	0.26		-	-	-	-	-	-	-	-	-	-	-	-
	Lazzeri 2012	-	-	0.09	1.005	(0.998 – 1.012)	0.16		✓	✓	✓				✓	✓	Free PSA
	Kim 2012	-	-	**0.04**		-	-	-	-	-	-	-	-	-	-	-	-

Prognostic factor	Study	Univariate analyses			Multivariate analyses			Variables include in multivariate model									
		OR	95% CI	p-value	OR	95% CI	p-value	Age	PSA	PSA	PSAd	PSAv	HG-PIN	ASAP	DRE	Volume	Other
	Campos-Fernandez 2009	-	-	**<0.001**		-	-	-	-	-	-	-	-	-	-	-	-
	Benecchi 2008	-	-	-	-	-	**<0.05**	✓	✓	✓	✓	✓	✓		✓		
	Eskicorapci 2007	-	-	**0.001**	-	-	-	-	-	-	-	-	-	-	-	-	-
PSAd: > 0.15	Wu 2012	-	-	-	2.3	(1.4 – 4.0)	**<0.05**		✓		✓				✓		TRUS; PCA3
	Campos-Fernandez 2009	2.60	-	**<0.001**	2.34	-	**0.012**	✓	✓	✓	✓	✓				✓	T-stage
PSAd: > 0.20		2.66	-	**<0.001**		-	-	-	-	-	-	-	-	-	-	-	-
PSA velocity at first biopsy (ng/ml/year)																	
≥ 0.75 vs < 0.75	Naya 2004	-	-	0.48	-	-	NS	✓	✓	✓	✓	✓	✓		✓		cPSA; no. cores HGPIN+; AGSC
> 0.75 vs ≤ 0.75	Campos-Fernandez 2009	-	-	0.797	-	-	0.701	✓	✓	✓	✓	✓	-	-	-	✓	T-stage
≤ 0.93 vs > 0.93	Singh 2004	3.39	(0.62 – 18.49)	0.14		-	-	-	-	-	-	-	-	-	-	-	-
PSAv (continuous)	Xu 2011	-	-	0.12	-	-	-	-	-	-	-	-	-	-	-	-	-
	Singh 2004	-	-	0.32		-	-	-	-	-	-	-	-	-	-	-	-
	Shimbo 2009	-	-	0.33		-	-	-	-	-	-	-	-	-	-	-	-
	Rochester 2009	-	-	**0.02**	1.34	(1.03 – 1.74)	**<0.05**	✓	✓	✓		✓			✓	✓	
	Mabjeesh 2012	-	-	**<0.001**	1.58	(1.06 – 2.35)	**0.03**	✓	✓			✓			✓	✓	Free PSA; histology; no. prior Bx
	Benecchi 2008	-	-	-	-	-	**<0.05**	✓	✓	✓	✓	✓	✓		✓		
	Auprich 2011	-	-	**0.03**	-	-	-	-	-	-	-	-	-	-	-		-
	Kumar 2009	-	-	**0.007**	-	-	-	-	-	-	-	-	-	-	-		-
	Campos-Fernandez 2009	-	-	0.813	-	-	-	-	-	-	-	-	-	-	-	-	-
Abnormal DRE at first biopsy (vs normal DRE)																	
Abnormal DRE	Naya 2004	-	-	0.99	-	-	NS	✓	✓	✓	✓	✓	✓		✓		cPSA; no. cores HGPIN+; AGSC
	Mian 2002[1]	-	-	-	0.63	(0.16 – 2.46)	0.51	✓	✓	✓			✓		✓	✓	TRUS; AGSC
	San Francisco 2003	-	-	0.12		-	-	-	-	-	-	-	-	-	-	-	-
	Xu 2011	-	-	**0.002**		(1.62 – 13.07)	**0.004**		✓	✓	✓				✓	✓	Volume-to-Bx ratio
	Wu 2012	-	-	-		(0.60 – 75.50)	NS		✓		✓				✓		TRUS; PCA3

Prognostic factor	Study	Univariate analyses			Multivariate analyses			Variables include in multivariate model									
		OR	95% CI	p-value	OR	95% CI	p-value	Age	PSA	PSA	PSAd	PSAv	HG-PIN	ASAP	DRE	Volume	Other
	Singh 2004	1.32	(0.13 – 4.63)	0.82		-	-	-	-	-	-	-	-	-	-	-	-
	Scattoni 2011	1.45	(0.69 – 3.06)	0.3	-	-	-	-	-	-	-	-	-	-	-	-	-
	Rochester 2009	-	-	0.44	-	-	NS	✓	✓	✓		✓			✓	✓	
	Ploussard 2010	-	-	-	-	-	**<0.001**		✓	✓					✓	✓	PCA3; no. prior Bx
	Moussa 2010	-	-	-	-	-	0.26	✓	✓			✓	✓	✓	✓	✓	No. –ive cores; BMI; family history; months since prior Bx; months since initial Bx
	Mabjeesh 2012	-	-	**0.04**	2.58	(0.45 – 14.90)	0.29	✓	✓			✓			✓	✓	Free PSA; histology; no. prior Bx
	Lee 2011	-	-	-	0.4	(0.1 – 1.5)	NS	✓	✓	✓			✓	✓	✓		Ethnicity; family history; > 20 cores;
	Lazzeri 2012	-	-	0.06	1.82	(0.76 – 4.37)	0.18		✓	✓	✓				✓	✓	Free PSA
	Chun 2007	2.80	-	**<0.001**		-	**0.002**	✓	✓	✓					✓	✓	NR; no. prior Bx
	Campos-Fernandez 2009	-	-	0.39		-	-	-	-	-	-	-	-	-	-	-	-
	Benecchi 2008	-	-	-	-	-	**<0.05**	✓	✓	✓	✓	✓	✓		✓		
	Auprich 2011	-	-	0.49	-	-	-	-	-	-	-	-	-	-	-	-	-
	Abdollah 2011	2.65	(1.24 – 5.67)	**0.01**	2.63	(1.14 – 6.08)	**0.02**	✓	✓				✓	✓	✓	✓	No. prior Bx
PIN at first biopsy																	
HGPIN	Naya 2004	-	-	0.57	-	-	NS	✓	✓	✓	✓	✓	✓		✓		cPSA; no. cores HGPIN+; AGSC
	Mian 2002[1]	-	-	-	0.13	(0.02 – 1.06)	0.06	✓	✓	✓			✓		✓	✓	TRUS; AGSC
	Merrimen 2009[2]	-	-	**0.02**	1.38	-	**0.03**	✓	✓	-	-	-	-	-	-	-	Sampling extent; pathologist
	Singh 2004	5.07	(1.54 – 16.74)	**0.01**		-	-	-	-	-	-	-	-	-	-	-	-
	Scattoni 2011	1.24	(0.72 – 2.13)	0.4	-	-	-	-	-	-	-	-	-	-	-	-	-
	Rochester 2009	-	-	0.78	-	-	NS	✓	✓	✓		✓			✓	✓	
	Moussa 2010	-	-	-	-	-	**<0.001**	✓	✓			✓	✓	✓	✓	✓	No. –ive cores; BMI; family history; months since prior Bx;

Prognostic factor	Study	Univariate analyses			Multivariate analyses			Variables include in multivariate model									
		OR	95% CI	p-value	OR	95% CI	p-value	Age	PSA	PSA	PSAd	PSAv	HG-PIN	ASAP	DRE	Volume	Other
																	months since initial Bx
	Mabjeesh 2012	-	-	0.28	-	-	-	-	-	-	-	-	-	-	-	-	-
	Lee 2011	-	-	-	3.2	(1.8 – 5.6)	**<0.05**	✓	✓	✓			✓	✓	✓		Ethnicity; family history; > 20 cores;
	Benecchi 2008	-	-	-	-	-	**<0.05**	✓	✓	✓	✓	✓	✓		✓		
	Abdollah 2011	1.27	(0.42 – 3.83)	0.6	1.26	(0.38 – 4.23)	0.7	✓	✓				✓	✓	✓	✓	No. prior Bx
PIN	San Francisco 2003	-	-	**0.01**	-	-	-	-	-	-	-	-	-	-	-	-	-
	Campos-Fernandez 2009	-	-	0.75	-	-	-	-	-	-	-	-	-	-	-	-	-
ASAP at first biopsy																	
ASAP	Scattoni 2011	3.12	(1.50 – 6.47)	**0.002**	-	-	-	-	-	-	-	-	-	-	-	-	-
	Moussa 2010	-	-	-	-	-	**0.01**	✓	✓			✓	✓	✓	✓	✓	No. –ive cores; BMI; family history; months since prior Bx; months since initial Bx
	Mabjeesh 2012	-	-	0.28	-	-	-	-	-	-	-	-	-	-	-	-	-
	Lee 2011	-	-	-	3.0	(1.3 – 6.7)	**<0.05**	✓	✓	✓			✓	✓	✓		Ethnicity; family history; > 20 cores;
	Campos-Fernandez 2009	-	-	0.13	3.65	(1.09 – 12.29)	**0.04**	✓			✓			✓		✓	
	Abdollah 2011	2.79	(1.50 – 5.18)	**0.001**	3.36	(1.68 – 6.71)	**<0.001**	✓	✓				✓	✓	✓	✓	No. prior Bx
AGSC at first biopsy																	
AGSC	Naya 2004	-	-	**<0.001**	-	-	**<0.001**	✓	✓	✓	✓	✓	✓		✓		cPSA; no. cores HGPIN+; AGSC
	Mian 2002[1]	-	-	-	20.71	(4.45 – 96.36)	**<0.001**	✓	✓	✓			✓		✓	✓	TRUS; AGSC
PCA3 score																	
PCA3 (continuous)	Wu 2012	-	-	-	1.02	(1.003 – 1.03)	**<0.05**		✓		✓				✓		TRUS; PCA3
	Ploussard 2010	-	-	**<0.001**	-	-	-	-	-	-	-	-	-	-	-	-	-
	Auprich 2011	-	-	**<0.001**	-	-	-	-	-	-	-	-	-	-	-	-	-
	Bollito 2012	-	-	**<0.001**	-	-	-	-	-	-	-	-	-	-	-	-	-

Prognostic factor	Study	Univariate analyses			Multivariate analyses			Variables include in multivariate model									
		OR	95% CI	p-value	OR	95% CI	p-value	Age	PSA	PSA	PSAd	PSAv	HG-PIN	ASAP	DRE	Volume	Other
PCA3 < 15 vs ≥ 15	Bollito 2012	4.82	(2.57 – 9.07)	**<0.001**	-	-	-	-	-	-	-	-	-	-	-	-	-
PCA3 < 20 vs ≥ 20	Bollito 2012	7.19	(3.84 – 13.48)	**<0.001**													
PCA3 > 25 vs <25	Ploussard 2010	-	-	**<0.001**	-	-	-	-	-	-	-	-	-	-	-	-	-
PCA3 > 30 vs <30	Ploussard 2010	-	-	-	3.01	(1.74 – 5.23)	**<0.001**			✓							PCA3
	Ploussard 2010	-	-	-	-	-	**0.03**		✓	✓					✓	✓	PCA3; no. prior Bx
PCA3 > 35 vs <35	Ploussard 2010	-	-	**<0.001**	-	-	-	-	-	-	-	-	-	-	-	-	-
	Goode 2013	-	-	**<0.001**	-	-	-	-	-	-	-	-	-	-	-	-	-
	Bollito 2012	6.89	(4.31 – 11.03)	**<0.001**	-	-	-	-	-	-	-	-	-	-	-	-	-
PCA3 < 39 vs ≥ 39	Bollito 2012	7.89	(4.94 – 12.62)	**<0.001**	9.44	(5.15 – 17.31)	**<0.001**		✓	✓							PCA3
PCA3 < 50 vs ≥ 50	Bollito 2012	7.43	(4.77 – 11.58)	**<0.001**	9.29	(5.11 – 16.89)	**<0.001**		✓	✓							PCA3
PCA3 < 70 vs ≥ 70	Bollito 2012	6.94	(4.39 – 10.96)	**<0.001**	-	-	-	-	-	-	-	-	-	-	-	-	-
Family history of PCa																	
Family history	Moussa 2010	-	-	-	-	-	**0.001**	✓	✓	-	-	✓	✓	✓	✓	✓	No. –ive cores; BMI; family history; months since prior Bx; months since initial Bx
	Lee 2011	-	-	-	3.1	(1.2 – 8.0)	**<0.05**	✓	✓	✓	-	-	✓	✓	✓	-	Ethnicity; family history; > 20 cores;
Ethnicity																	
Caucasian vs not Caucasian	Lee 2011	-	-	-	0.8	(0.4 – 1.6)	NS	✓	✓	✓	-	-	✓	✓	✓		Ethnicity; family history; > 20 cores;
Clinical stage																	
T2 vs T1	Campos-Fernandez 2009	-	-	0.813	-	-	0.867	✓	✓	✓	✓	✓	-	-	-	✓	T-stage

[1]Secondary to Naya 2004; [2]secondary to Merrimen 2010 [3]secondary to Pepe 2012a

Table 10. Diagnostic accuracy outcomes from studies comparing prognostic factors and re-biopsy (reference standard)

Abbreviations: AGSC = atypical glands suspicious for carcinoma; ASAP = atypical small acinar proliferation; DRE = digital rectal examination; ftPSA = free-to-total PSA; HGPIN = high grade prostatic intraepithelial neoplasia; PSAd = PSA density; PSAv = PSA velocity

Prognostic factor	Study	Number undergoing re-biopsy	Number included by cut-off	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
Age > 62.4	Singh 2004	149	99	*28.6*	*66.4*	*10.7*	*86.8*	-
PSA level (ng/ml)								
PSA > 1.0	Thompson 2008	687	-	87.5	28.7	19.3	92.2	-
PSA > 1.5	Thompson 2008	687	-	80.4	39.1	20.5	91.1	-
PSA > 2.0	Thompson 2008	687	-	73.2	49.2	21.9	90.4	-
PSA > 2.5	Thompson 2008	687	-	66.1	57.6	23.3	89.7	-
PSA > 3.0	Thompson 2008	687	-	58.0	63.1	23.5	88.5	-
PSA > 3.2	Lazzeri 2012	222	-	12.7	92.0	42.8	69.1	-
PSA > 4.0	Thompson 2008	687	-	48.2	76.5	28.6	88.4	-
	Goode 2013	167	-	79	27	-	-	-
PSA > 5.3	Auprich 2011	127	-	95.0	14.5	37.2	85.7	-
PSA > 5.9	Auprich 2011	127	-	85.0	18.1	35.2	68.2	-
PSA > 6.0	Thompson 2008	687	-	16.1	93.0	31.0	85.1	-
PSA > 6.7	Auprich 2011	127	-	75.0	30.1	36.3	69.4	-
PSA > 7.5	Lazzeri 2012	222	-	56.3	54.3	36.7	72.5	-
PSA > 8.0	Thompson 2008	687	-	6.3	97.4	31.8	84.2	-
PSA > 10.0	Thompson 2008	687	-	2.7	98.4	25.0	83.9	-
PSA ≥ 10	Wu 2012	103	39	40	61	40	62	-
PSA > 12.8	Mabjeesh 2012	92	76	58.3	62.7	35.9	80.8	-
PSA > 17.2	Lazzeri 2012	222	-	93.0	8.6	32.4	72.3	-
Free-to-total PSA								
ftPSA > 0.09	Lazzeri 2012	222	-	23.9	91.4	56.7	71.8	-
ftPSA > 0.1	Lee 2011	617	-	-	90.0	-	-	-
ftPSA ≥ 0.15	Engehausen 2012	96	33	*28.6*	*37.5*	*24.2*	*42.9*	-
ftPSA > 0.15	Pepe 2012a	74	43	66.7	51.0	42.8	73.5	56.6
	Lazzeri 2012	222	-	54.9	56.3	37.1	72.6	-
	Auprich 2011	127	-	75.0	65.1	52.5	81.8	-
ftPSA > 0.18	Auprich 2011	127	-	85.0	41.0	43.0	82.9	-
ftPSA > 0.20	Pepe 2012a	74	58	85.1	28.6	39.6	87.5	46.6

Prognostic factor	Study	Number undergoing re-biopsy	Number included by cut-off	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
ftPSA > 0.23	Auprich 2011	127	-	95.0	22.9	39.6	90.5	-
ftPSA > 0.24	Lazzeri 2012	222	-	91.6	13.9	33.4	77.9	-
ftPSA > 0.25	Pepe 2012a	74	66	96.3	14.3	32.9	88.9	44.8
PSA density								
PSAd > 0.15	Wu 2012	103	50	66	60	51	74	-
PSA velocity (ng/ml/year)								
NR	Kumar 2009	31	-	87.5	63.6	-	-	-
PSAv > 0.28	Auprich 2011	127	-	95.0	4.8	34.7	66.7	-
PSAv > 0.75	Auprich 2011	127	-	85.0	27.7	38.8	79.3	-
PSAv > 0.93	Singh 2004	57	29	*25.0*	*46.9*	*7.1*	*79.3*	-
PSAv > 1.19	Auprich 2011	127	-	75.0	42.2	40.7	76.1	-
PSAv > 2.13	Mabjeesh 2012	92	76	79.0	79.7	55.6	92.2	-
PIN								
PIN	San Francisco 2003	64	13	*83.3*	*72.4*	*23.8*	*97.7*	-
HGPIN	Naya 2004	175	57	*28.1*	*66.4*	*15.8*	*80.5*	-
	Singh 2004	99	14	*33.3*	*85.9*	*33.3*	*85.9*	-
	Merrimen 2010	225	120	*58.8*	*43.1*	*14.3*	*86.7*	-
	Rochester 2009	87	30	*37.0*	*66.1*	*33.3*	*69.6*	-
	Mabjeesh 2012	92	4	*8.3*	*97.1*	*50.0*	*75.0*	-
ASAP								
ASAP	Scattoni 2011	340	33	*23.6*	*91.6*	*51.5*	*76.0*	-
	Mabjeesh 2012	92	4	*8.3*	*97.1*	*50.0*	*75.0*	-
AGSC								
AGSC	Naya 2004	136	22	*21.9*	*96.5*	*58.3*	*84.7*	-
Abnormal DRE								
Abnormal DRE	San Francisco 2003	64	-	*0.0*	*56.3*	*0.0*	*64.3*	-
	Xu 2011	129	44	*55.9*	*73.7*	*43.2*	*82.4*	-
	Wu 2012	103	13	22	88	53	64	-
	Singh 2004	99	4	*5.0*	*95.9*	*20.0*	*80.0*	-
	Rochester 2009	87	18	*25.9*	*81.4*	*38.9*	*70.6*	-
	Mabjeesh 2012	92	12	*25.0*	*91.2*	*50.0*	*77.5*	-
	Grepl 2009	169	28	*33.3*	*88.0*	*42.9*	*83.0*	-
	Auprich 2011	127	14	*13.6*	*90.4*	*42.9*	*66.4*	-

Prognostic factor	Study	Number undergoing re-biopsy	Number included by cut-off	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
PCA3 score								
PCA3 > 10	Marks 2007	226	-	87	28	-	-	-
PCA3 > 12	Auprich 2011	127	-	95.0	12.0	36.5	83.3	-
PCA3 ≥ 15	Bollito 2012	509	-	88.2	34.6	36.9	87.1	-
PCA3 > 19	Auprich 2011	127	-	85.0	25.3	38.0	77.8	-
PCA3 > 20	Pepe 2012a	74	58	70.4	43.5	42.2	71.5	51.4
	Pepe 2012b	118	91	90.6	27.9	31.9	88.9	-
	Barbera 2013	177	140	91.7	25.6	31.5	89.5	43.5
PCA3 ≥ 20	Bollito 2012	509	-	88.2	44.3	40.7	89.6	-
PCA3 > 25	Wu 2012	103	47	67	64	52	78	-
	Ploussard 2010: Group I (ftPSA ≤ 0.1)	46	-	68.8	56.7	45.8	77.3	-
	Ploussard 2010: Group II (ftPSA 0.1-0.2)	138	-	72.7	62.9	38.1	88.0	-
	Ploussard 2010: Group III(ftPSA > 0.2	117	-	77.3	53.7	27.9	91.1	-
PCA3 > 30	Ploussard 2010: Group I (ftPSA ≤ 0.1)	46	-	50.0	66.7	44.4	71.4	-
	Ploussard 2010: Group II (ftPSA 0.1-0.2)	138	-	60.6	67.6	37.0	84.5	-
	Ploussard 2010: Group III (ftPSA > 0.2)	117	-	68.2	64.2	30.6	89.7	-
PCA3 > 35	Pepe 2012b	74	46	71.9	41.8	31.5	80.0	-
	Pepe 2012a	118	73	92.6	21.6	43.1	88.9	55.5
	Wu 2012	103	32	38	77	50	66	-
	Sciarra 2012: Group I	84	-	68.0	74.5	53.1	84.6	72.6
	Sciarra 2012: Group II	84	-	79.3	72.7	60.5	86.9	75.0
	Ploussard 2010: Group I (ftPSA ≤ 0.1)	46	-	43.8	66.7	41.2	69.0	-
	Ploussard 2010: Group II (ftPSA 0.1-0.2)	138	-	51.5	79.1	43.6	83.8	-
	Ploussard 2010: Group III (ftPSA > 0.2	117	-	59.1	67.4	29.6	87.7	-
	Marks 2007	226	82	58	72	-	-	-
	Goode 2013	167	-	42	70	-	-	-
	Bollito 2012: Group I (PSA < 4)	509	25	75.0	52.3	23.0	91.6	-
	Bollito 2012: Group II (PSA 4-10)	509	356	81.4	65.4	40.9	92.3	-
	Bollito 2012: Group III (PSA > 10)	509	128	70.7	72.4	54.7	84.0	-
	Barbera 2013	177	100	73.0	41.8	35.0	80.6	50.2
	Porpiglia 2013	100	-	16.7	55.7	13.6	60.9	44.0
PCA3 ≥ 35	Bollito 2012	509	-	75.2	69.8	52.0	86.7	-
	Busetto 2013	43	-	76.9	66.6	80.0	62.5	

Prognostic factor	Study	Number undergoing re-biopsy	Number included by cut-off	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
PCA3 > 39	Auprich 2011	127	-	75.0	57.8	48.5	81.4	-
PCA3 ≥ 39	Bollito 2012	509	-	74.1	74.4	55.7	86.9	74.4
PCA3 > 50	Marks 2007	226	60	47	81	-	-	-
PCA3 ≥ 50	Bollito 2012	509	-	65.8	81.1	60.2	84.5	76.5
PCA3 ≥ 70	Bollito 2012	509	-	65.8	65.8	45.5	81.6	-
Not reported	Fiori 2013	50	-	66.7	97.1	90.9	87.2	88.0

Figures in italics are calculated

Figure 1. ROC curve showing PSA level, free-to-total PSA (ftPSA), and PSA velocity (PSAv) at initial diagnosis

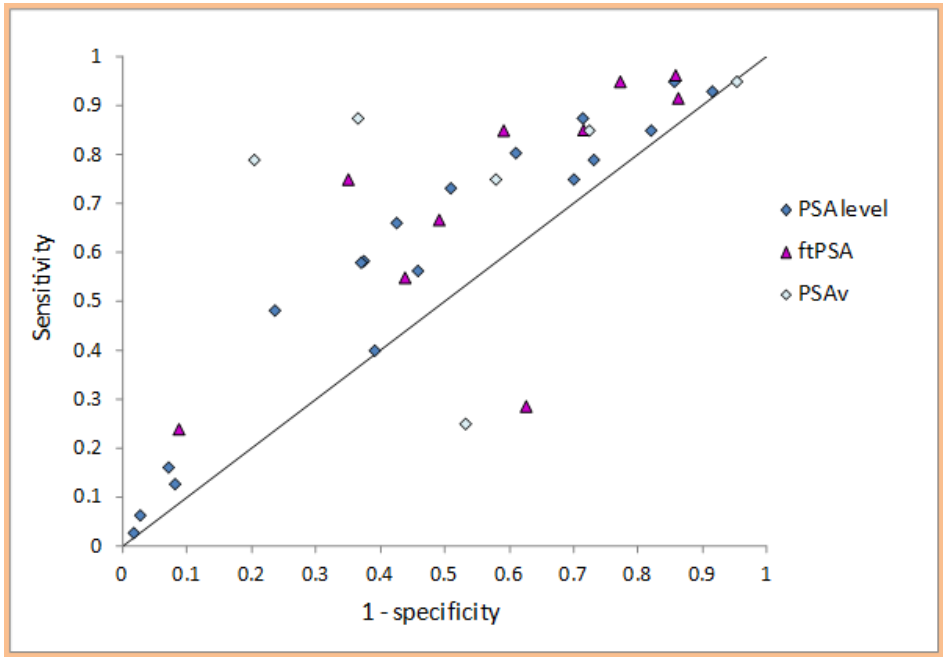


Figure 2. ROC curve showing presence of high grade prostatic intraepithelial neoplasia (HGPIN) and atypical small acinar proliferation (ASAP) at initial biopsy, and abnormal DRE findings

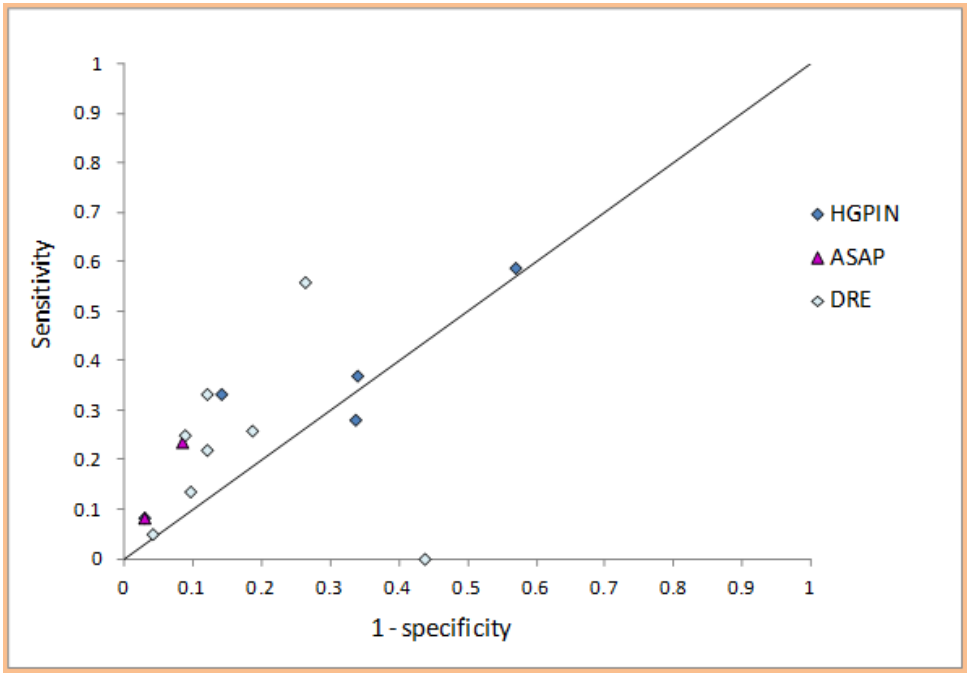


Figure 3. ROC curve showing diagnostic accuracy of biomarker PCA3, with three free-to-total PSA (ftPSA) subgroups

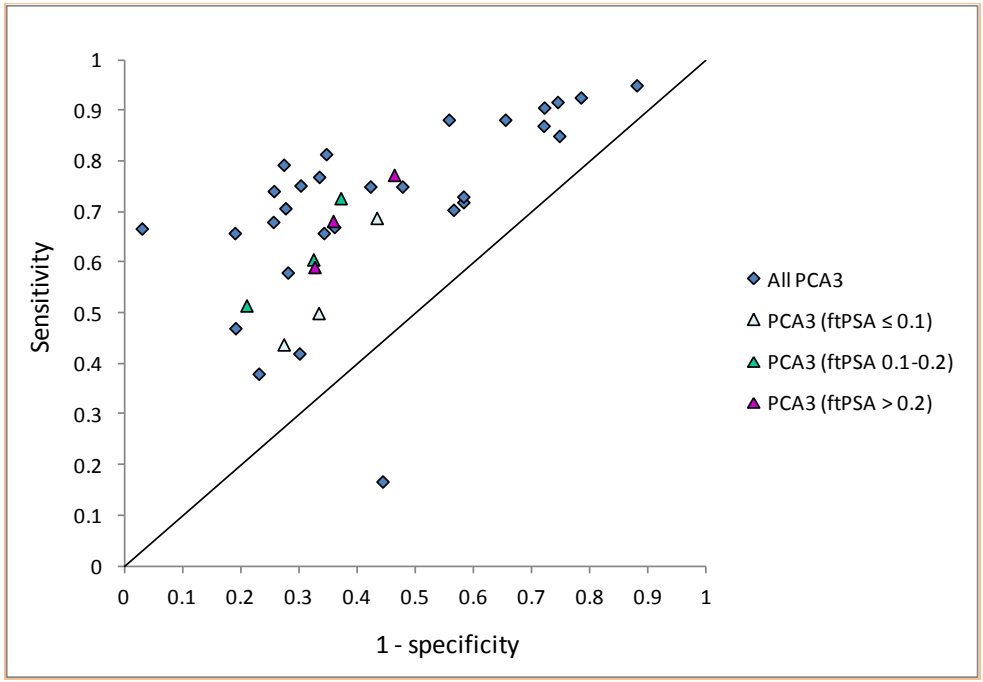


Table 11. Summary of included study characteristics

Abbreviations: ASAP = atypical small acinar proliferation; DRE = digital rectal examination; PCa = prostate cancer; HGPIN = high grade prostatic intraepithelial neoplasia; PSA = prostate specific antigen; TRUS = transrectal ultrasound.

Study	Type of study	Country	Time period	No. undergoing repeat biopsy	Exclusion criteria	Initial biopsy scheme	Repeat biopsy scheme	Time between biopsies (median)	Indications for repeat biopsy
Auprich et al. (2011)	Prospective cohort	Austria	2008-2009	127	Aged > 70 years;	(8-10 cores)	(12 or 24 cores)	> 12 months	Suspicious DRE &/or persistently elevated age-specific PSA (2.5-6.5 ng/ml); ASAP; HGPIN
Merrimen et al. (2009 & 2010)	Retrospective cohort	Canada	1999-2007	225	History of prior treatment; ASAP; < 10 cores in either initial or re-biopsy	(≥ 10 cores)	Extended	1.4 – 2.4 years*	
Xu et al. (2011)	Retrospective cohort	China	1999-2010	129	Stable PSA < 4.0 ng/ml	TRUS-guided	Sextant TRUS-guided		PSA continuously elevated (≥ 10 ng/mL) or persistently increasing (velocity ≥ 0.75 ng/mL/y)
Grepl et al. (2009)	Prospective cohort	Czech Republic	2006-2008	191	Adenosis; atrophy; PSA > 50 ng/ml	TRUS-guided		12 months	Abnormal DRE &/or PSA > 2.5 ng/ml
Campos-Fernandes et al. (2009) & Ploussard et al. (2013)	Prospective cohort	France	2001-2007	231		Extended (21 cores)	Extended (21 cores)	10 months*	Persistently elevated PSA (> 4 ng/ml); PSA increase during follow-up; PIN; ASAP
Chun et al. (2007)	Prospective cohort	Germany		721			(≥ 10 cores)		Suspicious DRE, persistently abnormal PSA or free-to-total PSA, HGPIN or ASAP
Engehausen et al. (2012)	Prospective cohort	Germany	2003-2007	96	Contraindications to MRI (e.g. cardiac pacemakers)	TRUS-guided	Endorectal MRI-guided (2-6 cores)		Continuing clinical suspicion of PCa
Kravchick et al. (2009)	Prospective cohort	Israel		600	Normal DRE and PSA ≤ 4 ng/ml	TRUS-guided lateral aspects (8-16 cores)	TRUS-guided medial aspects (8-16 cores)		
Mabjeesh et al. (2012)	Prospective cohort	Israel		92	< 2 previous negative biopsies	TRUS- guided transrectal (10-12 cores)	Transperineal saturation		Persistent PSA elevation despite ≥ 2 pervious biopsies
Abdollah et al. (2011)	Retrospective cohort	Italy	2005-2008	472		Transrectal (70%) or Transperineal (30%) (24 cores)	TRUS-guided saturation (24 cores)		Persistent PSA ≥ 10 ng/ml; PSA < 10 ng/ml & free-to-total PSA ≤ 0.2; abnormal DRE; HGPIN; ASAP
Benecchi et al. (2008)	Prospective cohort	Italy	2001-2007	419	PSA interference (e.g. 5-alpha-reductase therapy)		TRUS-guided (12-24 cores)		Abnormal DRE &/or abnormal PSA
Bollito et al. (2012)	Prospective cohort	Italy	2008-2010	515	Positive DRE or ASAP	Peripheral zone (10-14 cores)	Peripheral & transition zone		

Study	Type of study	Country	Time period	No. undergoing repeat biopsy	Exclusion criteria	Initial biopsy scheme	Repeat biopsy scheme	Time between biopsies (median)	Indications for repeat biopsy
							(14-18 cores)		
Lazzeri et al. (2012)	Prospective cohort	Italy	2010-2011	222	Medical therapy known to affect PSA; previous invasive treatment for BPH; UTI; acute proctatitis; blood protein alterations		TRUS-guided		Persistent suspicion of PCa (increasing &/or persistent elevation of PSA, DRE, ASAP or HGPIN)
Pepe et al. (2010)	Prospective cohort	Italy	2003-2008	262		Extended (12 cores)		15.2 months	Abnormal DRE; PSA > 10 ng/ml; PSA 4.1-10.0 & free-to-total PSA ≤ 0.25 or 2.6-4.0 ng/ml & free-to-total PSA ≤ 0.20; HGPIN; ASAP
Pepe et al. (2012a & b)	Prospective cohort	Italy	2009-2011	74/118	PSA > 10 ng/mL	Extended	Transperineal saturation		Persistently high or increasing PSA (PSA > 10 ng/ml; PSA 4.1-10 ng/ml with free-to-total PSA ≤ 25%; PSA 2.6-4.0 ng/ml with free-to-total PSA ≤ 20%
Scattoni et al. (2011)	Prospective cohort	Italy	2005-2008	340		TRUS-guided (≥ 12 cores)	TRUS-guided sextant saturation (24 cores)		PSA > 4 ng/ml &/or abnormal DRE &/or HGPIN or ASAP
Sciarra et al. (2012)	Cohort results from RCT	Italy	2008-2011	168	Positive for HGPIN or DRE; prior hormonal, surgical or radiation therapy; MRSI not possible	TRUS-guided laterally-directed (10 core)	TRUS-guided laterally-directed (10 core)	≤ 90 days	Persistently elevated PSA > 4 ng/ml
Shimbo et al. (2009)	Prospective cohort	Japan	2004-2005	77	Patients treated with transurethral resection due to an enlarged prostate with concomitant lower urinary tract symptoms	Transperineal TRUS-guided (10 cores)	Transperineal TRUS-guided (14 cores)		Persistent increase or continuing and fluctuating level of serum PSA between 4 & 20 ng/ml
Kim et al. (2012)	Retrospective cohort	Korea	2006-2012	42	PSA < 4 ng/ml; abnormal DRE; hypoechoic lesions; prior 5-alpha-reductasse inhibitors; prostatitis				Elevated PSA (≥ 4 ng/ml)
Eskicorapci et al. (2007)	Prospective cohort	Turkey	2001-2005	211		Sextant or 10-core	TRUS-guided (14 cores)		PSA > 4 ng/ml; increasing PSA */or abnormal DRE &/or HGPIN
Rochester et al. (2009)	Retrospective cohort	UK	-	110			TRUS-guided extended (≥ 10 cores)		
Goode et al. (2013)	Retrospective cohort	US		167	Prior history of PCa	TRUS-guided transrectal (12 core)	TRUS-guided transrectal (12 core)		Elevated PSA, abnormal DRE, or abnormal PIN or ASAP

Study	Type of study	Country	Time period	No. undergoing repeat biopsy	Exclusion criteria	Initial biopsy scheme	Repeat biopsy scheme	Time between biopsies (median)	Indications for repeat biopsy
Kumar et al. (2009)	Retrospective cohort	US	1999-2004	31	Atypia; HGPIN; < 3 PSA measurements between biopsies	(≥ 12 cores)		27.4 months*	Rising PSA
Lee et al. (2011)	Retrospective cohort	US	1999-2010	617	Lack of data; known diagnosis of PCa				Physician preference; family history, DRE, PSA, HGPIN, ASAP
Moussa et al. (2010)	Prospective cohort	US	1999-2008	408		Extended (10-12 cores) (91%)	Saturation transrectal (≥ 20 cores)		Included: persistently elevated PSA; abnormal DRE; HGPIN or ASAP
Naya et al. (2004) & Mian et al. (2002)	Prospective cohort	US	1997-2003	136	Patients undergoing sextant or directed biopsies	Extended multi-site directed	Any (extended, sextant or directed)	3 months < 1 year (78%) > 1 year (22%)	Persistently elevated PSA, rising PSA, low free-to-total PSA, abnormal DRE or TRUS, HGPIN, or AGSC
San Francisco et al. (2003)	Retrospective cohort	US	1996-1997	64	Cancer, atypia or prostatic biopsy with < 10 cores	TRUS-guided extended (≥ 10 cores)		29-30 months	Two successive increases in PSA level or any change in findings of DRE.
Singh et al. (2004)	Prospective cohort	US	1999-2002	99	No suspicion of cancer (normal DRE & PSA ≤ 2.5 ng/ml)	12 core	12 core		Free-to-total PSA ≤ 15 ng/ml &/or PSA velocity ≥ 0.75 ng/ml/y
Thompson et al. (2008)	Prospective cohort	US		687	Age < 55 years; abnormal DRE; PSA ≤ 3 ng/mL				Suspicious DRE; PSA ≥ 4 ng/ml
Wu et al. (2012)	Retrospective cohort	US		103	Missing data on PCA3, PSA, PSA density, DRE or TRUS		TRUS-guided sextant ≥ 12 cores		Suspicious DRE; persistently elevated PSA; previous suspicious histology; patient preference
Marks et al. (2007)	Prospective cohort	US & Canada	2004-2006	226	PSA < 2.5 ng/ml				
Ploussard et al. (2010)	Retrospective cohort	European	2006-2007	301	PSA < 2.5 or > 10 ng/ml; medical therapy known to affect PSA; UTI; invasive treatment for BPH	≥ 10 peripheral cores	≥ 10 peripheral cores		
Barbera et al. (2012)	Prospective cohort	Italy	2010-2012	177	Positive DRE	Extended (12-18 cores)	Saturation (median 28 cores)		PSA >10 ng/ml; PSA 4.1-10.0/2.6-4.0 with ftPSA < 25%/20%
Porpiglia et al. (2013)	Prospective cohort	Italy		100		≥ 12 samples	18 samples		Abnormal PSA, ASAP or PIN
Bhojani et al. (2013)	Retrospective cohort	US	1998-2011	1226	Patients not undergoing holmium laser enucleation of the prostate				Elevated PSA
Fiori et al. (2013)	Prospective cohort	Italy		50		12 samples	18 samples		Abnormal PSA, pathological (ASAP or HGPIN) or strong clinical suspicion

Study	Type of study	Country	Time period	No. undergoing repeat biopsy	Exclusion criteria	Initial biopsy scheme	Repeat biopsy scheme	Time between biopsies (median)	Indications for repeat biopsy
Busetto et al. (2013)	Prospective cohort	Italy		43	Prior hormonal, surgical or radiation therapy; < 10 core biopsy; positive DRE	≥ 10 core	Random 10-core TRUS-guided		PSA ≥ 4 ng/ml & < 10 ng/ml

*Mean reported where median not available.

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

Rationale

Few studies have been done that immediately do a repeat biopsy after a negative diagnosis. Normally other factors trigger the repeat biopsy – so a true false negative rate for TRUS biopsies will be difficult to assess. Triggers have included: PSA level, Free to total PSA, palpable nodule, PCNA, family history. Pathologists are also fallible and false negative biopsies due to errors occur, approximately 1%.

HGPIN: Repeat TRUS biopsies following HGPIN contain tumour in varying amounts according to studies over the last 15 years. 15 years ago only 6 core biopsies were the norm and as a result the positive rate following PIN was between 50 and 100%. With the introduction of 12 core biopsy sets this has decreased to 20-30%. Recent studies suggest multiple cores with HGPIN have a higher second positive biopsy rate, whereas a single core of HGPIN carries no increase risk above a negative first set of cores.

ASAP:Repeat TRUS biopsies following a diagnosis of ASAP have a positive rate of about 30%-50% in most recent studies.

There is a trend to use adjuncts following a negative first TRUS biopsy to improve the yield and PICO 2 will look at these. PICO 2 will concentrate on the techniques of sampling and imaging whilst PICO 3 looks at more biomarkers and risk factors. Most of these techniques have been introduced at a local level based on facilities available, rather than a systematic approach. We know that the majority of tumours are in the posterior zone of the prostate but there tumours in the anterior zone of the prostate, which are often missed with TRUS biopsies, particularly in large prostates. Sampling this area is improved with template (perineal) biopsies or with saturation biopsies. mpMRI will also highlight these areas enabling sampling. Both saturation and template biopsies require a general anaesthetic, whilst a repeat TRUS is under local, so there are cost implications between these. It maybe cheaper to use mpMRI to screen for anterior tumours, and direct these to saturation/template biopsies and use TRUS for the remainder. Other techniques also need to be examined in PICO 2.

PICO question

Population	Tests	Outcomes
Men whose initial biopsy proved negative for prostate cancer,	• Repeat TRUS biopsy • Multiparametric MRI (or MRS) + repeat TRUS biopsy • Extended/saturation TRUS biopsy • 3D ultrasound and biopsy • template biopsy • Review of initial biopsy • Contrast enhanced US and biopsy • Elastography and biopsy	• Diagnostic yield • Diagnostic process-related morbidity • Diagnostic process-related mortality • Health-related quality of life

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science and Biomed Central. Consideration will be given to subject-specific databases and used as appropriate.

Can we apply date limits to the search	This topic includes more tests than the equivalent topic in the 2008 guideline – so we can't limit to studies published since. Should we only consider studies using modern era biopsy techniques?
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	We will not use study design filters as evidence will come from case series or cohort studies.
List useful search terms.	

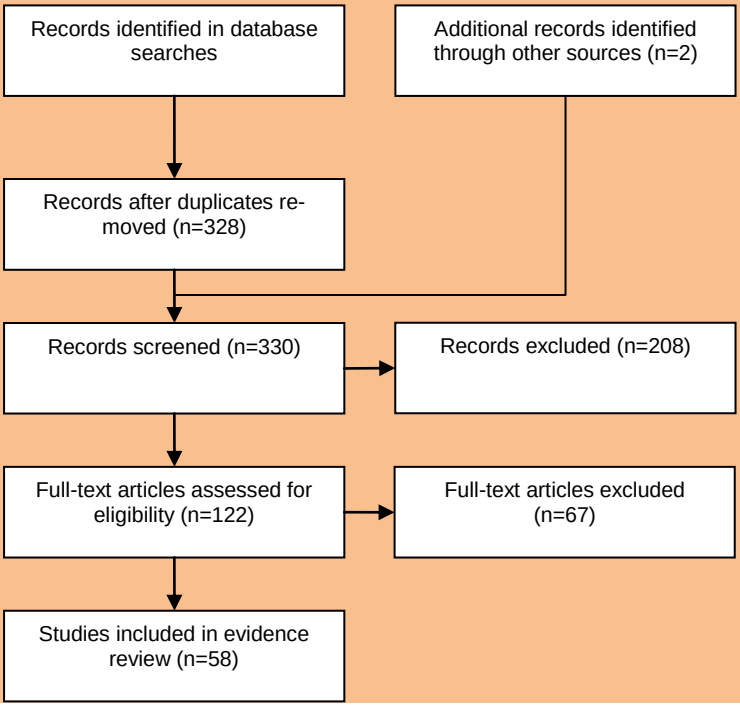
If we know before the literature search there is unlikely to be any evidence for the population or intervention is there a similar population or intervention (with high quality evidence) from which we could extrapolate?

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results?	We will use the evidence table for diagnostic studies (NICE guidelines manual appendix J). Diagnostic yield will be defined as the proportion of positive prostate re-biopsies. We will use the studies' definitions of diagnosis-related morbidity, diagnosis-related mortality.
Which quality checklist will we use for appraisal? (Normally checklists from the NICE manual – but irrelevant items could be omitted).	The QUADAS-2 quality checklist will be used (NICE guidelines manual appendix F).
List subgroups here and planned statistical analyses.(Recognised approaches to meta-analysis should be used, as described in the manual from the NHS Centre for Reviews and Dissemination, and the Cochrane Collaboration handbook).	We need to give consideration to the number of negative prostate biopsies the man has already had.

Results

Results of the literature searches



The literature searches identified 330 possibly relevant studies of which 122 were ordered as full text articles and 55 were included.

Evidence

Two systematic reviews (Mowatt et al, 2013 and Nelson et al, 2013) and one RCT of enhanced ultrasound was included. The other studies were cohort or case series studies.

Diagnostic yield

The diagnostic yield for cancer (the test positivity rate) of multi-parametric MRI was not reported in the Mowatt et al. (2013) systematic review but is estimated in Table 12 using the reported diagnostic accuracy and the average prevalence. Two further studies (Vourganti 2012; Portalez 2012) found diagnostic yields of 28.7% versus 23.1% and 43.4% versus 20.9% using multiparametric MRI and TRUS-guided biopsies following initial negative biopsy respectively. Arsov et al. (2012) found a diagnostic yield of 68.8% in patients undergoing multiparametric MRI guided rebiopsy following a suspicious lesion at MRI and prior negative biopsy.

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

For other tests, diagnostic yield was reported in all studies (see Table 13). For studies of saturation biopsy, cancer detection rates are reported by number of previous biopsies in Table 14. Cancer detection rates of enhanced ultrasound guided biopsies by standard and targeted cores

are reported in Table 15. Sensitivity and specificity rates of enhanced ultrasound biopsies as reported in three studies are shown in Table 16.

Table 12. Diagnostic accuracy and cancer yield of systematic biopsy, MRI, MRS and TRUS to predict re-biopsy result following an initial negative biopsy (Mowatt et al, 2013)

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

*Reference standard differs for extended cores TRUS/Bx and MRI methods. A 24 core TRUS-guided saturation biopsy serves as the reference standard for the extended cores estimate, whereas MRI methods were validated on histopathology of targeted cores and a varying number of additional cores taken under TRUS guidance.

† Cancer yield is defined as the proportion of men re-biopsied whose results are positive for cancer. The testing strategy assumes that only men with visible pathology on MRI/MRS would be re-biopsied and that both MRI/MRS targeted and 8 -12 systematic cores would be taken.

Table 13. Cancer yield of repeat biopsies and review of initial biopsy cores

No. of studies	Biopsy approach	Number of cores	Cancer yield range	Cancer yield pooled	% Significant cancer detected
Saturation/Extended biopsy					
21	Transperineal template saturation	Median ~29 Range: 13-124	23%-72%	38.8% (781/2011)	62% (222/358) Range: 25%-100%
19	Transrectal saturation	Median ~ 24 Range: 11-139	11%-45%	29.8% (904/3027)	56.7% (396/699) Range: 23%-100%
1	Transrectal + transperin-eal saturation	26 (12 TR + 14 TP)	-	37% (87/235)	52%
2	Transrectal extended	12-14	13%-25%	19.2% (142/740)	59.9% (85/142) Range: 43%-67%
Enhanced ultrasound biopsy					
2	Power Doppler enhanced US	[1]	26%-44%	29.5% (13/44)	-
2	Colour Doppler enhanced US	5-13[2]	16%-30%	20.8% (117/562)	-
1	ADF Doppler	8-core standard or 10-core with abnormalities	-	32% (30/95)	-
Repeat TRUS biopsy					
7	TRUS biopsy	10-12	13%-31%	19.3% (233/1205)	26.9% (7/26)[3]
3D ultrasound biopsy					
0	-	-	-	-	-
Review of initial biopsy (where initial diagnosis was not cancer)					
1	Not applicable	Not applicable	1.4%	1.4%	-

No. of studies	Biopsy approach	Number of cores	Cancer yield range	Cancer yield pooled	% Significant cancer detected
Elastography biopsy					
1	Elastosonography[4]	NR	-	33% (3/9)	-

1 Remzi (2004) and Morelli (2009). Neither study states number of cores. In Remzi each abnormal signal was targeted once, whereas in Morelli, suspected areas were double sampled.

2. Contrast enhanced ultrasound guided 5 core biopsies was performed in Ho (2009). In Taverna (2011) all patients received 13 core systematic biopsy plus additional cores from hypervascular areas.

3. One study reported rate of significant cancers, Gleason ≥7 (4+3) (Sciarra 2012)

4. One study (Morelli, 2009) reported as abstract only, compared elastosonography versus enhanced US

5. Miyagawa reported a mean of 2.3 targeted cores per lesion; Lee reported a median of 9 (up to 14) targeted cores.

Table 14. Saturation biopsy detection rate by number of previous biopsies

Ref	No. of patients	Mean/median total PSA, ng/mL	Cores	Detection rate with *n* previous biopsy sets (%)			
				Overall	1	2	3
Transrectal route							
Borboroglu	57	8.7	23	30	–	30	–
Stewart	224	8.6	22.5	34	36	31	41
Fleshner	37	22.4	32–38	14	–	–	14
Rabets	116	9.2	22.8	29	33	25	22
Simon	40	12.2	64	45	54	32	50
Sajadi	82	9.1	24	20	16	20	33
Stav	27	12.2	62	11	–	–	11 (≥3)
Transperineal route							
Bott	60	12.9	24	38	–	43	11
Satoh	128	10.4	22	23	–	19	28
Merrick	102	9.1	51.1	42	55	39	30
Moran	180	9.3	41	38	56	37	3
Pepe	74	8.9	28	37	–	17	15
Taira	294	9.9	58	47	56	42	34
Novara	143	9.0	24	26	32	16	19

Table 15. Detection rates of enhanced US – targeted biopsies compared with standard biopsies

Ref	Strategy	N cores	Overall cancer detection	Cancer detection by targeted cores	Cancer detection by standard cores
Taverna	TRUS	13	29% (29/100)	-	29% (29/100)
	CD-US	13 (+1 sample from each suspicious area)	28% (28/100)	21% (6/28)	78.5% (22/28)
	CD-US plus SonoVue	13 (+1 sample from each suspicious area)	31% (31/100)	81% (25/31)	19% (6/31)
Remzi	Power Doppler US	8-16 (+1 sample from each abnormal area)	26% (9/35)	11% (1/9)	89% (8/9)
Taymoorian	ADF Doppler	8 cores (+2 targeted cores)	32% (30/95)	80% (24/30)	27% (8/30)
Ho	Contrast-enhanced US	5	23% (83/362)	69.9% (58/83)	57.8% (48/83)
Morelli	Power Dop-	NR	44% (4/9)	NR	NR

	pler US				

Table 16. Sensitivity and specificity rates reported in enhanced US biopsy studies

Ref		Colour Doppler US	Colour Doppler US plus SonoVue	Power Doppler US	ADF Broadband Doppler plus SonoVue
Taverna	Sensitivity (%)	23	54		
	Specificity (%)	68	42		
	Accuracy (%)	53	47		
Remzi	Sensitivity (%)			20	
	Specificity (%)			13	
Taymoorian	Sensitivity (%)				100
	Specificity (%)				48

Diagnostic process-related morbidity

Saturation biopsy

Twenty-seven studies reported complications related to the repeat saturation biopsy (see Table 17). Complications reported by Stav (2007) not included below due to no numbers being reported. All 27 patients undergoing transrectal saturation biopsy (mean cores = 61.7, range 41 to 76) reported mild and transient haematuria, hemospermia, and rectal bleeding. No patients required hospitalization or blood transfusion.

Table 17. Complications related to repeat saturation biopsies

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

[1] Includes Novara (2011) where 115/143 patients reported gross haematuria

Enhanced ultrasound

One of the included studies reported on diagnostic process-related morbidity. Taymoorian (2007) reported that there were no complications arising from the ADF Broadband Doppler US or biopsy protocol.

Repeat TRUS biopsy

One study reported complications in patients undergoing a repeat TRUS biopsy (Hambrock, 2010). Out of 248 patients they reported one TUR haemorrhage and one UTI.

Elastography

One study reported as an abstract only was included for this test. It did not report on diagnostic process-related morbidity.

Multiparametric MRI

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

Nelson et al (2013) found that MRI targeted re-biopsy required fewer cores (mean 9.8 cores) than transperineal (mean 30.4 cores) or transrectal (mean 24.0 cores) saturation re-biopsy.

Diagnostic process-related mortality

None of the included studies reported this outcome.

Health-related quality of life

None of the included studies measured this outcome. Mowatt et al (2013) included a cost effectiveness model which estimated the differences in quality adjusted life years between testing strategies. This model is discussed in the health economic evidence section for this topic.

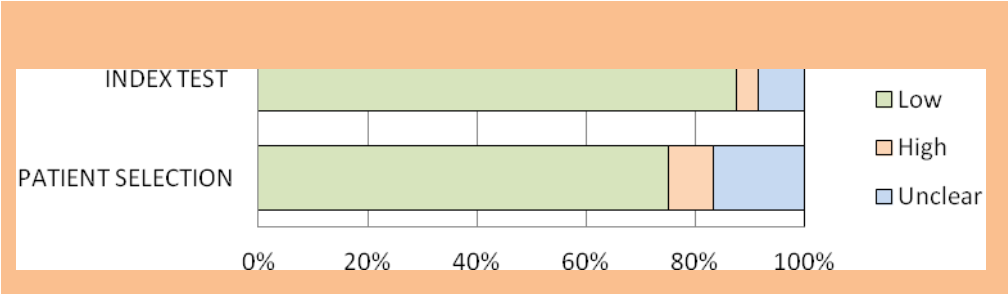
Quality appraisal

Selected criteria were used from the QUADAS-2 checklist for quality assessment. Namely, risk of bias in patient selection (was the sample representative, was the selection criteria clearly described) and risk of bias in the index test (was the repeat biopsy protocol described in sufficient detail).

Extended/saturation biopsy

Evidence for diagnostic yield came from 35 case-series studies and four cohort studies. Twelve studies were reported as abstracts only. All of the studies were considered to be applicable to the review question. Evidence from 38 studies included 16 studies reporting the results of repeat transrectal saturation biopsies only, 18 studies of repeat transperineal saturation biopsies only, two studies comparing transperineal and transrectal saturation biopsies (Abdollah, 2011; McCracken, 2011), two studies comparing extended versus saturation biopsies (Zaytoun 2011, 2012) and one study using both a transperineal and transrectal approach for repeat biopsies (Kawakami, 2007). A majority of the studies using a transperineal approach reported using a brachytherapy template under general anaesthetic. All studies report the results of repeat biopsies in men with one or more prior negative prostate biopsy. Indications for repeat biopsy generally included persistently elevated or rising PSA, abnormal DRE, or HGPIN or ASAP on previous biopsy. Risk of bias in patient selection and the index test was assessed as low in a majority of studies (see Figure 4). Patient selection criteria and biopsy protocol were generally clearly described. Most studies used a representative sample of patients, who were referred to repeat biopsy due to persistently elevated PSA levels and/or abnormal DRE despite previous negative biopsies.

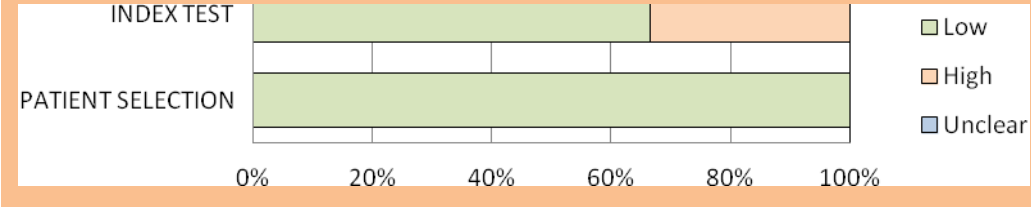
Figure 4. Proportion of extended/saturation biopsy studies with low, high, or unclear risk of bias (excludes studies reported as abstracts only)



Enhanced ultrasound (US) biopsy

Five studies were included which reported on the use of contrast-enhanced ultrasound for repeat prostate biopsies. Two of these were reported as abstracts only. One prospective cohort study (Morelli, 2009) and one prospective case series study (Remzi, 2004) reported utilising contrast enhanced Power Doppler transrectal ultrasound. One RCT (Taverna 2011) and one retrospective case series (Ho, 2009) used Colour Doppler ultrasound. One prospective case series study used the advanced dynamic flow (ADF) broadband Doppler technique with the contrast agent, SonoVue (Taymoorian, 2007). In all studies targeted biopsies were performed on hypervascularised areas identified in the gland. Remzi (2004) included 35 men with indications for repeat biopsy. Grey-scale TRUS and Power Doppler TRUS were performed before and during the biopsy to compare detection rates. Morelli (2009) compared elastosonography with Power Doppler ultrasound in 18 patients, and reported that all patents had suspected areas, with 3/9 cancers detected by targeted-biopsy after elastosonography and 4/9 cancers detected by targeted-biopsy after enhanced ultrasound. Figure 5 shows the results of the quality assessment.

Figure 5. Proportion of enhanced US biopsy studies with low, high, or unclear risk of bias (excludes studies reported as abstracts only)



Template guided biopsy

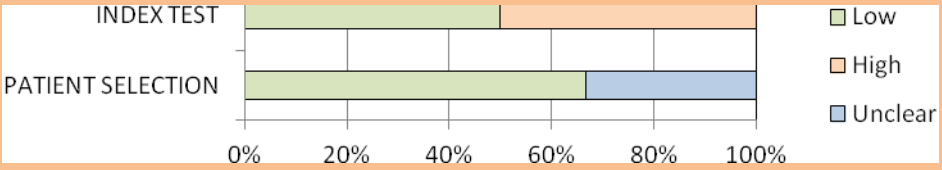
All studies of template guided biopsies used a saturation technique of more than 20 cores and are therefore included in the saturation guided biopsies section.

Repeat TRUS biopsy

Seven studies reporting the results of repeat TRUS were included. One study (Ho, 2009) was reported as abstract only. Two studies evaluated MRI-guided biopsy versus repeat standard

TRUS biopsy, and two studies evaluated contrast-enhanced ultrasound versus repeat standard TRUS. Data from the repeat standard TRUS group was extracted from these studies. In all the included studies patients had received one prior biopsy which was negative for prostate cancer. Indications for repeat biopsy were elevated PSA levels, abnormal DRE, or HGPIN/ASAP on previous biopsy. The quality assessment for these studies is shown in Figure 6. In three studies the index test was not well reported, due to the repeat TRUS data coming from the control group in studies of MRI or enhanced US guided biopsy. For example, in Hambrock (2010) the comparison group data was from a retrospective matched series of patients who had undergone at least two TRUS biopsies, and the details of the biopsy protocol are not provided.

Figure 6. Proportion of repeat TRUS biopsy studies with low, high, or unclear risk of bias (excludes studies reported as abstracts only)



Elastography biopsy

One study reported as an abstract only was included for this test (Morelli, 2009). This study compared nine men undergoing elastosonography rebiopsy with nine men undergoing contrast enhanced ultrasound rebiopsy. Not enough information was available for a quality assessment to be conducted.

Magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS) and transrectal ultrasound (TRUS)

Evidence about MRI, MRS and repeat TRUS came from a systematic review (Mowatt et al, 2013) including 51 studies and three further studies (Vourganti 2012; Portalez 2012; Arsov 2012). Eighteen studies in the Mowatt review reported diagnostic accuracy for MRS, 12 for dynamic contrast enhanced MRI (DCE-MRI), 11 for diffusion weighted MRI (DW-MRI), 26 for T2 weighted MRI and 23 for TRUS. Some of these studies also reported test combinations. Two of the new studies (Vourganti 2012; Portalez 2012) reported diagnostic yield for any multiparametric MRI. The third (Arsov 2012) used T1, T2, DWI and DCE MRI. Study quality was assessed using QUADAS 2 in the 42 studies published as full text papers. Mowatt et al (2013) had low concerns for applicability for the reference standard domain for all studies, however the reference standard was typically histopathology of image targeted cores plus a varying number of additional systematic cores. Thus the reference standard incorporates the index test and is also a potential source of bias given that the fewer additional systematic cores taken the better the apparent sensitivity of the imaging test. For this reason the sensitivity estimates calculated in Mowatt et al (2013) are maximum estimates – the true values could to be lower. Mowatt et al (2013) had low concerns for applicability for the patient selection domain in 37/39. Most of the studies (34/39) had low concern for applicability for the index test domain – in four studies applicability was questionable because the index test did not cover the entire prostate. Two studies (Vourganti 2012; Arsov 2012) were at risk of bias due to a potentially unrepresentative sample; having included patients were those with suspicious lesions on MRI.

Review of initial biopsy

One study was included for this test (Oxley and Sen, 2011). This study compared initial diagnosis by consultant pathologists with a reference standard diagnosis by consultant pathologists with a special interest in uropathology. The initial TRUS biopsy scheme varied from 6 to 12 cores in the non-screened population. There is potential issue with applicability since the men whose biopsies were reviewed did not necessarily have clinically suspected prostate cancer.

Evidence statements

Multi-parametric MRI targeted biopsy

Evidence suggests that a strategy in which only men with visible pathology on multi-parametric MRI were re-biopsied (using TRUS guided biopsy with both MRI targeted and systematic cores) would mean fewer men re-biopsied compared to a routine systematic re-biopsy strategy. The sensitivity for prostate cancer varies from around 79% to 96% depending on the MRI sequences used (see Table 12) - meaning that a proportion of cancers (approximately 4% to 21%) would be missed if such a testing strategy was used. (Mowatt 2013).

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

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

Extended/saturation biopsy:

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

Twenty-seven studies reported adverse events due to saturation biopsy (see Table 17). The pooled adverse event rates for transrectal saturation biopsy are 3.8% urinary retention, 5% rectal bleeding, 8.8% haematuria and 3.9% acute prostatitis. The corresponding rates for transperineal saturation biopsy are 6.8% urinary retention, 23.4% haematuria and 0.8% acute prostatitis.

Enhanced ultrasound biopsy:

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

Two studies reporting on Colour Doppler enhanced ultrasound gave a pooled cancer yield of 20.8% (117/562). Taverna (2011) compared Colour Doppler ultrasound with or without SonoVue against TRUS grey-scale 13-core systematic biopsy sampling, finding no differences in cancer detection rates between groups (29%vs28%vs31%).

Elastography:

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

Review of initial biopsy

A study of 3051 prostate biopsies in 2516 non screened men (Oxley and Sen, 2011) found that 1.2% of biopsies initially classified as benign were changed to cancer on review by a pathologist with special interest in uropathology. 1.5% of biopsies with an initial HGPIN diagnosis were changed to cancer on review and for biopsies an initial diagnosis of suspicious for malignancy the figure was 4.9%. Of those biopsies which were initially positive, 0.4% were changed to benign and 0.1% to suspicious.

Table 18. Summary of study characteristics - Transrectal saturation biopsy

Bx=Biopsy; SBx=Saturation biopsy; EBx=Extended biopsy; NR=not reported; UR=urinary retention; RP=radical prostatectomy; EBRT=external bean radiation therapy; BT=brachytherapy; WW=watchful waiting; TR=Transrectal; TP = Transperineal.; TZ= Transition zone. *Mean (range); †median (range);

Ref.	No. of patients	Mean age (range)	No. of previous Bx {n men}	Previous Bx approach	Mean PSA (range/SD) (ng/mL)	No. of cores†	Cancer detection rate	Complications, no. of patients	Definition of clinically significant disease	% significant disease	Treatment (n,%)	Comments
Borboroglu (2000)	57	61.4 (47-72)	2.1 (1–4)*	TRUS sextant	8.6 (5.4)	22.5 (15–31)*	30% (17/57)	6 UR; 1 rectal bleeding	tumour volume >0.5 cc	71	RP (13, 87);	1 patient PCa in TZ only
Stewart (2001)	224	64.2 (44-81)	1.8 (1–7)*	TRUS sextant	8.7†	23 (14–45)*	34% (77/224)	1 symptomatic bacteraemia; 12 haematuria; 10 UR	Patient age, Gleason grade + PCa doubling time (Dugen et al)	86% at RP	RP (52,68)	
Rabets (2004)	116	62 (47-83)	1.7 (1-7)*	22% sextant, 78% >6 cores	9.2 (1.7–48.6)	20–24	29% (34/116)	1 rectal bleeding; 2 lightheadedness	Gleason ≥6	92	RP (7,20); EBRT (4,12); BT (13,38); WW(4,12)	%Yield=41,31,22,25 and 30 when prior Bx 6,8,10,12, or 14 cores respectively
Fleshner (2002)	37	62.4 (39-75)	4.3 (3-6)*	TRUS including TZ	22.4 (7.8–73.8)†	30–36	14% (5/37)	7 acute prostatitis	Gleason ≥6	100	RP (1,20)	
Pryor (2002)	35 (+ TUR in 17)	(51-74)	2 {29} 3 {5} 5 {1}	TRUS sextant	4.5–46	21 (14–28)	37% (13/35)	NR	NR	NR	RP (7,54); EBRT (3,23); BT (2,15)	7 men with -ve TRUS/TUR biopsy had additional TRUS (45-60 cores). 5 cancers detected.
Walz (2006)	161	63.7 (43-84)	2.5 (2-7)*	≥8 cores	13.5 (3.3-125.7)	24.2 (18–32)	41% (66/161)	2 UR; 1 prostatitis; 1 reactive syncope	Clinically insignificant PCa - absence of high-grade components, tumour volume < 0.5 cc, pathologic organ confinement	84	RP (32,48); BT(9,14); EBRT (6,9)	
Abdollah (2011)	280 (TR= 140)	66.2 (48-82)	1 {67} 2 {52}, 3 {18} ≥4{3}	NR	9.7 (2.1-26.2)	24	31% (44/140)	NR	NR	NR	NR	
Patel (2004)	100	62.1 ± 7.9	1.65 (1-7)*	NR	9.4 (6.8)	20-24	25% (25/100)	1 prostatitis; 2 lightheadedness	Gleason ≥7	24	BT (12,48); RP (4,16); EBRT	Parasagittal cores detected Pca in 9 patients

Ref.	No. of patients	Mean age (range)	No. of previous Bx {n men}	Previous Bx approach	Mean PSA (range/SD) (ng/mL)	No. of cores†	Cancer detection rate	Complications, no. of patients	Definition of clinically significant disease	% significant disease	Treatment (n,%)	Comments
											(1,4)	
Sajadi (2007)	82	61 (43-76)	1 {43} ≥2 {39}	TRUS Median 8 cores (range 6-13)	9.1 (1-34)	24 (24-40)	19.5% (16/82)	NR	Gleason ≥6	89% (8/9 RP patients)	RP (10,63); EBRT (2,13); WW (3,19)	
Stav (2007)	27	62.1 (50-74)	3.48 (3-6)*	TRUS including TZ	19.4 (10.1-49)	61.7 (41-76)	11% (3/27)	1 asymptomatic bacteraemia; 27 bleeding complications; 2 epididymitis	NR	NR	RP (1, 33); WW (2, 66)	All patients reported mild and transient hematuria, hemospermia, and rectal bleeding
Simon (2008)	40	63 (48-72)†	2 (1–8)†	TRUS sextant	12.2†	64 (39–139)	45% (18/40)	16 haematuria	Gleason ≥7	50	RP (16,89); EBRT(1,16); BT (1,16)	Absolute number of cores = 1 or 2 cores/mL prostate volume
Zaytoun (2011)	1056 (393 EBx, 663 SBx)	64.3 (41-84)	All had 1 previous -ve biopsy	167 sextant, 889 extended	6.43 (0.3-19.65)	EBx: 12-14 cores; SBx 20-24 cores	29.8% (315/1056). 25% EBx, 33% SBx	NR.	Gleason ≥7, >3 positive cores, >50% cancer in any positive core	62	NR	In prior report of 1438 men TRUS (10-20 cores) 2.2% sepsis, 4.4% haematuria, 0.8% UR, 0.2% sepsis
Zaytoun (2012)	479 (347 EBx, 402 SBx)	64.7 (42-86)	2.6 (2-8)*	53% EBx, 47% SBx	11.4	EBx 12-14 cores; SBx ≥20 cores	25% (119/479). 19% SBx, 13% EBx	NR	Gleason ≥7, >3 positive cores, >50% cancer in any positive core	37 (25% SBx, 43% EBx)	NR	
Giulianelli (2011)	140	67.3	1	TR	(2.5-9.9)	24	36% (50/140)	3 severe rectal bleeding; 12 haematuria; 76 haemospermia; 8 prostatitis; 3 UTI	Gleason ≥7, tumour volume >0.5cc	94	RP (48, 96); EBRT (2,4)	70% PCa detected in anterior horn of peripheral zone
TP template and TR biopsy												
Kawakami (2007)	235	67 (61-71)†	1 (1-2)†	139 sextant, 96 12-cores	8.3 (5.8-12.2)†	26 (12 TR+14 TP)	37% (87/235)	2 acute prostatitis; 1 UR	Gleason 4/5 cancer	52	NR	Of the 87 cancers detected, 46 (53%), 69 (79%), and 71

Ref.	No. of patients	Mean age (range)	No. of previous Bx {n men}	Previous Bx approach	Mean PSA (range/SD) (ng/mL)	No. of cores†	Cancer detection rate	Complications, no. of patients	Definition of clinically significant disease	% significant disease	Treatment (n,%)	Comments
												(82%) cancers had positive cores within the TR6, TR12, and TP14 sampling sites, respectively
Abstract only												
Auprich (2010)	302	NR	NR	Assume 10 core	NR	24	36% (109/302)	NR	Gleason ≥7	40	NR	7.3% patients PCa in TZ only
Cole (2012)	64	65	1.7*	Mean 19 core	11.5 (9.8-13.3)	26 (17-38)	34% (22/64)	NR	Gleason ≥7	23	NR	No isolated TZ cancers. 3% AZ cancer only
Kanaroglou (2010)	33	65	2 (1-4)†	Mean 21 core	12.4	27 (17-42)	33% (11/33)	1 UR; 1 hematuria	NR	NR	NR	TZ cancer in 3 men, AZ cancer in 8. All positive AZ biopsies were significant
Scattoni (2010)	354	NR	NR	10-14	9.0 (15.2)	24	26% (91/354)	NR	NR	NR	NR	
McCracken (2011)	50	65 (52-77)	NR	NR	NR	18 (11-24)	22% (11/50)	4 UTI; 1 UR; 2 haematuria	NR	NR	NR	

Table 19. Summary of study characteristics - Transperineal template saturation biopsy

Bx=Biopsy; SBx=Saturation biopsy; EBx=Extended biopsy; NR=not reported; UR=urinary retention; RP=radical prostatectomy; EBRT=external bean radiation therapy; BT=brachytherapy; WW=watchful waiting; TR=Transrectal; TP = Transperineal.; TZ= Transition zone. *Mean (range); †median (range);

Ref.	No. of patients	Mean age (range)	No. of previous Bx {n men}	Previous Bx approach	Mean PSA (range/SD) (ng/mL)	No. of cores†	Cancer detection rate	Complications, no. of patients	Definition of clinically significant disease	% significant disease	Treatment (n,%)	Comments
Pinkstaff (2005)	210	66.3 (46-81)	1 {40} ≥2 {170}	TR	13.6 (10.2)	21.2 (12-41)*	37% (77/210)	24 UR	Gleason ≥7	45	RP (30,39); RT (16,21); WW (4,5)	46% PCa exclusively found in TZ
Abdollah (2011)	280 (TP=140)	66.4 (52-79)	1 {85}, 2 {37}, 3 {14}, ≥4 {4}	NR	10 (0.9-31.5)	24	26% (36/140)	NR	NR	NR	NR	
Satoh (2005)	128	67 (37-85)†	1 (1-5)*	TRUS Median 6 cores (range 4-12)	10.4 (2.4-170)†	22	23% (29/128)	1 acute prostatitis; 2 UR; 2 difficult urination	NR	NR	NR	Anterior core rates sig greater than posterior core rates
Novara (2010)	143	66.5 (6.1)	1.6 (0.8)*	12 cores	9 (6.1-12.8)	24	26% (37/143)	115 gross hematuria; 95 haematospermia; 4 UR; 12 UTI	Gleason ≥7	25	RP (21, 57)	
Bott (2006)	60	64 (6.4)	2 (2-8)†	Octant biopsies	12.9 (4.6-35.7)†	24 (18-36)	38% (23/60)	1 haematuria; 2 UR	≥2 cores containing PCa	92	NR	Cancer detected in anterior third in 12 men (60%), in anterior & mid region in 2 men (9%), in mid & posterior area in 4 (17%), only in posterior third in 4 (17%), and in anterior, mid & posterior zones in 1 (4%).
Moran (2006)	180	63.1 (44-81)	1.8 (1-6)*	TR, Median 12-cores (range 5-22)	9.3 (0.8-40.1)	41 (13-117)	38% (68/180)	18 UR	NR	NR	NR	There were no significant differences in the number of malignant cores in each of the octants, quadrants (anterior base, posterior base, anterior apex, posterior apex) and halves (base, apex, anterior, posterior)
Igel (2001)	88	65 (54–79)	100% had at least 1, 85% had	Mean 15.1 previous TR cores	13.1 (8.7)	17*	43% 38/88	2 UR; 3 haematuria; 1 UTI	T2A or B disease	53% (8/15)	RP (15,39)	76% TZ, 37% periphral, 16% lateral peripheral, 39% TZ only

Ref.	No. of patients	Mean age (range)	No. of previous Bx {n men} ≥2	Previous Bx approach	Mean PSA (range/SD) (ng/mL)	No. of cores†	Cancer detection rate	Complications, no. of patients	Definition of clinically significant disease	% significant disease	Treatment (n,%)	Comments
Pepe (2012)	74	64 (48-74)†	1	Extended median 18 cores	8.9 (4.5-10)†	28 (24-34)	37% (27/47)	NR	Gleason ≥6 and/or cancer volume >0.5ml	100	RP (27, 100)	Number of men offered active surveillance not reported
Pal (2011)	40	63(49-73)	2 (2-5)†	Mean cores =11.6 (10-18)	21.9 (4.7-119)	36	68% (27/40)	1 UR	Gleason ≥7	41	NR	44% cancer involved anterior zone
Mabjeesh (2012)	92	63.8 (5.8)	2.7 (1.1)*	TR 10-12 cores	14.1 (9.4)	30 (24-54)	26% (24/92)	1 sepsis after UR	Gleason ≥7	46	NR	83% men cancer found in anterior zones
Merrick (2007)	102	64.8 (50-80)	2.1 (1.1)*	TRUS mean 22.4 cores	9.1 (2.8-32.8)	50 (24-66)	42% (43/102)	1 haematuria; 9 required urinary catheter	Gleason ≥7, >3 positive cores, >50% in any positive core	93	NR	76% would be diagnosed with 12-core BPx
Taira (2010)	294	63.8	1 {146} 2 {84} ≥3 {64}	12-38 cores	9.9	58	47% (138/294)	NR	Gleason ≥7, >3 positive cores, >50% in any positive core	89	NR	In men with ≥2 previous biopsies cancer most frequent in anterior aspects of gland
Abstract only												
Honda (2009)	59	NR	NR	NR	NR	17-78	44% (26/59)	3 UR	Gleason ≥7 and/or tumour volume ≥0.5cm^3	73	RP (16, 62)	Pca detected in TZ in 69% specimens
Ekwueme (2010)	50	64 (43-82)	2 (1-4)†	TR	11 (2-66)†	27 (16-41)*	72% (36/50)	0	Gleason ≥7	80	NR	Modified SBx avoids periutheral area at base. 76% Pca in anterior third
Lacetera (2011)	3	NR	NR	NR	NR	50-124	66% (2/3)	2/6 moderate hematuria; 1/6 UR	NR	1 patient pT2c N0R0	1 RP; 1 RT	Complications include 3 men with low-risk cancer undergoing 3D-TTPSB for staging

Ref.	No. of patients	Mean age (range)	No. of previous Bx {n men}	Previous Bx approach	Mean PSA (range/SD) (ng/mL)	No. of cores†	Cancer detection rate	Complications, no. of patients	Definition of clinically significant disease	% significant disease	Treatment (n,%)	Comments
McCracken (2011)	100	62.9 (37-75)	NR	NR	NR	44 (24-65)	46% (23/50)	5 UR; 1 haematuria	NR	NR	NR	26% TP template cancers had apical cancer alone
Vassilios (2011)	22	65 (48-84)†	≥1	TR	6.22 (2.68-29)†	44 (18-75)	41% (9/22)	3 UR	NR	NR	NR	Complications refer to whole sample (n=67)
Rowley (2011)	41	NR	2.78 (1.46)*	NR	NR	Dependant on prostate size	54% (22/41)	3 UR; 4 Haematuria; 1 atrial fibrillation	Gleason ≥7	34		80% in anterior zone, 22% posterior zone
Gershman (2011)	16	64.6 ±4.4	3.6 (2-7)*	NR	23.8 ±16.1	22.8 ±8.5*	56% (9/16)	NR	NR	NR	RP (4,44); AS (1,11); RT (2,22)	90% cancer in anterior prostate
Hameed (2011)	69	NR	2	NR	15.35 (3.7-44.1)	40 (19-128)	56% (39/69)	11 UR; 3 haematuria; 2 septicaemia	NR	NR	NR	44% TZ, 46% PZ, 13% midline

Table 20 Enhanced Ultrasound

Bx=Biopsy; SBx=Saturation biopsy; EBx=Extended biopsy; NR=not reported; UR=urinary retention; RP=radical prostatectomy; EBRT=external bean radiation therapy; BT=brachytherapy; WW=watchful waiting; TR=Transrectal; TP = Transperineal.; TZ= Transition zone. *Mean (range); †median (range);

Ref.	No. of patients	Mean age (range)	No. of previous biopsies {n men}	Previous biopsy technique	Mean PSA (range/SD) (ng/mL)	Repeat PBx approach	No. of cores†	Cancer detection rate	Complications, no. of patients	% sig disease	Treatment (n,%)	Comments
Taverna (2011)	300	65.9 (45-76)†	NR (assume 1)	TRUS grey-scale	6 (2.5-9.9)†	Colour Doppler ultrasonography with and without Sonovue vs grey scale TRUS	13 (unless identified hypervascular areas)	29% (88/300) *ns between groups.* 29% TRUS, 28% Doppler US, 31% US+Sonovue	NR	NR	NR	

Taymoorian (2007)	95	66 (44-73)	2.4 (1-8)*	TRUS	10 (4-48)	ADF Doppler with echo enhancer SonoVue	8 without suspicious areas, 10 with vascular abnormalities	32% (30/95)	None	NR	NR	
Remzi (2004)	35	66 (8.5)	1	TRUS	6.45 (2.7)	Power Doppler TRUS	8-16 cores using Vienna nomogram	26% (9/35)	NR	NR	NR	
Abstract only												
Ho (2009)	362	60.7 (48-79)	1	NR	6.51 (3.12-14.65)	Contrast enhanced US vs. systematic TRUS	Contrast enhanced=5 cores, TRUS=10 cores	23 (83/362). Enhanced US 16% (58/362), TRUS 13% (48/362)	NR	NR	NR	
Morelli (2009)	18	68.2	NR	NR	NR	Elastosonography vs. Power Doppler TRUS	NR	33% (3/9) elastosonography, 44% (4/9) enhanced US	NR	NR	NR	

Table 21. Repeat TRUS biopsy

Bx=Biopsy; SBx=Saturation biopsy; EBx=Extended biopsy; NR=not reported; UR=urinary retention; RP=radical prostatectomy; EBRT=external bean radiation therapy; BT=brachytherapy; WW=watchful waiting; TR=Transrectal; TP = Transperineal.; TZ= Transition zone. *Mean (range); †median (range);

Ref.	No. of patients	Mean age (range)	No. of previous biopsies	Previous biopsy technique	Mean PSA (range/SD) (ng/mL)	Repeat PBx approach	No. of cores†	Cancer detection rate	Complications, no. of patients	Definition of clinically significant disease	% significant disease	Treatment (n,%)	Comments
Campodonico (2006)	81	67 (34-94)	1	TRUS 10-core	1.2-40	TRUS-10 core lateral PZ	10-core if PSA<10, 12-core if PSA>10	20% (16/81)	NR	NR	NR	NR	
de la Rosette (2009)	139	62.3 (7.3)	1	8-core lateral (n=76); 12-core (n=63)	5.5 (1.1-34.1)†	12-core TRUS (4TZ)	12	14% (20/139)	NR	NR	NR	NR	30% had positive cores from TZ only. No anasthesia used.
Grepl (2009)	191	63.6 (42-76)	1	TR, median 12 cores	11.9 (2.6-47.5)	same as previous Bx	12 (dependant on prostate volume)	21% (39/191)	NR	NR	NR	NR	

Sciarra (2012)	84	63.2 (46-75)	1	10 core random lareally directed TRUS	6.89 (4.1-13.1)	same as previous Bx	10	31% (26/84)	NR	Gleason score ≥7 (4+3)	27	NR	Data from trial evaluating MRI and PCA3 test
Hambrock (2010)	248	64 (47-80)	1	8-10 cores, including TZ	8 (0.1-63)†	same as previous Bx	8-10	22% (55/248)	1 TUR hemorrhage; 1 UTI	NR	NR	NR	Data from reference group in trial evaluating MRI guided biopsy
Taverna (2011)	100	65.9 (45-76)†	NR (assume 1)	TRUS grey-scale	6 (2.5-9.9)†	Grey scale TRUS	13	29% (29/100)	NR	NR	NR	NR	Data from trial of enhanced US
Abstract only													
Ho (2009)	362	60.7 (48-79)	1	NR	6.51 (3.12-14.65)	Systematic TRUS	10 cores	13% (48/362)	NR	NR	NR	NR	Data from study of enhanced US

Table 22. Review of initial biopsy

Bx=Biopsy; SBx=Saturation biopsy; EBx=Extended biopsy; NR=not reported; UR=urinary retention; RP=radical prostatectomy; EBRT=external bean radiation therapy; BT=brachytherapy; WW=watchful waiting; TR=Transrectal; TP = Transperineal.; TZ= Transition zone. *Mean (range); †median (range);

Ref.	No. of patients	Mean age (range)	No. of previous biopsies	Initial biopsy technique	Mean (range/SD) PSA level, ng/mL	Repeat PBx approach	Diagnosis changed to cancer on review	Complications (N)	Definition of clinically significant disease	% significant disease	Treatment (n,%)	Comments
Oxley (2011)	3051 biopsies in 2516 unscreened patients	Not reported	1	TRUS 6 to 12 cores	Range <20 to > 500 µg/ml	Not applicable	Men with initial benign diagnosis: 15/1244 (1.2%) Men with initial Atypia diagnosis: 0/27 (0%) Men with initial HGPIN diagnosis: 5/329 (1.5%) Men with initial suspicious diagnosis: 4/81 (4.9%) Men with any non-cancer diagnosis on initial biopsy: 24/1681 (1.4%)	NA	NA	NA	NA	

Table 23.MRI targeted biopsy

Bx=Biopsy; SBx=Saturation biopsy; EBx=Extended biopsy; NR=not reported; UR=urinary retention; RP=radical prostatectomy; EBRT=external bean radiation therapy; BT=brachytherapy; WW=watchful waiting; TR=Transrectal; TP = Transperineal.; TZ= Transition zone. *Mean (range); †median (range);

Ref.	No. of patients	Mean age (range)	No. of previous biopsies	Initial biopsy technique	Mean (range/SD) PSA level, ng/mL	Repeat PBx approach	Diagnosis changed to cancer on review	Com-plic-ations (N)	Definition of clinically significant disease	% sig-nifi-cant disease	Treat-ment (n,%)	Com-ments
Vourganti (2012)	195	Median = 62 (37-80)	Median = 2 (1-9)	TRUS: 12 cores	Median = 9.1 (0.3-103)	mpMRI/US fusion	Men with initial suspicious lesion on MRI: 28/150 (18.7%)	NR	NA	NR	NR	
Portalez (2012)	129	64.7 (47-79)	Mean = 1.3 (1-4)	TRUS	9.6 (2.7-40.0)	mpMRI/US fusion: both targeted & random cores taken	Men with initial negative diagnosis: 56/129 (43.4%) Men with initial negative diagnosis & no cancer on rebiopsy with TRUS: 35/129 (27.1%)	NR	NA	NR	NR	
Arsov (2012)	58	Median = 67	≥ 1 (1-6)	TRUS: ≥ 10 cores	Median = 9.3 (4.6-108.0)	mpMRI/US fusion: both targeted & random cores taken	Men with initial negative diagnosis & suspicious lesion on MRI: 11/16 (68.8%)	NR	NR	100	RP (8,73), RT or AS (3,27)	
Lee (2012)	87	Median = 67	Mean = 2 (1-4)	TRUS: 12 cores	7.9 / 9.5	mpMRI/US fusion: 12 random & ≤ 14 targeted	Men with initial suspicious lesion on MRI: 46/82 (56.0%)	NR	NR	94	NR	

Table 24. Systematic reviews

Ref.	No. of patients	Inclusion criteria	No. of previous biopsies	Initial biopsy technique	Repeat PBx approach	Number of cores	Cancer yield	Complications (N)	Comments
Mowatt et al (2013)	51 studies (over 10,000 patients)	Studies published before March 2012, in men with one or more negative TRUS biopsies and ongoing suspicion of prostate cancer – where mp-MRI was used to guide re-biopsy.	At least 1	6 or less cores: 11 studies 8 to 12 cores: 11 studies 29 studies did not report this	See Table 1.	Not analysed	Not reported – see Table1 for sensitivity and specificity.	10 studies reported serious adverse events including prostate haemorrhage (5% in one study), severe vasovagal episodes (1.4% to 1.5%), sepsis or fever (0.4% to 2.3%), acute urinary retention (2.3%), severe rectal bleeding (0.1% to 0.5%).	Study quality assessed using QUADAS
Nelson et al (2013)	46 studies (4657 patients)	Studies published 1995 to Jan. 2012, in men with one or more negative TRUS biopsies and ongoing suspicion of prostate cancer	TP-B: mean 1.5 TS-B: mean 1.8 MRI-B: mean 1.9	TRUS – cores not reported	TP-B: 14 studies TS-B: 12 studies MRI-B: 20 studies	TP-B: mean 30.4 TS-B: mean 24.0 MRI-B: mean 9.8	TP-B: 36.8% TS-B: 30.0% MRI-B: 37.6%	N.R.	Quality of included studies not addressed formally. Type of MR-sequence used is not analysed

Abbreviations: TP-B, transperineal saturation biopsy; TS-B, transrectal saturation biopsy; MRI-B, MRI guided biopsy

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Health Economic Evidence

Information sources and eligibility criteria

The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, COCHRANE, NHS EED. Studies conducted in OECD countries other than the UK were considered (Guidelines Manual 2009).

Studies were selected for inclusion in the evidence review if the following criteria were met:

Both cost and health consequences of interventions reported (i.e. true cost-effectiveness analyses)

Conducted in an OECD country

Incremental results are reported or enough information is presented to allow incremental results to be derived

Studies that matched the population, interventions, comparators and outcomes specified in PICO

Studies that meet the applicability and quality criteria set out by NICE, including relevance to the NICE reference case and UK NHS

Note that studies that measured effectiveness using quality of life based outcomes (e.g. QALYs) were desirable but, where this evidence was unavailable, studies using alternative effectiveness measures (e.g. life years) were considered.

Selection of studies

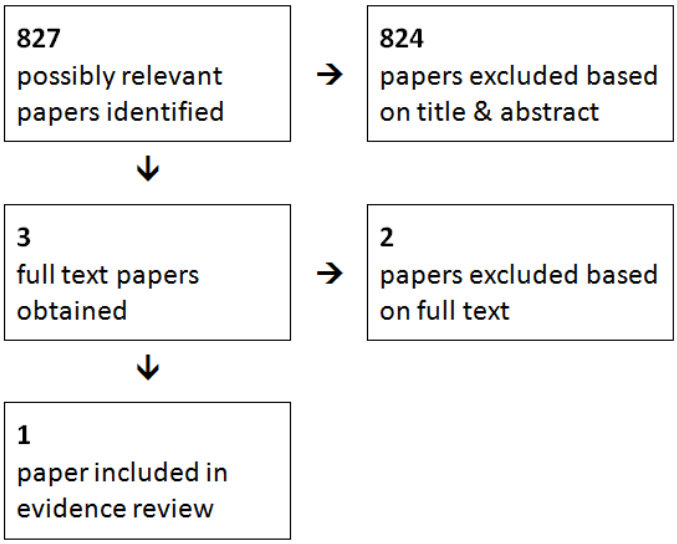
The health economist screened the literature search results obtained by the information specialist by checking the article's title and abstract for relevance to the review question. The full articles of non-excluded studies were then attained for appraisal and compared against the inclusion criteria specified above.

Results

The diagram below shows the results of the search and sifting process. It can be seen that 827 possibly relevant papers were identified. Of these, three full papers relating to this topic were obtained for appraisal. A further two papers were excluded as they were not applicable to the PICO or did not include an incremental analysis of both costs and health effects. Therefore only one paper (Mowatt et al. 2013) was included in the current review of published economic evidence for this topic.

Mowatt et al. 2013 was a comprehensive report conducted as part of the NIHR HTA programme. The study included a cost-effectiveness analysis where effectiveness was measured using quality adjusted life years (QALYs) i.e. a cost-utility analysis

Evidence search results



Quality and applicability of the included study

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

Table 25. Table showing methodological quality and applicability of the included study

Methodological quality	***Applicability***	
	Directly applicable	**Partially applicable**
Minor limitations	Mowatt et al. 2013	
Potentially serious limitations		
Very serious limitations		

Modified GRADE table

The primary results of the analysis by Mowatt et al. 2013 are summarised in the modified GRADE table below.

Table 26. Modified GRADE table showing the included evidence (Mowatt et al. 2013) comparing subsequent investigation methods following an initial negative biopsy

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
Mowatt et al. 2013 (NIHR HTA)	Men with suspected prostate cancer and elevated prostate specific antigen (PSA) but previously negative biopsy.	Systematic TRUS	£3,895	12.48432 QALYs	Reference case			Numerous one-way sensitivity analyses were conducted in areas of interest to the authors. The results showed the results to be highly sensitive to the input parameters and assumptions made. Depending on the scenario modelled, T2-MRI, systematic TRUS or MRS might be the most cost-effective option. Probabilistic sensitivity analysis (PSA) was also conducted. None of the diagnostic strategies were found to have a high probability of being preferred on the grounds of cost-effectiveness. At a willingness to pay threshold of £20,000 per QALY, each intervention had the following probability of being cost-effective†: Systematic TRUS - 51% T2-MRI - 33% MRS - 15% DCE-MRI - 1% T2-MRI or MRS - 0% T2-MRI or DCE-MRI - 0% Note that as DW-MRI was not considered part of the base case it was not included in the probabilistic sensitivity analysis.	Minor limitations. No applicability issues.
		T2-MRI	£3,902	12.48498 QALYs	£7	0.00066 QALYs	£10,626 per QALY		
		DW-MRI*	£3,943	12.48629 QALYs	£48	0.00197 QALYs	£24,221 per QALY		
		MRS	£3,952	12.48630 QALYs	£57	0.00198 QALYs	£28,502 per QALY		
		DCE-MRI	£3,984	12.48346 QALYs	£1	-0.00086 QALYs	Dominated		

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
		T2-MRI or MRS	£4,031	12.48714 QALYs	136	0.00282 QALYs	£48,367 per QALY		
		T2-MRI or DCE-MRI	£4,056	12.48538 QALYs	161	0.00106 QALYs	£152,323 per QALY		
	Comments: For simplicity ICER results have been presented in comparison to a common baseline (systematic TRUS). To find the most cost-effective diagnostic strategy a dominance rank should be used or the net monetary benefit (NMB) should be calculated.								

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

Evidence statements

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

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

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

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

References

Mowatt G, Scotland G, Boachie C, Cruickshank M, Ford JA, Fraser C, Kurban L, Lam TB, Padhani AR, Royle J, Scheenen TW, Tassie E. “Systematic review of the diagnostic accuracy and cost-effectiveness of magnetic resonance spectroscopy and enhanced magnetic resonance imaging techniques in aiding the localisation of prostate abnormalities for biopsy.” Aberdeen HTA Group, Institute of Applied Health Sciences, University of Aberdeen, 2013.

Full evidence table

The full details of the study included in the evidence review are presented in the evidence table below.

Table 27. Full evidence table showing the included evidence (Mowatt et al. 2013) comparing subsequent investigation methods following an initial negative biopsy

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Study 1						
Author: Mowatt et al. **Year:** 2012 **Country:** UK	**Type of analysis:** Cost-effectiveness analysis (CEA) **Model structure:** Markov cohort model **Cycle length:** Three months **Time horizon:** 30 years **Perspective:** Third party payer perspective (NHS) **Source of base-line data:** In the base case, the underlying cancer prevalence rate was sourced from a study identified in the literature review. It's based on a cohort of patients with a previous benign biopsy result but persistently elevated prostate-specific antigen (>4ng/ml) and/or abnormal DRE. Alternative cancer prevalence rates were applied in several sensitivity analyses. These were also sourced from the literature identified in the systematic review. Men with cancer were initially spread across the undiagnosed cancer states in the model. This was based on the reported Gleason scores in the studies included in the systematic review plus other available data on the clinical and/or pathological stages/ grades of cancers detected at second biopsy. **Source of effectiveness data:** The sensitivity and specificity of the vari-	**Inclusion criteria:** Men with suspected prostate cancer and elevated prostate specific antigen (PSA) but previously negative biopsy. **Exclusion criteria:** Not reported **Base case (population):** Men with suspected prostate cancer and elevated prostate specific antigen (PSA) but previously negative biopsy. **Sample size:** The size of the hypothetical cohort is not stated. **Age:** Base case results are presented for men aged 60 and 70 years old. **Gender:** Men **Subgroup analysis:** Subgroup analysis is conducted in patients of different ages (60 and 70) with varying underlying prevalence of prostate cancer.	A. Systematic TRUS B. T2-MRI C. MRS D. DCE-MRI E. T2-MRI or MRS F. T2-MRI or DCE-MRI	**Average QALYs:** Systematic TRUS T2-MRI MRS DCE-MRI T2-MRI or MRS T2-MRI or DCE-MRI **Average cost:** Systematic TRUS T2-MRI MRS DCE-MRI T2-MRI or MRS T2-MRI or DCE-MRI **ICER results (cost per QALYs) in comparison to common baseline (systematic TRUS):** T2-MRI MRS DCE-MRI T2-MRI or MRS T2-MRI or DCE-MRI **ICER results (cost per QALYs) using dominance rank:** T2-MRI in comparison to systematic TRUS MRS in comparison to T2-MRI DCE-MRI in comparison to MRS T2-MRI or MRS in comparison to MRS T2-MRI or DCE-MRI in comparison to T2-MRI or MRS **Uncertainty:** **One-way and two-way sensitivity analysis:** Numerous one-way and two-way sensitivity analyses were conducted in areas of interest to the authors.	12.48432 12.48498 12.48630 12.48346 12.48714 12.48538 £3,895 £3,902 £3,952 £3,984 £4,031 £4,056 £10,626 £28,502 Dominated £48,367 £152,323 £10,626 £37,382 Dominated £95,481 Dominated	**Funding:** This report was commissioned by the NIHR HTA Programme **Comments** Authors had no competing interests.

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	ous MRI/MRS diagnostic strategies were sourced from the systematic review. The sensitivity and specificity of systematic extended cores were sourced from a published study (Scattoni et al. 2011). The probability associated with developing complications following prostate biopsy was based on the ProtecT trial (Rosario et al. 2012). In addition, probabilities relating to hospital admission (such as probability of admission, consultation and location of consultation etc.) were also based on the ProtecT trial. Patients in a cancer state were assumed to be at risk of progressing towards metastatic disease. The progression risk for localised cancer was based on data reported by Bill Axelson et al. The progression risk for men in the locally advanced state was based on data from a European Organisation for Research and treatment of Cancer (EORTC) study reported by Bolla et al. Weibull functions were fitted to the data to derive three-monthly transition probabilities for developing metastatic disease. For patients with metastatic disease, a constant three-monthly risk of death from prostate cancer was estimated from English observational data. The age-specific risk of death from other causes was based on age and sex specific UK life tables (Office for National Statistics 2012). **Source of utility data:** Authors assumed that patients with no cancer or undiagnosed localised cancer have the same utility as prostatectomy patients at baseline.			Given the number of sensitivity analyses conducted and the number of comparators considered, the full list of ICER results will not be reproduced here. Rather the most cost-effective diagnostic method will be listed for each scenario (as identified by the authors who appear to use a WTP = £30,000 per QALY). **The following one-way and two-way sensitivity analyses were performed (list is not exhaustive):** **60 year old men** Prevalence = 50% Prevalence = 10% **70 year old men** Prevalence = 50% Prevalence = 10% **Alternative utility values:** 1. Additional utility decrement for persistently elevated PSA without a diagnosis 2. Multiplicative model to further adjust for adverse treatment effects 3. Combination of utility scenarios 1 and 2 Increased pathology cost for TRUS-guided biopsies and NHS reference costs used for MRI/MRS Sensitivity of MRS adjusted to only miss low risk cancer Comparator for MRI/MRS assumed to be a 10-12 core TRUS biopsy with the lowest sensitivity value. Sensitivity/specificity estimates obtained from	**Most cost-effective diagnostic method** MRS T2-MRI Systematic TRUS T2-MR MRS Systematic TRUS T2-MRI MRS	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Quality of life in patients with localised cancer was characterised using EQ-5D utility weights reported for a cohort of patients undergoing prostatectomy (utilities at baseline, 6 months, 1 and 4 years). For prostate cancer found to be locally advanced and for local recurrence following initial treatment, utility weights from another published study (Korfage). This study evaluated patients undergoing EBRT (cohort was slightly older and with more advanced disease than in the study used for localised cancer). For patients with metastatic disease, an average of the time trade-off weights for metastatic and castration resistant metastatic disease was applied (elicited from a sample of 45-70 year old males with no history of prostate cancer presenting at primary care medical facility in the US). The authors state that the study by Korfage included a cohort of patients where a substantial proportion of patients experienced the main complications associated with prostatectomy or EBRT. Thus, in the base case, further utility decrements associated with adverse events were not included. Further utility decrements were considered in the sensitivity analysis. **Source of cost data:** The costs associated with TRUS guided biopsies, open radical prostatectomies and EBRT (including its use as salvage therapy) were sourced from NHS reference costs 2009-2010. The costs associated with performing MRI sequences to guide biopsies were estimated using a bottom-up costing ap-			the indirect comparison Assumed a 14 core TRUS biopsy is £86 more than MRI/MRS-directed biopsy, and £112 more than MRS scan. Assumed that MRI/MRS-directed biopsy reduces the risk of biopsy complications by 50% Subsequent repeat biopsies have 95% sensitivity with 80% uptake Lower discount rate (1.5%) for QALYs Lower baseline risks of progression (calibrated to PIVOT trial) Use extended 14 core biopsy for all patients negative on MRI/MRS **Probabilistic sensitivity analysis (PSA):** **Mean QALY results from probabilistic analysis:** Systematic TRUS T2-MRI MRS DCE-MRI T2-MRI or MRS T2-MRI or DCE-MRI **Mean cost results from probabilistic analysis:** Systematic TRUS T2-MRI MRS DCE-MRI T2-MRI or MRS T2-MRI or DCE-MRI **ICER results (cost per QALYs):** T2-MRI in comparison to systematic TRUS MRS in comparison to T2-MRI DCE-MRI in comparison to MRS	MRS T2-MRI T2-MRI T2-MRI T2-MRI T2-MRI T2-MRI T2-MRI Systematic TRUS 12.47303 12.47357 12.47478 12.47213 12.47562 12.47392	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	proach. The time taken to perform the MRI sequences was estimated by radiologists involved in the project. This was then multiplied by the relevant unit costs associated with the treatment, which were sourced from Curtis' Unit Costs of Health and Social Care (2010). Unit costs included capital equipment, salaries, 'oncosts' and an apportionment of capital space and overhead costs. Cost per unit of time (e.g. cost per minute of scanning) were estimated using current market prices obtained from NHS Grampian, which were then annuitized and discounted (to account for depreciation) and divided by its estimated runtime. The costs associated with hormone therapy were calculated using unit cost and dosages from the British National Formulary 63rd edition (BNF 63). **Currency unit:** UK pound sterling (£) **Cost year:** 2009/2010 financial year **Discounting:** 3.5% per annum Alternative discount rates were considered in the sensitivity analysis.			T2-MRI or MRS in comparison to MRS T2-MRI or DCE-MRI in comparison to T2-MRI or MRS **ICER results (cost per QALYs) in comparison to common baseline (systematic TRUS):** T2-MRI MRS DCE-MRI T2-MRI or MRS T2-MRI or DCE-MRI	£3,910 £3,916 £3,967 £3,999 £4,045 £4,069 £12,315 £41,927 Dominated £92,865 Dominated £12,315 £32,811 Dominated £52,378 £178,746	

2.3 Staging classification for prostate cancer

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?

Short Summary

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

Two studies (reviewed in (National Institute for Clinical Excellence, Improving Outcomes in Prostate Cancer Guidance, 2002)) showed better staging accuracy with MRI than with CT. Other systematic reviews have considered the staging accuracy of MRI (Engelbrecht *et al.* 2002; Sonnad *et al.* 2001) and CT (Abuzallouf *et al.* 2004) separately. There was contradictory evidence, from small observational studies, about the benefit of adding of MRS to MRI.

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

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

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Men with clinically localized prostate cancer ▪ for whom radical treatment is intended ▪ who opt for active surveillance	• MRI • MRI • CT • MRI • Isotope Bone Scan • Chest X-Ray	• CT • No MRI • No CT • MRI + MRS • No Isotope Bone Scan • No Chest X-Ray	▪ Staging accuracy ▪ Influence on management ▪ Cost-effectiveness

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

Evidence Summary

MRI vs. CT for staging

The systematic review conducted for the NICE improving outcomes in urological cancers guidance (National Institute for Clinical Excellence 2002) identified only two studies directly comparing MRI and CT for the staging of prostate cancer. Both studies showed increased accuracy of MRI over CT for the detection of seminal vesicle involvement (SVI) and pelvic lymph node involvement (LNI). One of the studies reported increased accuracy of MRI over CT for the detection of extracapsular extension (ECE). Both studies, however, had methodological weaknesses.

Systematic reviews of MRI staging accuracy studies in prostate cancer (Engelbrecht *et al.* 2002; Sonnad *et al.* 2001) derived summary ROC curves for ECE, SVI and pathological T3 disease (pT3). In one of the reviews (Engelbrecht *et al.* 2002), MRI characteristics associated with an increased

area under the ROC curve (and improved accuracy) were: two or more imaging planes, turbo-spin echo and the use of an endorectal coil. There was evidence (although from fewer studies) that using voxels less than 3mm^2 and contrast agents increased staging accuracy.

In one case series (Harisinghani *et al.* 2003), the use of superparamagnetic particles improved the sensitivity of MRI for the detection of LNI from 40% to 100%.

A systematic review of the accuracy of CT for the detection of LNI in newly diagnosed prostate cancer (Abuzallouf *et al.* 2004) combined data from 27 studies. Most studies used a lymph node size of 15 mm or more to determine LNI and the combined sensitivity was 16% with a specificity of 99.9%, but other variations in the imaging protocols may reduce the validity of a combined estimate.

MRI vs. CT for radiotherapy planning

Five studies compared MRI with CT for radiotherapy planning (Dubois *et al.* 1998; Rasch *et al.* 1999; Roach, III *et al.* 1996; Villiers *et al.* 2005; Sannazzari *et al.* 2002). Prostate volume was greater when estimated using CT alone than when MRI (or combined CT–MRI) was used (Rasch *et al.* 1999; Roach, III *et al.* 1996; Villiers *et al.* 2005; Sannazzari *et al.* 2002). Two studies reported that volumes estimated using MRI (or combined CT–MRI) were more precise than those estimated using CT alone (Dubois *et al.* 1998; Villiers *et al.* 2005). No studies compared patient outcomes after treatment planning with CT or MRI. Smaller treatment volumes could mean reduced treatment related morbidity, but could also mean poorer disease control.

MRI vs. TRUS for staging

Four studies compared MRI with TRUS for staging in men before prostatectomy (Bates *et al.* 1997; Presti Jr *et al.* 1996; Sanchez-Chapado *et al.* 1997; Vapnek *et al.* 1994). In all studies, MRI was more sensitive than TRUS for the detection of ECE, but not consistently more specific. MRI was more sensitive than TRUS for detection of SVI in three of the four studies, but with similar specificity.

MRI vs. MRS

The addition of MRS to MRI, in one series, increased the accuracy of prostate tumour volume estimation compared to MRI alone (Coakley *et al.* 2002). A second study reported slightly better accuracy for discrimination between unilateral and bilateral cancers when MRS was combined with MRI (Hasumi *et al.* 2003) than for MRI alone.

The incorporation of MR findings improved the accuracy of a staging nomogram for the prediction of organ confined prostate cancer after prostatectomy (Wang *et al.* 2006). The addition of both MRS and MR findings to the nomogram did not significantly improve its accuracy. MRI and MRI+MRS stage were similarly correlated with pathological stage, in the small series reported by Pucar and co-workers (Pucar *et al.* 2004). The addition of MRS findings to MRI improved the sensitivity for ECE, but only in the less experienced of the two radiologists in the study by Yu and co-workers (Yu *et al.* 1999). In the small series reported by Wetter and co-workers (Wetter *et al.* 2006) there was no statistically significant improvement in the sensitivity and specificity for T3 tumours when MRS was added to MRI.

Imaging and treatment outcome

Three case series looked at MRI tumour stage as a prognostic factor for PSA relapse after prostatectomy or radiotherapy in men with prostate cancer (Cheng *et al.* 2003; D'Amico *et al.* 2000; Nguyen *et al.* 2004). In all three studies, MRI tumour stage was a statistically significant prognostic factor for PSA relapse. In a case series of patients at high risk of PSA relapse (Pucar *et al.* 2004), MRI tumour stage was a statistically significant prognostic factor for relapse after treatment, but a risk score derived using MRS was not.

One of the studies considered the clinical significance of MRI tumour stages T2 and T3 (D'Amico *et al.* 2000). The authors concluded that MRI tumour staging only added clinically meaningful information for men at intermediate pretreatment risk of PSA relapse. MRI tumour stage did not stratify PSA failure risk well enough to guide clinical decision making for patients in the low or high risk groups.

One case series considered the effect of pretreatment tumour staging using MRI or TRUS on PSA relapse after radiotherapy (Pinover *et al.* 1996). Men whose palpation stage (from DRE) was increased after imaging did not experience greater PSA failure 3 years after radiotherapy than men who were not upstaged. The authors concluded that the pretreatment imaging did not add clinically relevant information to palpation stage.

Bone scans

Two systematic reviews (Abuzallouf *et al.* 2004; National Institute for Clinical Excellence 2002) looked at the role of radioisotope bone scans in the staging of men with newly diagnosed prostate cancer. Primary studies of the diagnostic accuracy of bone scans or of their influence on patient outcomes were lacking. Most of studies included in the reviews were case series reporting prognostic factors for positive bone scans, to identify situations where such scans can be omitted.

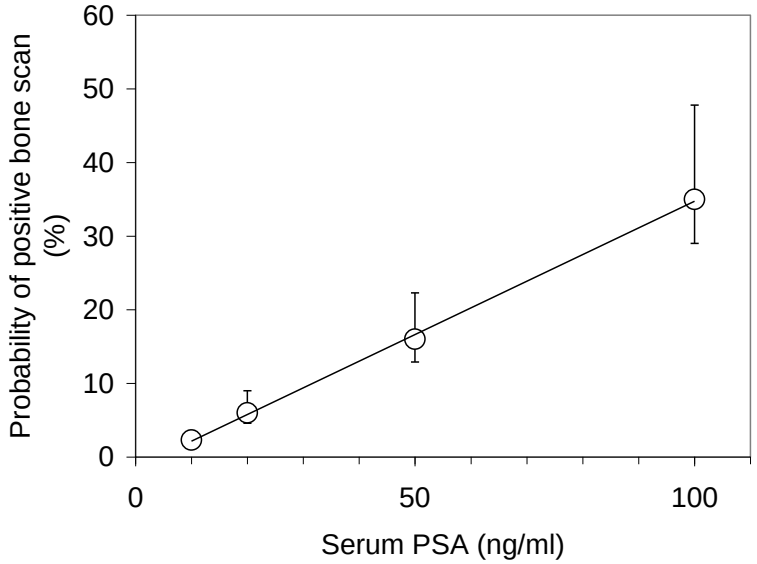
The review by Abuzallouf and co-workers (Abuzallouf *et al.* 2004) summarised bone scan results by serum PSA level in men with newly diagnosed prostate cancer. The relationship between serum PSA level and risk of a positive bone scan was linear (see Figure 7 below). The other review (National Institute for Clinical Excellence 2002) concluded that PSA level was the best means of identifying those at risk of a positive bone scan and that men with PSA less than 10 ng/ml were unlikely to have a positive bone scan.

Chest X-ray

The literature search did not identify any relevant studies on the use of chest X-rays in men with newly diagnosed prostate cancer.

Figure 7. Risk of positive bone scan versus PSA level (from Abuzallouf *et al.* 2004)

Risk of positive bone scan in men with newly diagnosed prostate cancer grouped by serum PSA level.
The 4 groups were: <10, 10-19.9, 20-49.9, 50-99.9 and >100 ng/ml. Error bars show 95% C.I.



Clinical Evidence 2014

Does staging with MRI improve outcomes in men with prostate cancer?

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

Rationale

Treatment intention is (almost invariably) to improve survival. Morbidity and mortality from treatment is balanced against the pre-treatment predicted survival benefit, which in turn relies on having accurate T, N and M stage. Clinical staging results in about 60% under-staging; if the clinical stage is upgraded by MRI, treatment morbidity and mortality may be avoided when there is no possibility of cure. T stage also guides surgical approach (nerve sparing or not) and radiotherapy field planning.

Depending on the PSA level, DRE findings, TRUS findings and histology, treatment is determined. MRI may add additional information to refine this decision. In low risk patients, MRI may be useful in gauging the suitability of active surveillance or the feasibility of nerve sparing surgery. In intermediate risk patients, MRI may be useful when looking for stage T3 disease. While in high risk patients, an MRI of the spine may be more useful than a bone scan. Lymph node staging has a low accuracy, but should be used when a prior threshold of having nodal metastases is >40%.

PICO question

Population	Intervention	Reference standard	Outcomes
Men with biopsy-confirmed prostate cancer before primary treatment. Subgroups: • PSA < 10 • PSA 10 – 20 • PSA > 20 • Gleason 3+3 • Gleason 3+4 • Gleason 4+3 • Gleason score 8+ • Percentage of positive core • T stage	MRI staging	Clinical staging	Question 3.5.1 • Overall survival • Biochemical recurrence-free survival • Treatment related morbidity • Health related quality of life Question 3.5.2 • Change in management • Change in stage • Diagnostic accuracy

How the information will be searched

Sources to be searched	
Can we apply date limits to the search	This is an update of a topic in the 2008 guideline so we can limit the search to studies published since.
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	Although an RCT in this area is possible, we will not use study design filters as evidence will most likely come from case series or cohort studies.
List useful search terms.	

The review strategy

Question 3.5.1

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results?	We will use the evidence table for RCTs or cohort studies (NICE guidelines manual appendix J). We will need a definition of biochemical relapse, although in practise we may have to accept whatever was reported in the individual studies
Which quality checklist will we use for appraisal?	The RCT or cohort quality checklist will be used (NICE guidelines manual appendix C,D).
List subgroups here and planned statis-	Patient subgroups are specified in PICO

tical analyses	

Question 3.5.2

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? List subgroups here and planned statistical analyses	We will use the evidence table for diagnostic studies (NICE guidelines manual appendix J). The QUADAS-2 checklist will be used (NICE guidelines manual appendix F). Patient subgroups are specified in PICO

Methods

Search strategy

The full strategy will be available in the full guideline. The search was not restricted by study type or date.

Selection of studies

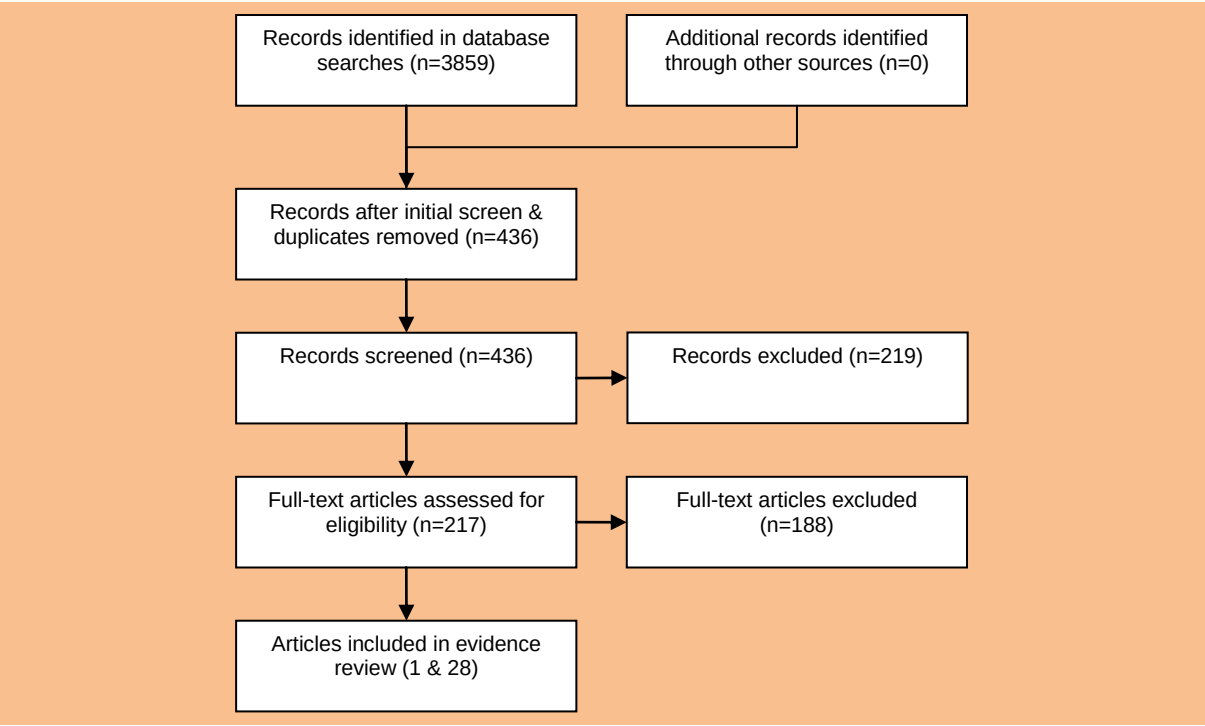
The information specialist (EH) did the first screen of the literature search results. One reviewer (KC) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO question. A second reviewer (NB) checked the included studies. The full articles were then obtained and studies were checked against the inclusion criteria.

Analysis

Only T and N stages were extracted from studies as it was agreed by the subgroup that M stage could not be estimated clinically and would require some form of imaging. For diagnostic accuracy outcomes, only studies which compared both clinical staging and MRI staging against prostatectomy as the reference standard were included. The QUADAS tool for studies of diagnostic test accuracy was used to determine the quality of the evidence base. Where available, data for different risk groups were summarized in sub-group analyses. Where available, data for different risk groups were summarised in sub-group analyses.

Results

Results of the literature searches



The literature was screened for both questions simultaneously. The literature searches identified 436 potentially relevant articles of which 217 were ordered in full text. One study was included for question 3.5.1 and 28 studies were included for question 3.5.2.

Characteristics of included studies

Question 3.5.1

Only one retrospective cohort study was found which compared patients who had undergone both clinical staging and imaging with MRI, CT or bone scans to those who had undergone clinical staging alone. Clinical staging was found to be T1c in 94% and T2a in 6% of those who were not imaged, compared to T1c in 87% and T2a in 13% of those imaged. Median follow-up in the two groups was 16.5 and 12.4 months respectively.

Question 3.5.2

Only cohort studies were found which reported the relevant outcomes; 16 of these were prospective, nine were retrospective, and two were unclear. Six of the studies were only available as abstracts (Porcaro 2005; Johnston 2011; Romano 2011; Schiavina 2011; Harat 2012; Terakedis 2012).

Population

Fourteen studies (Vapnek 1994; Bates 1997; Sanchez-Chapado 1997; Rørvik 1999; Soulie 2001; Nguyen 2004; Poulakis 2004; Porcaro 2005; Augustin 2009; Ploussard 2010; Novis 2011; Romano 2011; Panebianco 2012; Hedge 2013) reported only including patients with clinical stage T1-T2 and one study (Zhang 2009) only included patients with stage T1c. Two of the studies (Ploussard 2010; Novis 2011) also only included patients with PSA ≤ 10 ng/ml and Gleason score ≤ 6. Presti et al. (1996) only included patients with PSA ≤ 10 ng/ml with no bone pain. While Pucar et al. (2004) only included patients with T1 or T2 if PSA > 20 ng/ml. Schiavina et al. (2011) report including only intermediate- and high-risk patients but no details of the criteria for this classification were given. Brown et al. (2009) included patients who subjectively felt at increased risk of ECE and Cabrera et al. (2008) only included patients who choose active surveillance.

Eighteen of the studies (Vapnek 1994; Bates 1997; Sanchez-chapado 1997; Rørvik 1999; Soulie 2001; Kwek 2004; Poulakis 2004; Porcaro 2005; Augustin 2009; Brown 2009; Johnston 2011; La-

banaris 2009; Novis 2011; Panebianco 2012; Hegde 2013; Ploussard 2010; Renard-Penna 2011; Zhang 2009) only included patients who were to undergo radical prostatectomy and three studies (Nguyen 2004; Joseph 2009; Romano 2011) only included patients who subsequently underwent radiotherapy. Terakedis et al. (2012) only included patients who were referred for radiotherapy consultation. Pucar et al. (2004) included patients undergoing MRI as part of a clinical trial, who then went on to receive neoadjuvant, combined chemotherapy/hormone therapy prior to prostatectomy, radiotherapy or continued hormone therapy.

Three studies (Presti 1996; Labanaris 2009; Zhang 2009) excluded patients who had received any prior hormone or radiotherapy. Zhang et al. (2009) also excluded patients with prior chemotherapy. Three studies (Novis 2011; Soulie 2001; Renard-Penna 2011) excluded patients who had prior hormone therapy but placed no restriction on radiotherapy or chemotherapy. Poulakis et al. (2004) excluded any patients receiving any form of neoadjuvant therapy alongside the prostatectomy. Pucar et al. (2004) excluded patients who were planning to undergo any major surgery, radiotherapy, chemotherapy, or immunological therapy less than 4 weeks following MRI.

Time elapsed between intervention and outcomes

Twelve studies set a minimum duration between biopsy and MRI, which ranged from 3 to 10 weeks. A further four studies reported the median duration and range; the latter ranged from -117 to 2437 days (Poulakis 2004; Cabrera 2008; Zhang 2009; Hegde 2013). It is important to note that three of the studies which gave an estimated time from biopsy to MRI, reported using DRE for clinical staging (Cabrera 2008; Augustin 2009; Renard-Penna 2011).

Two studies (Labanaris 2009; Novis 2011) reported the mean time from MRI to radical prostatectomy which ranged from 16 to 49 days. Three studies (Poulakis 2004; Zhang 2009; Hegde 2013) reported the median time from MRI to radical prostatectomy to be between 3 and 48 days. One study (Novis 2011) reported the mean time from biopsy to radical prostatectomy to be 48 days and one study (Zhang 2009) reported the median time to be 3.5 months. Vapnek et al. (1994) required all patients undergo prostatectomy within 1 month of biopsy, while Panebianco et al. (2012) required MRI to be performed 7 days or less prior to prostatectomy.

Clinical and MRI tests

Of the 28 included studies, 16 (57%) reported how the disease was staged clinically. In six studies (Kwek 2004; Pucar 2004; Cabrera 2008; Joseph 2009; Labanaris 2009; Renard-Penna 2011) this was done by DRE. In another three studies (Bates 1997; Novis 2011; Harat 2012) this was done by TRUS, one study (Nguyen 2004) used TRUS-guided biopsy, four studies (Vapek 1994; Presti 1996; Sanchez-Chapado 1997; Schiavina 2011) used both DRE and TRUS, one study (Augustin 2009) used PSA and DRE, and one used DRE, PSA and TRUS (Panebianco 2012).

Many (67%) of the studies reported using 1.5-T MRI, however, one study (Bates 1997) reported using 0.5-T, four studies (Rørvik 1999; Soulie 2001; Poulakis 2004; Labanaris 2009) reported using 1.0-T, and three studies (Augustin 2009; Panebianco 2012; Hegde 2013) reported using 3.0-T. Eleven studies (Presti 1996; Sanchez-Chapado 1997; Pucar 2004; Brown 2009; Cabrera 2008; Cirillo 2008; Joseph 2009; Novis 2011; Zhang 2009; Panebianco 2012; Hegde 2013) reported using an endorectal coil and a pelvic phased-array coil. Five studies (Soulie 2001; Kwek 2004; Poulakis 2004; Augustin 2009; Renard-Penna 2011) reported using a pelvic phased-array coil and no endorectal coil. Five studies (Rørvik 1999; Nguyen 2004; Porcaro 2005; Ploussard 2010; Romano 2011) used only an endorectal coil, and one study (Labanaris 2009) used an endorectal phased-array coil.

Johnston et al. (2011) reported using a standard non-contrast enhanced MRI without an endorectal coil. Labanaris et al. (2009) included patients who had undergone both conventional endorectal MRI and functional endorectal MRI (either dynamic contrast or diffusion weighted). Novis et al. (2011) undertook a comparison of conventional MRI, magnetic resonance spectroscopy (MRS), and dynamic contrast-enhanced MRI. Schiavina et al. (2011) used both conventional MRI and dynamic contrast-enhanced MRI, while four studies (Pucar 2004; Cabrera 2008; Joseph 2009; Zhang 2009) used both conventional MRI and MRS. The results of the MRI were interpreted twice by two separate radiologists in seven (25%) of the studies (Poulakis 2004; Cabrera 2008; Johnston 2011; Renard-Penna 2011; Schiavina 2011; Zhang 2009; Panebianco 2012).

Summary of evidence

Does staging with MRI improve outcomes in men with prostate cancer?

Biochemical recurrence-free survival

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

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

Quality appraisal

The quality appraisal of included studies was based on the QUADAS tool for studies of diagnostic test accuracy. Overall, 13 (46%) studies were considered low quality evidence and the remainder were considered very low quality.

All included studies were cohort studies; in 26 (93%) they were further marked down for the spectrum of patients included being unrepresentative of the patients who would receive MRI in practice. Two (7%) were also marked down for the time period between biopsy and reference standard (MRI in studies reporting change in staging outcomes). Zhang et al. (2009) reported a median of 69 days (range -117 – 442) between biopsy and MRI, while Cabrera et al. (2008) reported a median of 254 days (range 30 – 2437) and Brown et al. (2009) required a minimum of 8-10 weeks between biopsy and MRI. However, Cabrera et al. (2008) used digital rectal examination (DRE) for clinical staging and the other two studies did not report how the patients were staged clinically. In 17 (61%) studies, the time period between clinical staging or biopsy and the reference standard was not reported.

In 19 (68%) studies the reference standard for the outcomes reported was MRI and therefore considered not to likely to classify the target condition correctly. One (4%) study reported that the index test results were interpreted without knowledge of the results of the reference standard, though the rest (96%) did not provide this information. Twelve (43%) studies reported that the reference standard test results were interpreted without knowledge of the results of the index test(s), though 15 (54%) did not report this information.

Evidence statements

Change in management

Two studies (Romano 2011; Terakedis 2012) provided very low quality evidence of a change in the management of radiotherapy strategy following MRI. In one study treatment plans prior to MRI were prostate-only radiotherapy in all patients (97 in total). Following MRI, prostate-only radiotherapy was planned for 67 (69%) patients, extended pelvic IMR fields for 13 (13%) patients, and limited IMRT fields for 17 (18%) patients. The number of patients with planned neoadjuvant and adjuvant androgen deprivation therapy (ADT) increased from four (4%) to 30 (31%); all patients identified as stage T3 at MRI. A second study found that of 68 patients who underwent an MRI following radiotherapy consultation, the MRI led to a change in treatment for six (9%). Two patients received combined rather than single modality therapy, two underwent treatment to larger radiotherapy fields than initially planned, and the treatment modality changed in two patients.

Two studies (Labanaris 2008; Panebianco 2012) provided very low quality evidence of a change in surgical procedure in 44% and 30% of patients following MRI respectively. Labanaris et al. (2008) found the MRI resulted in the preservation of the neurovascular bundle in 22 (29%) patients who would not have undergone nerve-sparing surgery based on the clinical staging. Eleven (15%) patients who were planned for nerve-sparing surgery based on clinical staging underwent resection of the neurovascular bundle due to a high risk of extraprostatic disease perceived on the MRI. Panebianco et al. (2012) found that the post-MRI surgical plan differed to the initial clinical evaluation in 32/105 (30%) of cases. Following MRI 21/105 patients instead underwent unilateral nerve-sparing surgery and 11/105 did not undergo nerve-sparing surgery. Based on findings from the prostatec-

tomy, 70/73 (96%) of those who underwent bilateral surgery underwent the appropriate plan; 28/32 (88%) of those who underwent unilateral surgery underwent the appropriate plan; and 8/11 (73%) of those who did not undergo nerve-sparing surgery underwent the appropriate plan.

Change in stage

Twenty-three studies provided very low quality evidence of a change in staging following MRI (see Table 28). All studies found MRI resulted in up-staging of a proportion of their patients, ranging from at least 5% to 100% of all patients. Three studies reported MRI to also have resulted in down-staging of some patients; two found that 5% of patients were down-staged and one found 19% were down-staged (Pucar 2004; Cirillo 2008; Harat 2012). However, it was not clear in many (50%) studies whether any patients had been down-staged.

In the studies which initially staged patients using TRUS (Presti 1996; Bates 1997; Sanchez-Chapado 1997; Nguyen 2004; Hedge 2013), the proportion of patients which were staged as T3a increased by 0% - 50% and the proportion which were staged as T3b by 33% - 300% following MRI. Nguyen et al. (2004) found that the proportion of patients staged as T3b increased from none to 17, while Hedge et al. (2013) and Presti et al. (1996) found that the proportion of patients staged as any T3 increased by 81% and 76% respectively.

In the studies which initially staged patients using DRE, three found that the proportion of patients which were staged as T3 increased by between 0% and 200% (Sanchez-Chapado 1997; Kwek 2004; Pucar 2004; Joseph 2009; Renard-Penna 2011). Presti et al. (1996) found that the number of patients staged as any T3 increased from none to 66% and Cabrera et al. (2008) found that it increased from none to 5% or 17% depending on the reader.

Two studies reported results for two separate readers of the MRI and both found substantial variation. Cabrera et al. (2008) found that the two readers upstaged at least 8% versus 38% T1 patients and re-staged 5% versus 17% of the T1-T2 patients as T3. While both readers for Zhang et al. (2009) up-staged all 158 T1 patients, 92% versus 82% became stage T2, and 6% versus 17% became stage T3a.

Change in stage: subgroup analyses

Eleven studies only included patients with clinically localised disease and one study (Zhang 2009) only included patients with stage T1c. The proportion of patients which were staged as T3 clinically increased by 43% - 840% at MRI (Bates 1997; Sanchez-Chapado 1997; Poulakis 2004). In seven of the studies (Rørvik 1999; Soulie 2001; Porcaro 2005; Augustin 2009; Ploussard 2010; Romano 2011; Hedge 2013) the number of patients staged as T3 increased from none to 14% - 61% at MRI. In five of the studies (Soulie 2001; Augustin 2009; Romano 2011; Zhang 2009; Hedge 2013) all patients clinically staged as T1 were up-staged (49, 17, 91 158 and 79 respectively), some of which became stages T3a and T3b on MRI.

Brown et al. (2009) also reported results separately for patients found to have stage T2 and T3 at prostatectomy. Of 41 stage T2 patients, 63% and 83% were correctly staged clinically and by MRI respectively. The remaining patients were staged as T1 (56%) clinically or as T3 (17%) by MRI. Of the 21 stage T3 patients, 0% and 33% were correctly staged clinically and MRI respectively.

One study (Cirillo 2008) reported the change in stage at MRI for different risk groups. Of the 82 low risk patients (PSA ≤ 10 ng/ml or Gleason 2-6), 28 (34%) were re-staged of which 26 (32%) were up-staged and 2 (2%) were down-staged. Of 44 intermediate risk patients (PSA 10-20 ng/ml or Gleason 7), 21 (48%) were re-staged of which 19 (43%) were up-staged and two (5%) were down-staged at MRI. Of 17 high risk patients (PSA > 20 ng/ml or Gleason 8-10), 11 (65%) were re-staged of which eight (47%) were up-staged and three (18%) were down-staged.

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

Brown et al. (2009) also reported results separately for patients with Gleason 6 or 7-10 at biopsy. Of the 30 patients with Gleason score of 6, 21 (70%) versus 0 were staged as T1, nine (30%) versus 26 (87%) were staged as T2, and none versus four (13%) were staged as T3 clinically or by MRI respectively. Of the 32 patients with Gleason score of 7-10, 15 (47%) versus 0 were staged as T1, 17

(53%) versus 22 (69%) were staged as T2, and none versus ten (31%) were staged as T3 clinically or by MRI respectively.

Diagnostic accuracy

Eight studies provided very low quality evidence of the diagnostic accuracy of both clinical and MRI staging, using prostatectomy as reference standard (see Table 29). Four studies (Vapnek 1994; Presti 1996; Bates 1997; Kwek 2004) reported on the overall ability of MRI to stage prostate cancer clinically. MRI was not consistently more sensitive, specific or accurate than staging by DRE or TRUS.

Six studies (Vapnek 1994; Presti 1996; Bates 1997; Sanchez-Chapado 1997; Novis 2011; Schiavina 2011) found MRI to be more sensitive than clinical staging in identifying patients with extracapsular extension (stage T3a). MRI was not found to be consistently more specific or accurate than clinical staging. MRI was not consistently more sensitive, specific or accurate than clinical staging in identifying patients with seminal vesicle invasion (stage T3b).

Diagnostic accuracy: subgroup analyses

Three studies (Vapnek 1994; Bates 1997; Sanchez-Chapado 1997) only included patients with clinically localised disease. Vapnek et al. (1994) found MRI to have higher sensitivity but lower specificity than DRE or TRUS for overall staging of prostate cancer, while Bates et al. (1997) found MRI to have higher accuracy. In these studies, MRI was more sensitive than clinical staging when identifying extracapsular extension or seminal vesicle invasion. However, MRI was not consistently more specific or accurate at detecting extracapsular extension or seminal vesicle invasion.

Presti et al. (1996) only included patients with PSA < 10 ng/ml; Ploussard et al. (2010) only included patients with a Gleason score ≤ 6; while Novis et al. (2011) only included patients with stage T1c-T2a, PSA ≤ 10 ng/ml, and Gleason score ≤ 6. Presti et al. (1996) found the accuracy of overall staging to be the same between MRI and TRUS. Both Presti et al. (1996) and Novis et al. (2011) found MRI to be more sensitive but less specific than TRUS when identifying extracapsular extension. Both studies also found MRI to be less sensitive than TRUS when identifying seminal vesicle invasion and not consistently more specific. Ploussard et al. (2010) found MRI to have the same rate of false positives as clinical staging when identifying stage T3-T4 disease.

Sanchez-Chapado et al. (1997) conducted a subgroup analysis by PSA level and found MRI to be more sensitive than TRUS in identifying both extracapsular extension and seminal vesicle invasion in patients with either PSA > 17 ng/ml or PSA < 10 ng/ml.

Shiavina et al. (2011) reported only including intermediate- and high-risk patients, but no definition of these risk categories was given. They found MRI to be more sensitive but less specific than clinical staging when identifying extracapsular extension, and to be more sensitive but have the same specificity when identifying seminal vesicle invasion.

Table 28. Change in clinical stage following MRI

Abbreviations: AS = active surveillance; DRE = digital rectal examination; ECE = extracapsular extension (T3a); MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopic imaging; NR = not reported; PCa = prostate cancer; RP = radical prostatectomy; RT = radiotherapy; TRUS = transrectal ultrasound.

Study	Population	Total no. patients	Duration biopsy to MRI	Clinical staging					MRI staging					No. (%) patients re-staged	No. (%) up-staged	No. (%) Down-staged
				Method	T1	T2	T3a	T3b	Type of MRI	T1	T2	T3a	T3b			
Presti (1996)*	Pca patients with PSA < 10 ng/ml & no bone pain.	56	NR	DRE	0	56	0		1.5-T endorectal & phased-array coils MRI.	0	19	37		≥ 37 (66)	37 (66)	0
				TRUS	0	35	21							≥ 16 (29)	≥ 16 (29)	-
Bates (1997)	Clinically localised Pca patients undergoing RP.	20	NR	TRUS	15		4	1	0.5-T body coil MRI.	12		4	4	≥ 3 (15)	≥ 3 (15)	-
Sanchez-Chapado (1997)	Patients with clinically localised Pca who underwent radical RP.	20	≥ 3 weeks	DRE	-		2	3	1.5-T endorectal coil & phased-array coil MRI.	-		6	4	≥ 1 (5%)	≥ 1 (5%)	-
				TRUS	-		4	3						≥ 1 (5%)	≥ 1 (5%)	-
Rørvik (1999)	Patients with clinically localised Pca who underwent RP.	31	≥ 3 weeks	NR	31		0	0	1.0-T endorectal coil MRI	12		10	9	≥ 19 (61)	≥ 19 (61)	-
Soulie (2001)	Pca stage T1-T2 patients undergoing RP	176	2-9 weeks; mean 35 days	NR	49	127	0	0	1.0-T pelvic phased-array coil MRI	0	131	39	6	≥ 49 (28)	≥ 49 (28)	0
Kwek (2004)	Pca patients who underwent MRI and RP.	21	NR	DRE	0	17	4		1.5-T pelvic phased-array coil MRI.	0	9	9	3	≥ 8 (38)	≥ 8 (38)	-
Nguyen (2004)	Patients with clinically localised Pca 'beyond low risk' receiving MRI prior to external beam RT with/without hormonal therapy before PSA failure.	158	≥ 3 weeks	TRUSbx	62	96	0	0	1.5-T endorectal coil MRI.	141			17	≥ 17 (11)	≥ 17 (11)	-
Poulakis (2004)	Patients with clinically localised Pca undergoing RP with pelvic lymphadenectomy & MRI.	201	Median 33 days (range 21 – 56	NR	42	149	10	0	1.0-T pelvic phased array coil MRI.	107		64	30	≥ 84 (42)	≥ 84 (42)	-
Pucar (2004)	Stage T1-T2 Pca with PSA > 20 ng/ml or stage T3-T4 or any stage with Gleason ≥ 8 Pca patients enrolled in a phase I/II clinical trial	16	NR	DRE	1	6	3	6	1.5-T phase array & endorectal coil MRI & MRSI combined.	1	2	4	9	11 (69)	8 (50)	3 (19)
Porcaro (2005)	Early Pca patients undergoing RP	90	NR	NR	29	61	0	0	Endorectal coil	65		10	15	≥ 25 (28)	≥ 25 (28)	-
Cabrera (2008)*†	Pca patients who selected AS	92	Median 254 days (range 30 – 2437)	DRE	61	22	0	0	1.5-T endorectal coil & pelvic phased array coil MRI & MRS	54 26	33 50	5 16		≥ 7 (8) ≥ 35 (38)	≥ 7 (8) ≥ 35 (38)	-
Cirillo (2008)	Pca undergoing MRI for Pca	143	NR	NR	18	113	12		1.5-T endorectal & pelvic phased-array coils MRI.	3	89	49		61 (43)	54 (38)	7 (5)
	Low risk Pca patients (PSA ≤ 10 ng/ml or Gleason = 2-6)	82			-	-	-			-	-	-		28 (34)	26 (32)	2 (2)
	Intermediate risk Pca patients (PSA 10-20 ng/ml or Gleason = 7)	44			-	-	-			-	-	-		21 (48)	19 (43)	2 (5)

	High risk Pca patients (PSA > 20 ng/ml or Gleason = 8-10)	17			-	-	-		-	-	-		11 (65)	8 (47)	3 (18)
Augustin (2009)	Clinically localised Pca patients referred for RP.	27	≥ 6 weeks	PSA & DRE	17	10	0	3.0-T pelvic phased-array coil MRI	0	23	4	0	≥ 17 (63)	≥ 17 (63)	0 (0)
Brown (2009)	Pca patients undergoing RP who subjectively felt at increased risk for ECE	57	≥ 8-10 weeks	NR	36	26	0	1.5-T endorectal coil & pelvic phased array coil MRI	0	48	14		≥ 36 (63)	≥ 36 (63)	0 (0)
	Pca patients with Gleason 6	30			21	9	0		0	26	4		≥ 21 (70)	≥ 21 (70)	0 (0)
	Pca patients with Gleason 7-10	32			15	17	0		0	22	10		≥ 15 (47)	≥ 15 (47)	0 (0)
	Pathological stage T2	41			23	18	0		0	34	7		≥ 23 (56)	≥ 23 (56)	0 (0)
	Pathological stage T3	21			13	8	0		0	14	7		≥ 13 (62)	≥ 13 (62)	0 (0)
Joseph (2009)	Pca patients undergoing MRI & MRSI before RT	67	NR	DRE	17	21	29	1.5-T pelvic phased-array coil MRI & MRSI.	8	30	21	8	≥ 9 (13)	≥ 9 (13)	-
Zhang (2009)*	Pca patients stage T1c undergoing RP	158	Median 69 days (range -117 – 442)	NR	158	0	0	0	1.5-T endorectal coil MRI combined with proton MRS	0 0	146 130	10 27	2 1	00) 00)	.00) .00)	0 (0) 0 (0)
Ploussard (2010)	PSA velocity > 0.7 ng/mL/ year; abnormal DRE; PSA > 4 & ≤ 10 ng/mL &/or free-to-total PSA < 10%; Gleason ≤ 6; life expectancy > 10 years; undergoing RP	96	≥ 6 weeks	NR	87%	13%	0%	0%	T2-weighted endorectal coil 1.5-T	68		28		≥ 28 (29)	≥ 28 (29)	-
Johnston (2011)	Pca patients undergoing RP	350	NR	NR	61%	35%	5%		Non-contrast enhanced 1.5-T MRI without endorectal coil	7%	62%	31%		≥ (54)	≥ (54)	-
Renard-Penna (2011)	Pca patients undergoing RP within 1 month of MRI	101	≥ 8 weeks	DRE	75	15	6	5	1.5-T pelvic phased array coil MRI	80		13		≥ 10 (10)	≥ 10 (10)	-
Romano (2011)	Early Pca undergoing primary RT	97	≥ 45 days	NR	91	6	0	0	Endorectal coil MRI	0	67	17	13	≥ 91 (94)	≥ 91 (94)	0 (0)
Harat (2012)	Newly diagnosed PCa	174	NR	DRE, TRUS & biopsy	-	-	-	-	NR	-	-	-	-	95 (55)	87 (50)	8 (5)
Terakedis (2012)	PCa patients attending for radiotherapy consultation	114	NR	NR	43	35	5	2	NR	30	27	11	11	≥ 13 (11)	≥ 13 (11)	-
Hedge (2013)	PCa patients undergoing RP	118	Median 6.0 weeks	DRE, PSA & TRUS	91	27	0	0	3.0-T endorectal coil & phased array coil T1, T2, DCE & DWI	0	102	16		**91 (77)**	**91 (77)**	0 (0)

*Results reported for two separate readers of the MRI. †Clinical stage missing for nine patients.

Table 29. Diagnostic accuracy outcomes from studies comparing clinical staging and MRI staging with prostatectomy (reference standard)

Abbreviations: DCE-MRI = dynamic contrast-enhanced MRI; ECE = extracapsular extension (T3a); MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopic imaging; NPV = negative predictive value; Pca = prostate cancer; PPV = positive predictive value; RP = radical prostatectomy; SVI = seminal vesicle invasion (T3b).

Study	No. Of patients	Outcome	Prevalence*	Clinical staging (%)								MRI staging (%)							
				Staging	Time to RP‡	Sensitivity	Specificity	PPV	NPV	False positives	Accuracy	Type of MRI	Time to RP‡	Sensitivity	Specificity	PPV	NPV	False positives	Accuracy
Vapnek (1994)	64	Overall staging	NA	DRE	≤ 1 month	0	100	0	42	0	42	MRI	≤ 1 month	62	74	77	59	11	67
				TRUS		46	85	81	53	6	63								
		ECE (stage T3a)	55%			49	86	-	-	-	66			57	79	-	-	-	67
		SVI (stage T3b)	13%			25	96	-	-	-	88			75	84	-	-	-	83
Presti (1996)	56	Overall staging	NA	TRUS	NR	-	-	63	38	-	63	MRI	NR	-	-	63	38	-	63
		ECE (stage T3a)	NR			48	71	50	69	-	-			91	49	51	90	-	-
		SVI (stage T3b)	NR			75	98	75	98	-	-			50	94	40	96	-	-
Bates (1997)		Overall staging	NA	TRUS	NR	-	-	-	-	-	50	MRI	NR	-	-	-	-	-	75
		ECE (stage T3a)	65%			23	86	-	-	-	-			38	100	-	-	-	-
		SVI (stage T3b)	15%			33	-	100	-	-	-			100	-	75	-	-	-
Sanchez-Chapado (1997)	20	ECE (stage T3a)	30%	DRE	NR	25	83	50	62	-	60	MRI	NR	66	85	66	85	-	79
				TRUS		33	77	50	64	-	60								
				DRE+TRUS		-	-	-	-	-	60								
		SVI (stage T3b)	20%	DRE		33	71	33	71	-	60			75	93	75	93	-	89
				TRUS		25	82	33	75	-	66								
Kwek (2004)	21	Overall staging	NA	DRE	NR	27	90	75	53	57	-	MRI	NR	27	90	75	53	57	-
Plousard (2010)	96	Stage T3-T4	-	NR	NR	-	-	-	-	18	-	MRI	NR	-	-	-	-	18	-
Novis (2011)	35	ECE (stage T3a)	23%	TRUS	48 days	33	92	14	97	-	90	MRI	49 days	50	78	14	96	-	76
		SVI (stage T3b)	9%			67	86	22	98	-	85			40	83	15	95	-	80
Schiavina (2011)	46	ECE (stage T3a)	15%	DRE & TRUS	NR	27	100	100	81	-	-	MRI	NR	82	91	75	94	-	-
		SVI (stage T3b)	9%			0	100	91	-	-	-			25	100	100	93	-	-

*Estimated by prostatectomy. †86 locations of cancer in 52 patients. ‡Mean; from biopsy for clinical staging.

Evidence Tables

MRI AND CT FOR STAGING

Harisinghani, Barentsz, Hahn, Deserno, Tabatabaei, van de Kaa, de la & Weissleder . Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. N Engl J Med 348[25]. 2003.

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

Country: International, setting: Tertiary care

Inclusion criteria Patients with potentially resectable, clinical stage T1, T2, or T3 prostate cancer who underwent surgical lymph-node resection or biopsy at one of two institutions between 1999 and 2002.

Exclusion criteria -

Population number of patients = 80, age range 54 to 75 years, mean age = 64 years.

Interventions Patients were examined by MRI before and 24 hours after the intravenous administration of lymphotropic superparamagnetic nanoparticles (2.6 mg of iron per kilogram of body weight). The imaging results were correlated with histopathological findings.

MRI was performed at 1.5T using state-of-the-art (1999-2002) imaging systems and pelvic phased array coils. On conventional MRI, nodes were classified as malignant if they were elongated and longer than 10mm or rounded and longer than 8mm. The classification of malignancy using superparamagnetic nanoparticles plus MRI also used a signal intensity criterion.

Outcomes Sensitivity, specificity of conventional MRI and MRI with lymphotropic superparamagnetic nanoparticles.

Results Using a pretreatment nomogram 15% of patients were at low risk of nodal metastases, 60% at intermediate risk and 25% at high risk. Of the 334 resected or biopsied lymph nodes, 63 (18.9 %) from 33 patients (41%) had histopathologically detected metastases. Of these 63 nodes, 45 (71.4 percent) did not fulfil the conventional MRI criteria for malignancy. Results per patient (rather than per node) are reported below.

COMPARISON IN MEN BEFORE PROSTATECTOMY FOR PROSTATE CANCER	MRI	MRI WITH LYMPHOTROPIC SUPERPARAMAGNETIC PARTICLES	OVERALL RESULT
Sensitivity	45.4%	100%	Favours MRI+LSP ($p<0.001$)
Specificity	78.7%	95.7%	No significant difference
Accuracy	65.0%	97.5%	No significant difference
PPV	60.0%	94.2%	No significant difference
NPV	67.2%	100%	No significant difference

General comments Patient selection criteria unclear. Time between MRI and surgery is not

reported

Engelbrecht, Jager, Laheij, Verbeek, van Lier & Barentsz . Local staging of prostate cancer using magnetic resonance imaging: a meta-analysis. Eur Radiol. 12[9]. 2002.

Design: Systematic review of diagnostic studies (diagnosis, screening), evidence level: II

Inclusion criteria MEDLINE and EMBASE were searched for articles published between 1984 and 2000 about the use of MRI for staging prostate cancer. Reference lists of retrieved articles and conference proceedings were also searched.

Exclusion criteria Repeat publication or reviews. Only data on nodal staging. No comparison with the surgically resected prostate. Insufficient information to calculate sensitivity and specificity.

Interventions 76 papers were included in the area under the curve (AUC) analysis. 80% of papers were published between 1993 and 2001. MRI findings were compared with those from the prostatectomy specimen (the gold standard). 55 papers (where all patients had the gold standard staging) were included in the summary ROC curves.

Outcomes The sensitivity and specificity of MRI for the detection of extracapsular extension, seminal vesicle invasion and pT3 disease. Area under the various ROC curves was calculated using these figures. Subgroup analyses were carried out for variations in the MRI protocol: 1 plane vs. 2 or more planes; spin echo vs. turbo spin echo; endorectal coil vs. non-endorectal coil; voxels less than 3 mm^2 vs. larger voxels; and with vs. without contrast agents.

Results Publication year, prevalence of pT3 disease, sample size, histologic gold standard, number of imaging planes, turbo spin echo, endorectal coil, and contrast agents influenced staging accuracy (p=0.05).

Summary ROC curves were generated, allowing estimation of sensitivity and specificity of MRI using different criterion values.

COMPARISON IN MEN BEFORE PROSTATECTOMY FOR PROSTATE CANCER	MRI, 1 IMAGING PLANE	MRI, 2 OR MORE IMAGING PLANES	MISSING VALUE	OVERALL RESULT
Extracapsular extension	AUC 0.50 (S.E 0.21; n=22)	AUC 0.57 (S.E 0.23; n=49)	AUC 0.62 (S.E 0.14; n=21)	Higher AUC using 2 or more planes (p<0.01)
Seminal vesicle invasion	AUC 0.43 (S.E 0.19; n=16)	AUC 0.66 (S.E 0.22; n=41)	AUC 0.70 (S.E 0.15; n=23)	Higher AUC using 2 or more planes (p=0.012)
pT3 disease	AUC 0.52 (S.E 0.10; n=33)	AUC 0.64 (S.E 0.13; n=26)	AUC 0.68 (S.E 0.12; n=24)	Higher AUC using 2 or more planes (p<0.01)
COMPARISON IN	MRI, SPIN ECHO	MRI, TURBO	MISSING VALUE	OVERALL RE-

MEN BEFORE PROSTATECTOMY FOR PROSTATE CANCER		SPIN ECHO		SULT
Extracapsular extension	not reported	not reported	not reported	No significant difference
Seminal vesicle invasion	AUC 0.49 (S.E 0.24; n=22)	AUC 0.69 (S.E 0.19; n=44)	AUC 0.60 (S.E 0.16; n=14)	Higher AUC using turbo spin echo (p=0.05)
pT3 disease	AUC 0.55 (S.E 0.12; n=39)	AUC 0.65 (S.E 0.14; n=33)	AUC 0.66 (S.E 0.09; n=11)	Higher AUC using turbo spin echo (p<0.01)
COMPARISON IN MEN BEFORE PROSTATECTOMY FOR PROSTATE CANCER	MRI, NON-ENDORECTAL COIL	MRI, ENDORECTAL COIL	MISSING VALUE	OVERALL RESULT
Extracapsular extension	not reported	not reported	not reported	No significant difference
Seminal vesicle invasion	AUC 0.58 (S.E 0.23; n=27)	AUC 0.67 (S.E 0.21; n=46)	AUC 0.51 (S.E 0.21; n=7)	Favours endorectal coil (p=0.01)
pT3 disease	AUC 0.54 (S.E 0.11; n=29)	AUC 0.65 (S.E 0.13 n=41)	AUC 0.60 (S.E 0.12; n=13)	Favours endorectal coil (p=0.01)
COMPARISON IN MEN BEFORE PROSTATECTOMY FOR PROSTATE CANCER	MRI, VOXEL MORE THAN 3MM^2	MRI, VOXEL 3MM^2 OR LESS	MISSING VALUE	OVERALL RESULT
Extracapsular extension	not reported	not reported	not reported	No significant difference
Seminal vesicle invasion	AUC 0.59 (S.E 0.24; n=13)	AUC 0.74 (S.E 0.19; n=12)	AUC 0.61 (S.E 0.22; n=55)	Favours higher resolution (p=0.05), but few studies
pT3 disease	AUC 0.60 (S.E 0.16; n=9)	AUC 0.76 (S.E 0.11; n=6)	AUC 0.59 (S.E 0.12; n=68)	Favours higher resolution (p=0.02), but few studies
COMPARISON IN MEN BEFORE PROSTATECTOMY FOR PROSTATE CANCER	MRI, WITH CONTRAST AGENTS	MRI, WITHOUT CONTRAST AGENTS	MISSING VALUE	OVERALL RESULT
Extracapsular extension	AUC 0.70 (S.E 0.15; n=8)	AUC 0.55 (S.E 0.21; n=80)	AUC 0.70 (S.E 0.19; n=4)	Favours contrast agents (p<0.001), but few studies
Seminal vesicle invasion	AUC 0.74 (S.E 0.17; n=7)	AUC 0.61 (S.E 0.22; n=71)	AUC 0.85 (S.E 0.14; n=2)	Favours contrast agents (p=0.02), but few studies
pT3 disease	AUC 0.76 (S.E	AUC 0.59 (S.E	AUC 0.58 (S.E	Favours contrast

	0.12; n=7)	0.13; n=74)	0.08; n=2)	agents (p<0.01), but few studies

General comments No references given for the primary studies. Authors report problems with quality of the primary studies: small numbers, prevalence of pT3 was not reported in most studies, missing data about voxel size and number of image planes. Possible publication bias: small studies had higher accuracy than larger ones. Possible underestimation of MRI accuracy due to outdated technology.

Sonnad, Langlotz & Schwartz . Accuracy of MR imaging for staging prostate cancer: a meta-analysis to examine the effect of technologic change. Acad Radiol. 8[2]. 2001.

Design: Systematic review of diagnostic studies (diagnosis, screening), evidence level: II

Inclusion criteria English language papers indexed in MEDLINE, published between 1984 and 1996. Studies describing the performance of MRI for staging prostate cancer were included if pathologic proof of disease stage was used as the gold standard.

Exclusion criteria Studies of less than 10 patients. Papers where specificity and sensitivity could not be calculated. Patients with clinically advanced disease.

Interventions 23 papers met the inclusion criteria. Patients had a staging MRI, and then prostatectomy with pathological confirmation of stage.

Outcomes A summary receiver operating characteristic (ROC) curve was calculated for MRI tumour stage. Subgroup analyses were conducted for variations in the MRI protocol: magnetic field strength, endorectal coil, use of fast spin echo imaging and study size.

Results The summary ROC curve for all studies had a maximum joint sensitivity and specificity of 74%. At a specificity of 80% on this curve, sensitivity was 69%. Subgroup analyses showed that fast SE imaging was statistically significantly more accurate than conventional SE techniques (P < .001). Contrary to expectations, studies employing higher magnetic field strength (1.5T vs. <0.5T) and those employing an endorectal coil were less accurate.

General comments Possible publication bias - small studies tended to report higher MRI accuracy.

National Institute for Clinical Excellence. Guidance on cancer services - improving outcomes in urological cancers. The manual. 2002.

Design: Systematic review of diagnostic studies (diagnosis, screening), evidence level: Ia

Inclusion criteria Studies directly comparing the efficacy of CT scanning with MRI in the staging of prostate cancer.

Interventions 2 studies met the inclusion criteria. Both studies investigated the accuracy of

MRI and CT in the staging of prostate cancer before radical prostatectomy. Pathological evaluation of the surgical specimen was the reference standard.

Outcomes Sensitivity, specificity, PPV and NPV of CT and MRI for extracapsular extension(ECE), seminal vesicle invasion (SVI) and lymph node involvement (LNI).

Results Both studies showed a 7.5% increased accuracy of MRI over CT for detection of SVI. For detection of LNI MRI was between 12 and 13% more accurate than CT. One of the studies reported that MRI was 26% more accurate than CT for the detection of ECE.

The review noted that there were flaws in both studies, in one, not all patients received both MRI and CT; in the other, there were only 18 patients.

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

Design: Systematic review of diagnostic studies (diagnosis, screening), evidence level: II

Country: International

Inclusion criteria Studies reporting the staging of men with newly diagnosed prostate cancer (with no previous management) were included. English language papers only, published between 1966 and 2002.

Exclusion criteria Insufficient description of patient population or results.

Population number of patients = 4264.

Interventions 27 studies examining the role of CT in evaluating lymph node status were included. The upper limit for normal sized nodes was usually 15mm although some studies used smaller sizes (6, 8 or 10mm). The use of contrast medium was mentioned in 11 studies. Results were extracted for patients who had both CT and pathological evaluation of pelvic lymph nodes.

Outcomes Sensitivity, specificity, accuracy, positive and negative predictive values.

Results Overall prevalence of lymph node metastases in the combined case series was 654/4264 (15%).

COMPARISON IN MEN BEFORE PROSTATECTOMY FOR PROSTATE CANCER	CT SCAN, FOR PELVIC LYMPH NODES	OVERALL RESULT
Sensitivity	16%	
Specificity	99.9%	
COMPARISON IN MEN BEFORE PROSTATECTOMY FOR PROSTATE CANCER	CT SCAN	OVERALL RESULT
PPV	97%	
NPV	87%	

General comments Summary ROC curve would have been more appropriate, given variations in node size thresholds and use of contrast. Inclusion of older papers raises the problem of stage migration, lower sensitivity may be expected if patients are presenting with less advanced disease.

Marchetti, LaPensee & Wang . A pharmacoeconomic evaluation of staging modalities for patients with newly diagnosed and occult recurrent adenocarcinoma of the prostate. Urologic Oncology 3. 1998.

Design: Systematic review of diagnostic studies (diagnosis, screening), evidence level: III

Inclusion criteria Clinical trial studies on individuals, regardless of age, with newly diagnosed or recurrent prostate cancer, published in English between 1980 and 1997, and indexed on MEDLINE.

Interventions 10 studies of the diagnostic accuracy of CT for the detection of pelvic lymph node involvement, and 3 studies of MRI. Studies were published between 1981 and 1995.

Outcomes The authors calculated the mean PPV and NPV for the detection of lymph node involvement.

Results For CT mean PPV was 40% and NPV 87%. For MRI mean PPV was 32% and NPV 89%.

General comments Outdated and questionable analysis. Primary aim of this paper is an economic evaluation of ProstaScint for assessing lymph node involvement. The study is funded by the manufacturer of ProstaScint.

TREATMENT PLANNING

Dubois, Prestidge, Hotchkiss, Prete & Bice, Jr. Intraobserver and interobserver variability of MR imaging- and CT-derived prostate volumes after transperineal interstitial permanent prostate brachytherapy.[see comment]. Radiology 207[3]. 1998.
Design: Retrospective cohort study (diagnosis, screening), evidence level: III Country: United States, setting: Tertiary care **Inclusion criteria** Men who had received transperineal interstitial prostate brachytherapy for prostate cancer. **Population** number of patients = 41. **Interventions** Within 24 hours of brachytherapy implantation patients had both CT and MR imaging. The CT scans and MR images were then evaluated by a radiologist and a clinical oncologist who delineated the prostate. The prostate volume was then calculated from these images. The process was repeated using 5 randomly selected CT and 5 MRI images to measure intra-observer variability. **Outcomes** The inter-observer and intra-observer variability of prostate volume estimates. **Results** There was greater inter-observer variability in the CT prostate volume estimates than in the MRI estimates ($p<0.001$). The intra-observer variability was less marked

Rasch, Barillot, Remeijer, Touw, van & Lebesque . Definition of the prostate in CT and MRI: a multi-observer study. Int J Radiat. Oncol Biol. Phys. 43[1]. 1999.
Design: Prospective case series, evidence level: III Country: The Netherlands, setting: Tertiary care **Inclusion criteria** Men with clinically localised prostate cancer treated with EBRT at a single institution. None had hormonal treatment before radiotherapy. **Population** number of patients = 18, age range 56 to 76 years, mean age = 67 years. **Interventions** Magnetic resonance (MR) and computer tomography (CT) images for radiotherapy treatment planning. Three experienced clinical oncologists delineated the prostate without seminal vesicles both on CT, and axial, coronal, and sagittal MR images . The CT and MR scans were matched in three-dimensions and the delineated volumes compared. **Outcomes** Prostate volume measured on CT and MRI. **Results** 7/18 patients had sagittal MRI scans. 1/18 was excluded because the CT and MR scans could not be aligned (due to lack of bony structures).

COMPARISON IN MEN	CT SCAN BEFORE	AXIAL MRI	CORONAL MRI	OVERALL RESULT

IMRT FOR PROSTATE CANCER				
Prostate volume	group mean 63.7 ml	group mean 44.5 ml	group mean 40.7 ml	The average CT:MRI volume ratio was 1.4 (p<0.005).

General comments -

Roach, III, Faillace-Akazawa, Malfatti, Holland & Hricak . Prostate volumes defined by magnetic resonance imaging and computerized tomographic scans for three-dimensional conformal radiotherapy. Int J Radiat.Oncol Biol. Phys. 35[5]. 1996.

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

Country: United States, setting: Tertiary care

Inclusion criteria Ten consecutive patients being treated with radiotherapy for prostate cancer at a single institution who consented to participate in the study.

Exclusion criteria -

Population number of patients = 10.

Interventions Prostate volume was delineated on magnetic resonance imaging (MRI), and non-contrast computerized tomographic (CT) scans, for three-dimensional (3D) treatment planning. Retrograde urethrograms were used to help to estimate the inferior border of the prostate.

Outcomes Prostate volume. Difference between CT and MRI estimates of prostate volume in the posterior and inferior regions.

Results Prostate volumes estimated from CT scans were consistently greater than those from MRI scans. The area of greatest and most consistent discrepancy was posterior followed by the apex inferiorly.

On average, the maximum discrepancy for the posterior prostate was 7mm and 4.5mm for the inferior apical prostate.

COMPARISON IN MEN BEFORE EBRT FOR PROSTATE CANCER	CT SCAN	MRI	OVERALL RESULT
Prostate volume	group mean 38.4 ml (95% CI 26.6 to 50.8 ml)	group mean 29.6 ml (95% CI 18.8 to 40.4 ml)	In 9/10 cases the prostate was larger on CT than MRI (p=0.001, paired t-test)

Villiers, Van Vaerenbergh, Vakaet, Bral, Claus, De Neve, Verstraete & De Meerleer . Interobserver delineation variation using CT versus combined CT plus MRI in intensity-modulated radiotherapy for prostate cancer. Strahlentherapie und Onkologie 181[7]. 2005.

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

Country: Belgium, setting: Tertiary care

Inclusion criteria 13 men were randomly selected from 187 treated with IMRT for prostate cancer at a single institution between 2000 and 2003.

Exclusion criteria -

Population , age range 57 to 74 years, mean age = 68 years.

Interventions 3 clinical oncologists delineated the prostate and seminal vesicles of each man on CT images for the purposes of treatment planning. The oncologists then repeated the process 2 weeks later with additional data from MR (pelvic phased array coil) and in consensus with a radiologist specialised in pelvic imaging.

Outcomes Clinical target volume (CTV), prostate volume and seminal vesicle volume, estimated from imaging.

Results The addition of MRI to CT in consensus reading with a radiologist resulted in a moderate decrease of the delineated clinical target volume, prostate volume and seminal vesicle volume, compared with CT alone. There was also a decrease of the variability of inter-observer delineation when MRI+CT was used, compared to CT alone.

COMPARISON IN MEN BEFORE IMRT FOR PROSTATE CANCER	CT SCAN	CT + MRI	OVERALL RESULT
Clinical target volume	group mean 67.95 ml (SD 8.21 ml)	group mean 63.50 ml (SD 3.03 ml)	Mean volume was significantly less for CT+MRI ($p<0.05$), and the variability in CTV was less for CT+MRI ($p<0.05$)
Prostate volume	group mean 50.74 ml (SD 7.43 ml)	group mean 48.10 ml (SD 2.77 ml)	Mean volume was significantly less for CT+MRI ($p<0.05$), and the variability in CTV was less for CT+MRI ($p<0.05$)
Seminal vesicle volume	group mean 17.21 ml (SD 2.47 ml)	group mean 15.41 ml (SD 1.36 ml)	Mean volume was significantly less for CT+MRI ($p<0.05$), and the variability in CTV was less for CT+MRI ($p<0.05$)

General comments The decrease in variability of CTV cannot be attributed to MRI alone since a radiologist was also involved in the reading of the images.

Sannazzari, Ragona, Redda, Giglioli, Isolato & Guarneri . CT-MRI image fusion for delineation of volumes in three-dimensional conformal radiation therapy in the treatment of localized prostate cancer. British Journal of Radiology 75[895]. 2002.

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

Country: Italy, setting: Tertiary care

Inclusion criteria Patients with localised prostate cancer treated with radical 3D-CRT at a single institution in 1999.

Population number of patients = 8, age range 61 to 76 years, median age = 71 years.

Interventions Patients had CT and MRI (pelvic phased array coil) studies for treatment planning before radiotherapy. The clinical target volume (CTV) (prostate plus seminal vesicles) was delineated on CT and MRI studies and image fusion was done using anatomical landmarks

Outcomes Prostate volume.

Results Using the dose-volume histogram the authors estimated that using MRI to delineate the CTV would spare approximately 10% of rectal volume and around 5% of bladder volume. They argue that organ motion during radiotherapy and the minimal differences between MRI and CT CTVs should be considered when deciding whether to base the CTV on MRI.

COMPARISON IN MEN BEFORE EBRT FOR PROSTATE CANCER	CT SCAN	MRI	OVERALL RESULT
Prostate volume	mean not reported	mean not reported	Authors report that the CT:MRI prostate volume ratio was 1.34:1. Their graph suggests a constant overestimation of 10 ml using CT.

General comments -

MRI vs. TRUS

Bates, Gillatt, Cavanagh & Speakman . A comparison of endorectal magnetic resonance imaging and transrectal ultrasonography in the local staging of prostate cancer with histopathological correlation. British Journal of Urology 79[6]. 1997.

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

Country: United Kingdom, setting: Tertiary care

Inclusion criteria Patients with clinically localised prostate cancer (based on serum PSA level, DRE, bone scan and body-coil MRI) who underwent radical prostatectomy.

Exclusion criteria -

Population number of patients = 20, age range 55 to 69 years, median age = 62 years.

Interventions Tumour stage was measured in all patients using transrectal ultrasound (TRUS) and endorectal MRI (ER-MRI) with a 0.5 T magnet. Preoperative tumour stage was compared with the histologic findings from the surgical specimen.

Outcomes Overall staging accuracy. Sensitivity and specificity of ER-MRI and TRUS for extracapsular extension (ECE) and seminal vesicle involvement (SVI). Rate of positive surgical margins.

Results Histological analysis showed 7/20 patients had stage T2 disease and 13/20 stage T3 disease. 13 patients had ECE and 3 SVI.

COMPARISON IN MEN BEFORE PROSTATECTOMY FOR PROSTATE CANCER	TRUS	MRI, ENDORECTAL COIL	OVERALL RESULT
Tumour staging accuracy	50%	75%	
Sensitivity for ECE	23%	38%	
Specificity for ECE	86%	100%	
Sensitivity for SVI	33%	100%	
Specificity for SVI	100%	94%	
Under-staging rate	50%	40%	

General comments Small sample

Presti Jr, Hricak, Narayan, Shinohara, White & Carroll . Local staging of prostatic carcinoma: Comparison of transrectal sonography and endorectal MR imaging. American Journal of Roentgenology 166[1]. 1996.

Design: Prospective case series (), evidence level: III

Country: United States, setting: Tertiary care

Inclusion criteria Patients with clinically localised prostate cancer who received radical prostatectomy.

Population number of patients = 56, mean age = 61 years.

Interventions Patients who had no evidence of gross ECE by transrectal ultrasound (TRUS) underwent endorectal coil MR imaging prior to radical prostatectomy. The pathological examination of the surgical specimen was the reference standard for ECE and SVI.

Outcomes Sensitivity and specificity of preoperative imaging for ECE and SVI.

Results 34/56 patients had pT2 disease and 22/56 had pT3 disease. 21/56 had ECE and 4/56 had SVI.

COMPARISON IN MEN BEFORE PROSTATECTOMY FOR PROSTATE CANCER	TRUS	MRI, ENDORECTAL COIL	OVERALL RESULT
Sensitivity for ECE	48% [95% CI 26 to 85]	91% [95% CI 70 to 99]	
Specificity for ECE	71% [95% CI 54 to 86]	49% [95% CI 31 to 66]	
Sensitivity for SVI	75% [95% CI 19 to 99]	50% [95% CI 7 to 93]	
Specificity for SVI	98% [95% CI 90 to 100]	94% [95% CI 84 to 99]	

General comments Imprecise estimates of sensitivity for SVI due to low prevalence.

Vapnek, Hricak, Shinohara, Popovich & Carroll . Staging accuracy of magnetic resonance imaging versus transrectal ultrasound in stages A and B prostatic cancer. Urologia Internationalis 53[4]. 1994.

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

Country: United States, setting: Tertiary care

Inclusion criteria Men with histologically confirmed, clinically localised prostate cancer who underwent radical prostatectomy and pelvic lymphadenectomy at a single institution between 1988 and 1992

Population number of patients = 64, age range 44 to 77 years, mean age = 67 years.

Interventions Presurgical staging involved body coil MRI (MRI), digital rectal examination (DRE) and transrectal ultrasound (TRUS). The histologic analysis of the lymphadenectomy and prostatectomy specimens was the reference standard for stage.

Outcomes Sensitivity and specificity of MRI and TRUS for the detection of extracapsular tumour extension (ECE) and seminal vesicle involvement (SVI).

Follow up Presurgical imaging was completed within a month before surgery.

Results 35/64 patients had ECE. 8/64 patients had SVI. 6/64 patients had LNI. 27/64 patients had T2 disease.

COMPARISON IN MEN BEFORE PROSTATECTOMY FOR PROSTATE CANCER	TRUS	MRI, NON-ENDORECTAL COIL	DRE	OVERALL RESULT
Accuracy	63%	67%	42%	
Sensitivity for ECE	49%	57%	not reported	
Specificity for ECE	86%	79%	not reported	
Sensitivity for SVI	25%	75%	not reported	
Specificity for SVI	96%	84%	not reported	
Under-staging rate	31%	22%	58%	
Over-staging rate	6%	11%	0% (by definition)	

Sanchez-Chapado, Angulo, Ibarburen, Aguado, Ruiz, Viano, Garcia-Segura, Gonzalez-Esteban & Rodriguez-Vallejo . Comparison of digital rectal examination, transrectal ultrasonography, and multicoil magnetic resonance imaging for preoperative evaluation of prostate cancer. European Urology 32[2]. 1997.

Design: Prospective case series (), evidence level: III

Country: Spain, setting: Tertiary care

Inclusion criteria Men treated with radical prostatectomy and lymphadenectomy for clinically localised, histologically confirmed, prostate cancer.

Population number of patients = 20, age range 54 to 73 years, mean age = 64 years.

Interventions Patients received digital rectal examination (DRE, n=10), transrectal ultrasound (TRUS, n=15), and magnetic resonance imaging (MRI, n=19) using integrated endorectal and pelvic phased-array coils for preoperative estimation of tumour volume and local extent of prostate cancer. The accuracy of presurgical staging was assessed using the pathological examination of the surgical specimens.

Outcomes Staging accuracy, sensitivity and specificity for SVI, ECE.

Results Histological analysis showed that 12/20 patients had stage pT2 disease and 8/20 stage pT3. 6/20 patients had ECE and 4/20 SVI

COMPARISON IN MEN BEFORE PROSTATECTOMY FOR PROSTATE	TRUS	MRI, ENDORECTAL COIL	DRE	OVERALL RESULT

CANCER			
Sensitivity for ECE	33%	66%	25%
Specificity for ECE	77%	85%	83%
Sensitivity for SVI	25%	75%	33%
Specificity for SVI	82%	93%	71%

MRI vs. MRS

Coakley, Kurhanewicz, Lu, Jones, Swanson, Chang, Carroll & Hricak . Prostate cancer tumor volume: measurement with endorectal MR and MR spectroscopic imaging. Radiology 223[1]. 2002.

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

Country: United States, setting: Tertiary care

Inclusion criteria Patients who underwent both MRI-MRS of the prostate and radical prostatectomy for histologically confirmed prostate cancer at a single institution in 1999.

Population number of patients = 37, age range 43 to 75 years, mean age = 57 years.

Interventions Endorectal MR and 3D MR spectroscopic imaging were performed using a 1.5T whole body machine. Two independent readers recorded peripheral zone tumour nodule location and volume. The criterion for malignant nodules on MR was not stated. The [choline + creatine] / citrate ratio was used to determine the malignancy of each MRS voxel. Any voxel with a ratio of at least 3 SDs greater than the normal (mean) ratio was designated malignant. One with a ratio of 2 to 3 SDs greater than normal was designated possibly malignant.

The reference standard to the MR and MRS reports was the histopathologic analysis of the surgical prostate specimen.

Outcomes Volume of peripheral zone tumour nodules, estimated from MR, MRS, and combined MR+MRS. Correlations between volume estimates from imaging and histopathology were calculated.

Follow up Mean interval from MR to surgery was 6 weeks.

Results 58 tumour nodules were identified in total, of these 51 were in the peripheral zone. 19 patients had a single nodule, 15 had 2 nodules and 3 had 3 nodules each. 33 patients had organ confined tumour and 4 extracapsular extension. Tumor volume estimation with all three methods was more accurate for higher tumour volumes.

COMPARISON IN MEN BEFORE PROSTATECTOMY FOR PROSTATE CANCER	MRI	MRS	MRI + MRS	OVERALL RESULT
Correlation between imaging and histological estimates of tumour volume	0.21 [95% CI -0.22 to 0.54]; for nodules >0.5 cm^3 0.49 [95% CI -0.06 to 0.80]	0.44 [95% CI 0.13 to 0.66]; for nodules >0.5 cm^3 0.59 [95% CI -0.28 to 0.79]	0.32 [95% CI -0.22 to 0.65]; for nodules >0.5 cm^3 0.55 [95% CI -0.04 to 0.82]	Measurements with MRS and combined MRS+MRI were significantly correlated with histological estimates ($p<0.05$)

General comments Authors conclude that the addition of 3D MR spectroscopic imaging to MR imaging increases overall accuracy of prostate cancer tumour volume measurement, although measurement variability limits consistent quantitative tumour volume estimation, particularly for small tumors

Hasumi, Suzuki, Taketomi, Matsui, Yamamoto, Ito, Kurokawa, Aoki, Endo & Yamanaka . The combination of multi-voxel MR spectroscopy with MR imaging improve the diagnostic accuracy for localization of prostate cancer. Anticancer Research 23[5B]. 2003.

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

Country: Japan, setting: Tertiary care

Inclusion criteria Patients with histologically confirmed prostate cancer, treated with radical prostatectomy at a single institution between 2001 and 2002

Exclusion criteria Patients with positive biopsy cores from the transition zone alone,

Population number of patients = 21, age range 52 to 82 years, median age = 70 years.

Interventions MR and MRS were performed using a 1.5T machine with an endorectal coil. The MR criterion for prostate cancer was based on low signal intensity focus in the peripheral zone on the T2 weighted images. The criterion for cancer on MRS was a threshold ratio of [choline+creatine] / citrate of 0.86. The reference standard diagnosis was the pathological examination of the surgical specimen.

Outcomes The diagnostic ability of MR and MRS for the diagnosis of unilateral versus bilateral prostate cancer.

Results On pathological findings 11/21 patients had unilateral prostate cancer and 10/21 patients bilateral prostate cancer. On MRI 4 unilateral tumours were not detected at all compared to 2 unilateral tumours on MRS.

COMPARISON IN	MRI	MRI + MRS	OVERALL RESULT

MEN BEFORE PROSTATECTOMY FOR PROSTATE CANCER		
Sensitivity for unilateral cancer	6/11 (55%)	8/11 (73%)
Sensitivity for bilateral cancer	9/10 (90%)	9/10 (90%)
Specificity for unilateral cancer	9/10 (90%)	9/10 (90%)
Specificity for bilateral cancer	10/11 (91%)	10/11 (91%)
Accuracy	15/21 (74%) for all cancers	17/21 (81%) for all cancers

Pucar, Koutcher, Shah, Dyke, Schwartz, Thaler, Kurhanewicz, Scardino, Kelly, Hricak & Zakian . Preliminary assessment of magnetic resonance spectroscopic imaging in predicting treatment outcome in patients with prostate cancer at high risk for relapse. Clinical Prostate Cancer 3[3]. 2004.

Design: Retrospective case series (prognosis), evidence level: III

Country: United States, setting: Tertiary care

Inclusion criteria Patients who had combined endorectal MRI/MRS examination before enrolment in a clinical trial of neoadjuvant chemo/hormonal therapy prior to RP, RT or continued hormonal therapy. Untreated histologically confirmed prostate cancer with metastasis or at high risk of metastasis (detailed criteria available in paper).

Exclusion criteria MRSI examinations of insufficient quality to be diagnostic. Patients who did not complete the trial for reasons other than treatment failure

Population number of patients = 16.

Interventions Combined endorectal MRI/MRS examination on a 1.5T scanner using a phased array coil and an endorectal coil. Voxels with a [choline+creatine]/[citrate] ratio of less than 0.5 were designated healthy, 0.5 to 0.6 were low grade, 0.7 to 3 were intermediate grade and greater than 3 were high grade.

Patients with then treated with neoadjuvant chemo/hormonal therapy prior to RP, RT or continued hormonal therapy.

Outcomes Time to PSA relapse, MRS and MRI TN stage. MRS cancer risk score was derived from the relative percentages of normal, low and high grade MRS voxels. In patients who had

RP, the pathologic T and N stage was the reference standard to the MRS and MRI estimates.

Follow up Median follow up was 26 months (range was 19 to 29 months).

Results 10/16 patients had RP, 3 of these patients had pathological stage pT2bN0 the remainder had locally advanced disease (in 2 cases with lymph node involvement). 6/16 patients experienced PSA relapse and 1 developed metastasis during the treatment phase of the trial. MRSI did not provide added prognostic value to MRI.

COMPARISON IN PROSTATE CANCER	MRI	MRI + MRS	OVERALL RESULT
Prediction of PSA relapse	MRI TN stage predicted PSA relapse p=0.02 (n=16)	MRS risk score did not predict PSA relapse (p=0.13) (n=16)	MRI TN stage appeared to be of more prognostic value
Correlation with pathological stage	for TN stage: r=0.78, p<0.01 (n=10)	for T stage: r=0.79, p<0.01; for TN stage r=0.68, p=0.03 (n=10)	both methods were similarly correlated with pathologic stage

General comments Small study. Univariate correlation of the two test results is an inappropriate comparison.

Wang, Hricak, Kattan, Chen, Scardino & Kuroiwa . Prediction of organ-confined prostate cancer: Incremental value of MR imaging and MR spectroscopic imaging to staging nomograms. Radiology 238[2]. 2006.

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

Country: United States, setting: Tertiary care

Inclusion criteria Patients referred for MR imaging before radical prostatectomy and pelvic lymphadenectomy for histologically confirmed prostate cancer, at a single institution between 1999 and 2004.

Exclusion criteria Neoadjuvant hormonal therapy or radiotherapy.

Population , age range 32 to 74 years, mean age = 58 years.

Interventions The likelihood of organ confined prostate cancer (OCPC) was calculated both using the Partin tables alone, and using a combination of the Partin tables and MR imaging. Authors divided patients into low, intermediate or high risk of extracapsular extension. 229 patients underwent endorectal MR imaging and 383 underwent combined endorectal MR imaging-MR spectroscopic imaging before radical prostatectomy. The accuracy of the nomogram and MR predictions of OCPC were determined using the pathology report after surgery.

Outcomes Using the MR reports, the risk of extracapsular extension (ECE), seminal vesicle invasion (SVI), and lymph node metastasis (LNI were scored from 1 to 5 ; the highest score was subtracted from 6 to determine a score (from 1 to 5) for the likelihood of organ confined prostate cancer. The area under the ROC curve was calculated for the MR, nomogram and

combined MR-nomogram predictions. The jack-knife method was used for bias correction

Results The final pathologic stage was pT2 in 72% of cases and pT3 or greater in the remaining 28% of cases. The contribution of MR findings was significant in all risk groups but was greatest in the intermediate- and high-risk groups (P <.01 for both).

COMPARISON IN MEN AFTER RADICAL RETRO-PUBIC PROSTATECTOMY	PARTIN TABLES	MRI	MRI + MRS	PARTIN TABLES + MRI	PARTIN TABLES + MRI + MRS	OVERALL RESULT
AUC for prediction of OCPC	0.80	0.77	0.84 (n=383)	0.84 (n=229)	0.90 (n=383)	MR findings contributed significant incremental value (P <=.02) to the nomograms. Accuracy in the prediction of OCPC with MR was higher when MR spectroscopic imaging was used, but the difference was not significant.

General comments Not all patients had both MR and MRS. The readers of the MR imaging were not blinded to the clinical data. Verification bias - only patients receiving RP were included.

Yu, Scheidler, Hricak, Vigneron, Zaloudek, Males, Nelson, Carroll & Kurhanewicz . Prostate cancer: prediction of extracapsular extension with endorectal MR imaging and three-dimensional proton MR spectroscopic imaging. Radiology 213[2]. 1999.

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

Country: United States, setting: Tertiary care

Inclusion criteria Patients with histological diagnosis of prostate cancer referred for combined endorectal and phased coil MRI and 3D MRS within 3 months before radical prostatectomy. Patients were treated between 1992 and 1997.

Exclusion criteria Non-diagnostic signal to noise ratio on MRS. Hormonal therapy before prostatectomy.

Population number of patients = 53, mean age = 60 years.

Interventions MR and MRS imaging were performed using a 1.5T system. The system used an endorectal coil combined with a pelvic phased array coil. Images were interpreted by two readers, one with 5 years experience of reporting prostate MR images and the other with 2 years experience.

Outcomes The presence of extracapsular extension (ECE) was graded on a five-point scale. For 3D MR spectroscopic imaging, a ratio of choline plus creatine to citrate 2 or more SDs above normal was diagnosed as cancer. The accuracy of MR imaging alone and combined MR imaging and 3D MR spectroscopic imaging, were compared with histopathologic results as the reference standard.

Results On pathological examination 33/53 (62%) of patients had organ confined prostate cancer.

COMPARISON IN MEN BEFORE PROSTATECTOMY FOR PROSTATE CANCER	MRI	MRS	MRI + MRS	OVERALL RESULT
AUC for detection of ECE	0.62 to 0.78 (for the two readers)	0.76	0.75 to 0.86	Combined MRS and MR improved the diagnostic performance of both readers ($p<0.01$)
Sensitivity for ECE	17 to 54%	50%	46 to 54%	The more experienced reader showed better sensitivity ($p<0.01$). Use of MRS improved sensitivity for the less experienced reader.
Specificity for ECE	94 to 95%	91%	93 to 96%	
PPV	44 to 76%	63%	65 to 81%	
NPV	79 to 88%	86%	85 to 88%	

General comments Exclusion of non-diagnostic MRS introduces bias.

IMAGING AND OUTCOME

Pinover, Hanlon, Lee, Kaplan & Hanks . Prostate carcinoma patients upstaged by imaging and treated with irradiation. An outcome-based analysis. Cancer 77[7]. 1996.
Design: Prospective case series (prognosis), evidence level: 3 Country: United States, setting: Tertiary care **Inclusion criteria** Men with clinically localised prostate cancer who had pretreatment (TRUS or MRI) imaging and were treated with radical radiotherapy at a single institution between 1986 and 1993. **Exclusion criteria** - **Population** number of patients = 348. **Interventions** Pretreatment staging included H&P, DRE, and bone scan. 333/348 patients had a serum PSA measurement. Patients received at least one of the following: transrectal ultrasound (TRUS), pelvic MRI or endorectal MRI. Patients were assigned 2 stages: the first used only palpation criteria whereas the second incorporated findings from imaging. All men received definitive radiotherapy to the prostate, and to the pelvic lymph nodes in cases where estimated of risk lymph node involvement was greater than 15%. **Outcomes** PSA relapse free survival, **Follow up** Median follow-up was 23 months (range 3 to 106 months). Men were followed up a 6 monthly intervals and none was lost to follow-up. **Results** Men with palpation stage T1a and T1b tumours (n=20) were excluded from analysis due to small numbers. Upstaging after imaging occurred in 115/312 men with palpation stage T1c to T2c tumours, and in 5/36 men with palpation stage T3 tumours. No patients were downstaged after imaging. The authors report that for a given palpation stage there was no difference in PSA relapse free survival between patients who were upstaged and those who were not. In men with palpation stage T1c to T2c tumours, 3 year PSA relapse free survival was 84% in the 115 men who were upstaged after imaging, and 71% in the 197 not upstaged (p=0.05). The authors argued that imaging does not add clinically relevant information to palpation staging. **General comments** Imaging criteria not fully defined and likely to differ between modalities. Unclear whether imaging played a part in the decision whether to irradiate the pelvic lymph nodes.

Cheng, Chen, Whittington, Malkowicz, Schnall, Tomaszewski & D'Amico . Clinical utility of endorectal MRI in determining PSA outcome for patients with biopsy Gleason score 7, PSA <or=10, and clinically localized prostate cancer. Int J Radiat.Oncol Biol. Phys. 55[1]. 2003.
Design: Retrospective case series (), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men with high grade but clinically localised prostate cancer treated with radical prostatectomy and pelvic lymphadenectomy at a single institution between 1989 and 2000. Men had clinical stage T1c or T2a prostate cancer, N0 on bone scan, with biopsy Gleason score of 7 or more.

Exclusion criteria -

Population number of patients = 147.

Interventions Preoperative staging included DRE, serum PSA measurement, endorectal and pelvic MRI (ER-MRI), bone scan, and TRUS sextant biopsy with Gleason score histological grading. All patients had bilateral pelvic lymph node sampling followed by radical prostatectomy.

Outcomes Time to PSA failure, defined as 2 consecutive detectable PSA values greater than 0.1 ng/ml after an undetectable value. Men were grouped for analysis by T2 or T3 on ER-MRI. Men were also stratified by PSA level

Follow up Median follow up was 4.5 years (range 1 to 10 years). Follow up frequency was 3 monthly, 6 monthly and yearly at 0 to 2, 2 to 5 and more than 5 post operative years respectively.

Results 132/147 patients had T2 disease on ER-MRI and 12/147 T3 disease. The 3 year PSA failure free survival rate was 78% and 25% for ER-MRI stage T2 and T3 respectively ($p<0.0001$).

The 3 year PSA failure free survival rate was 83%, 64%, 15% and 43% for ER-MRI stage T2 and PSA <= 10 ng/ml, ER-MRI stage T2 and PSA > 10 ng/ml, ER-MRI stage T3 and PSA <= 10 ng/ml and ER-MRI stage T3 and PSA > 10 ng/ml respectively.

General comments Same patient cohort as D'Amico et al 2000. Unclear whether the PSA subgroup analysis was decided beforehand or data-driven.

D'Amico, Whittington, Malkowicz, Schnall, Schultz, Cote, Tomaszewski & Wein . Endorectal magnetic resonance imaging as a predictor of biochemical outcome after radical prostatectomy in men with clinically localized prostate cancer. J Urol 164[3 Pt 1]. 2000.

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men with screen detected or clinically localised prostate cancer treated with radical prostatectomy and pelvic lymphadenectomy at a single institution between 1989 and 1999.

Exclusion criteria Men in whom MRI was contraindicated.

Population number of patients = 1025.

Interventions Preoperative staging included DRE, serum PSA measurement, endorectal and pelvic MRI, bone scan, and TRUS sextant biopsy with Gleason score histological grading.

Outcomes Time to PSA failure, defined as 2 consecutive detectable PSA values greater than 0.1 ng/ml after an undetectable value. Men were grouped for analysis according to low, intermediate or high risk of PSA failure (using pretreatment prognostic factors). Men were also grouped for analysis according to organ-confined disease on ER-MRI.

Follow up Median follow up was 3.5 years (range 0.25 to 10 years). Follow up frequency was 3 monthly, 6 monthly and yearly at 0 to 2, 2 to 5 and more than 5 post operative years respectively.

Results 623 patients were judged at low risk, 191 at intermediate risk and 211 at high risk of PSA failure. The 5 year actuarial freedom from PSA failure in men with ER-MRI T2 vs. T3 disease in the low, intermediate and high risk groups was: 91% vs. 70% (p=0.008), 72% vs. 33% (p<0.0001), and 33% vs. 5% (p<0.0001).

The authors argue that ER-MRI only added clinically meaningful information in the intermediate risk group. ER-MRI did not result in a great enough stratification of PSA failure risk in the low and high risk groups on which to base a clinical decision.

General comments ER-MRI criteria for T2 and T3 not well described. T2 and T3 dichotomisation may weaken ER-MRI as a prognostic factor.

Nguyen, Whittington, Koo, Schultz, Cote, Loffredo, Tempany, Titelbaum, Schnall, Renshaw, Tomaszewski & D'Amico . Quantifying the impact of seminal vesicle invasion identified using endorectal magnetic resonance imaging on PSA outcome after radiation therapy for patients with clinically localized prostate cancer. Int J Radiat.Oncol Biol. Phys. 59[2]. 2004.

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men were selected from the records of 2 doctors. Patients had clinically localised prostate cancer, treated with EBRT, but without hormonal therapy before PSA failure. Patients had an endorectal MRI (ER-MRI) for pretreatment staging.

Exclusion criteria Patients who refused MRI or in whom MRI was contraindicated.

Population number of patients = 250, median age = 72 years.

Interventions Pretreatment staging included TRUS sextant biopsy, endorectal MRI, DRE, serum PSA measurement and bone scan. All patients then received 3D-CRT. Men considered low risk for PSA relapse had 70 Gy to the prostate only, whereas patients at increased risk had 46 Gy to the prostate and seminal vesicles followed by 24 Gy to the prostate alone.

Outcomes PSA failure, defined as 3 consecutive rises above a nadir (1997 ASTRO definition). PSA failure was analysed according to the involvement of the seminal vesicles (SVI) and extracapsular extension (ECE) on ER-MRI.

Follow up After the end of treatment, the men attended follow-up examinations every 3 months for 2 years and every 6 months thereafter.

Results Using pretreatment PSA, clinical T-stage and Gleason score, 92/250 patients were judged as low risk of PSA failure and 158/250 patients were at increased risk of PSA failure.

18/250 patients had ER-MRI positive for SVI, only 1/18 of these patients was in the pretreatment low-risk group.

In multivariate analysis, SVI on ER-MRI was a significant adverse prognostic factor for PSA relapse (HR = 3.1; p=0.003), as was risk group (increased vs. low: HR = 5.1; p = 0.001). ECE on ER-MRI was not an significant independent prognostic factor.

BONE SCANNING

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

Design: Systematic review of diagnostic studies (diagnosis, screening), evidence level: II

Country: International

Inclusion criteria Studies reporting the staging of men with newly diagnosed prostate cancer (with no previous management) were included. English language papers only, published between 1966 and 2002.

Exclusion criteria Insufficient description of patient population or results.

Population number of patients = 8644.

Interventions The review included 23 studies reporting baseline bone scan tabulated by PSA level in newly diagnosed prostate cancer. The studies were published between 1991 and 2002, all but one of the studies were retrospective case series.

Outcomes The rate of positive bone scans in men with serum PSA levels of <10 ng/ml, 10 to 19.9 ng/ml, 20 to 49.9 ng/ml, 50 to 99.9 ng/ml and >100 ng/ml. The NPV of serum PSA <10 ng/ml and PSA <20 ng/ml for positive bone scan.

Results In the 23 studies combined, 1453/8644 bone scans were positive. The rates of positive bone scans by serum PSA level were:

<10 ng/ml : 53/2261 (2.3%; 95% CI 1.7 to 3.0%)

10 to 19.9 ng/ml : 61/1012 (6.0%; 95% CI 4.6 to 7.6%)

20 to 49.9 ng/ml : 86/540 (15.9%; 95% CI 12.9 to 19.2%)

50 to 99.9 ng/ml : 80/227 (35.2%; 95% CI 12.9 to 19.2%)

100 ng/ml : 86/540 (15.9%; 95% CI 12.9 to 19.2%)

The NPV of serum PSA for positive bone scan was between 84 and 100% for PSA <10 ng/ml . For PSA <20 ng/ml it was between 87 and 100%.

General comments There appears to be a linear relationship between PSA level and probability of positive bone scan. This review does not consider the possibility of false positive bone scans.

National Institute for Clinical Excellence . Guidance on cancer services - improving outcomes in urological cancers. The manual. 2002.

Design: Systematic review of diagnostic studies (diagnosis, screening), evidence level: II

Inclusion criteria Studies reporting the efficacy of bone scans for the detection of bone metastasis in urological cancer.

Exclusion criteria -

Population -

Interventions Bone scans for the detection of bone metastasis. Serum PSA levels, histological grade, clinical stage and bone pain as predictors of bone metastasis.

Outcomes The bone scan was used as the standard investigation and the other predictors of metastasis (PSA, histological grade, clinical stage and bone pain) were compared with bone scan results.

Results 18 prostate cancer case series reporting bone scans were identified, none however was a true diagnostic accuracy study.

The authors of the review concluded that the bone scan is well established in prostate cancer, the process is time consuming and expensive and there are questions about its specificity. The use of other prognostic markers could identify a group of patients in whom bone scanning may be omitted. Of the prognostic markers examined it appears that serum PSA level offers the best means of identifying those at increased risk of metastasis. The research suggests that men with PSA less than 10 ng/ml are unlikely to have bone metastases.

General comments -

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Table 30. Summary of included study characteristics: Does staging with MRI improve outcomes in men with prostate cancer?

Abbreviations: CT = computed tomography; PSA = prostate specific antigen; DRE = digital rectal examination; PCa = prostate cancer; RP = radical prostatectomy.

Study	Type of study	Country	Time period	No. of patients	Inclusion criteria	Exclusion criteria	Imaging	Clinical staging
Lavery et al. (2011)	Retrospective cohort	US	2005-2010	677	Low risk PCa patients (PSA ≤ 10 ng/ml & biopsy Gleason score ≤ 6) who underwent RP.	Patients who received imaging studies as part of an external research protocol, or for clinical reasons other than staging. International patients who received pre-operative workup outside the US were excluded.	Endorectal coil MRI in 60 (18%) patients (with or without CT or bone scan); CT in 53 (16%) patients; bone scan in 28 (9%) patients; CT & bone scan in 187 (57%) patients.	DRE

Table 31. Summary of included study characteristics: In which patients with prostate cancer will MRI staging alter treatment?

Abbreviations: AS = active surveillance; DCE = dynamic contrast enhanced; DRE = digital rectal examination; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopic imaging; NR = not reported; Pca = prostate cancer; RP = radical prostatectomy; TRUS = transrectal ultrasound; TRUSbx = TRUS-guided biopsy.

Study	Type of study	Country	Time period	No. of patients	Inclusion criteria	Exclusion criteria	Clinical staging group	MRI staging group	Notes
Augustin et al. (2009)	Prospective cohort	Austria	2006-2007	27	Clinically localised Pca patients who underwent RP.	Incomplete MRI data.	PSA & DRE	3.0-T pelvic phased-array coil MRI ≥ 6 weeks after biopsy.	
Bates et al. (1997)	Prospective cohort	UK	NR	20	Clinically localised Pca patients undergoing RP.	NR	TRUS	0.5-T body coil MRI.	
Brown et al. (2009)	Retrospective cohort	US	2002-2005	57	Patients undergoing MRI prior to RP for Pca; who subjectively felt at increased risk for extracapsular extension.	NR	NR	1.5-T endorectal & pelvic phased array coils MRI ≥ 8-10 weeks after biopsy.	
Cabrera et al. (2008)	Retrospective cohort	US	2000-2001	92	Patients with Pca who underwent MRI & selected AS for management.	Patients without baseline PSA level or Gleason score available or follow-up PSA monitoring < 3 months.	DRE	1.5-T endorectal coil & pelvic phased array coil MRI & MRS.	
Cirillo et al. (2008)	Retrospective cohort	Italy	2002-2005	143	Patients undergoing MRI for Pca.	NR	NR	1.5-T endorectal & pelvic phased-array coils MRI.	
Harat et al. (2012)	Cohort	Poland	2007-2011	174	Patients with newly diagnosed Pca.	NR	TRUS	MRI	Abstract only
Hegde et al. (2013)	Retrospective cohort	US	2008-2011	118	Pca patients treated with RP; T1-T2; presence of other adverse factors causing concern	NR	DRE, PSA, & TRUS	3.0-T endorectal coil & phased array coil T1, T2, DCE & DWI	

Johnston et al. (2011)	Cohort	UK	2006-2010	350	Patients undergoing RP for Pca who had a pre-operative MRI.	NR	NR	Standard non-contrast enhanced 1.5-T MRI without use of an endorectal coil.	Abstract only
Joseph et al. (2009)	Retrospective cohort	US	1998-2003	67	Patients with Pca who underwent combined MRI & MRSI followed by whole-pelvis external beam RT.	NR	DRE	1.5-T endorectal coil & pelvic phased-array coil MRI & MRSI.	
Kwek et al. (2004)	Prospective cohort	Japan	1999-2001	21	Pca patients who underwent MRI and RP.	NR	DRE	1.5-T pelvic phased-array coil MRI without endorectal coil.	
Labanaris et al. (2009)	Retrospective cohort	Germany	2004-2007	75	Patients undergoing RP for Pca who were sexually active & had satisfactory erectile function.	Extracapsular extension at posterolateral margin, palpable disease at apex, prior RT or hormone therapy, or pre-operative impotence	DRE	1.0-T endorectal phased-array coil conventional MRI & functional endorectal MRI (DCE or diffusion-weighted)	
Nguyen et al. (2004)	Retrospective cohort	US	1992-2001	250	Patients with clinically localised (T1c or T2) Pca receiving MRI prior to external beam RT with or without hormonal therapy before PSA failure.	Patient was claustrophobic, had indwelling pacemaker or aneurysm clips, or refused MRI.	TRUSbx	1.5-T endorectal coil MRI.	
Novis et al. (2011)	Prospective cohort	Brazil	2005-2006	35	Patients with TRUS-proven Pca stage T1c-T2a, Gleason ≤ 6 & PSA ≤ 10 ng/mL, who underwent RP.	Any previous hormonal blockade.	TRUS	1.5-T endorectal & pelvic phased array coils MRI, MRS & DCE-MRI ≥ 21 days after biopsy.	
Panebianco et al. (2012)	Prospective cohort	Italy	2006-2010	125	Patients with biopsy-proven Pca scheduled to undergo bilateral nerve-sparing RP; T1c-T2a; PSA < 10ng/ml; Gleason < 8.	More than one biopsy with Gleason > 6 at ipsilateral side.	DRE, PSA & TRUS	3.0-T endorectal coil & 8-channel phased array coil	
Ploussard et al. (2010)	Prospective cohort	France	2001-2008	96	Patients undergoing MRI before RP with PSA ≤ 10 ng/mL, stage T1-T2a, Gleason ≤ 6, & life expectancy > 10 years; who met AS criteria on biopsy.	Tumour involvement ≥ 3 cores or tumour length per core ≥ 3 mm at pathological biopsy.	NR	1.5-T endorectal coil MRI ≥ 6 weeks after biopsy.	
Porcaro et al. (2005)	Prospective cohort	Italy	NR	90	Patients with early Pca who underwent RP.	NR	NR	Endorectal coil	Abstract only
Poulakis et al. (2004)	Prospective cohort	Germany	1995-1998	201	Clinically localised Pca patients who underwent MRI, RP & pelvic lymphadenectomy.	Neoadjuvant therapy.	NR	1.0-T pelvic phased array coil MRI.	
Presti et al. (1996)	Prospective cohort	US	1992-1994	56	Pca patients with PSA < 10 ng/ml & no bone pain.	Positive bone scan or prior radiotherapy or hormone therapy.	DRE & TRUS	1.5-T endorectal & phased-array coils MRI.	
Pucar et al. (2004)	Prospective cohort	US	1997-2000	16	Stage T1-T2 Pca with PSA > 20 ng/ml or stage T3-T4 or any stage with Gleason ≥ 8 Pca patients receiving MRI prior to neoadjuvant, combined chemotherapy/hormone therapy prior to RP, RT or continued hormone therapy	< 4 weeks from major surgery, radiotherapy/chemotherapy, or immunological therapy; severe comorbidities or deep vein thrombosis or cardiovascular disease exacerbated within previous 6 months.	DRE	1.5-T phase array & endorectal coil MRI & MRSI combined.	
Renard-Penna et al. (2011)	Prospective cohort	France	2009-2010	101	Patients with Pca who underwent preoperative MRI & RP within 1 month of MRI.	No prior hormone blockade.	DRE	1.5-T pelvic phased array coil MRI ≥ 8 weeks after biopsy.	
Romano et al. (2011)	Prospective cohort	Italy	NR	97	Patients with early Pca referred for definitive radiation.	NR	NR	Endorectal coil MRI at least 45 days after biopsy.	Abstract only
Rørvik et al. (1999)	Prospective cohort	Norway	1995-1997	31	Patients with clinically localised Pca who underwent MRI prior to RP.	NR	NR	1.0-T endorectal coil MRI	

Sanchez-Chapado et al. (1997)	Prospective cohort	Spain	1993-1995	20	Patients with clinically localised Pca who underwent RP.	NR	DRE & TRUS	1.5-T endorectal coil & phased-array coil MRI ≥ 3 weeks after biopsy.	
Schiavina et al. (2011)	Prospective cohort	Italy	NR	46	Patients with intermediate- or high-risk Pca.	NR	DRE & TRUS	1.5-T conventional MRI & dynamic contrast-enhanced MRI at least 6 weeks after biopsy.	Abstract only
Soulie et al. (2001)	Prospective cohort	France	1995-1999	176	Pca stage T1-T2 patients undergoing RP	Prior ADT	NR	1.0-T pelvic phased-array coil MRI	
Terakedis et al. (2012)	Retrospective cohort	US	2008-2011	114	PCa patients referred for radiation therapy consultation	NR	NR	NR	Abstract only
Vapnek et al. (1994)	Prospective cohort	US	1988-1992	64	Patients with clinically localised PCa who underwent radical RP & pelvic lymphadenectomy.	NR	DRE & TRUS	1.5-T body coil MRI.	
Zhang et al. (2009)	Retrospective cohort	US	2003-2004	158	Patients who had undergone MRI before RP for PCa stage T1c.	Any previous neoadjuvant hormonal therapy, neoadjuvant chemotherapy, or radiotherapy of the pelvis.	NR	1.5-T endorectal & pelvic phased-array coils MRI combined with proton MRS.	

Health Economic Evidence

Information sources and eligibility criteria

The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, COCHRANE, NHS EED. Studies conducted in OECD countries other than the UK were considered (Guidelines Manual 2009).

Studies were selected for inclusion in the evidence review if the following criteria were met:

Both cost and health consequences of interventions reported (i.e. true cost-effectiveness analyses)

Conducted in an OECD country

Incremental results are reported or enough information is presented to allow incremental results to be derived

Studies that matched the population, interventions, comparators and outcomes specified in PICO

Studies that meet the applicability and quality criteria set out by NICE, including relevance to the NICE reference case and UK NHS

Note that studies that measured effectiveness using quality of life based outcomes (e.g. QALYs) were desirable but, where this evidence was unavailable, studies using alternative effectiveness measures (e.g. life years) were considered.

Selection of studies

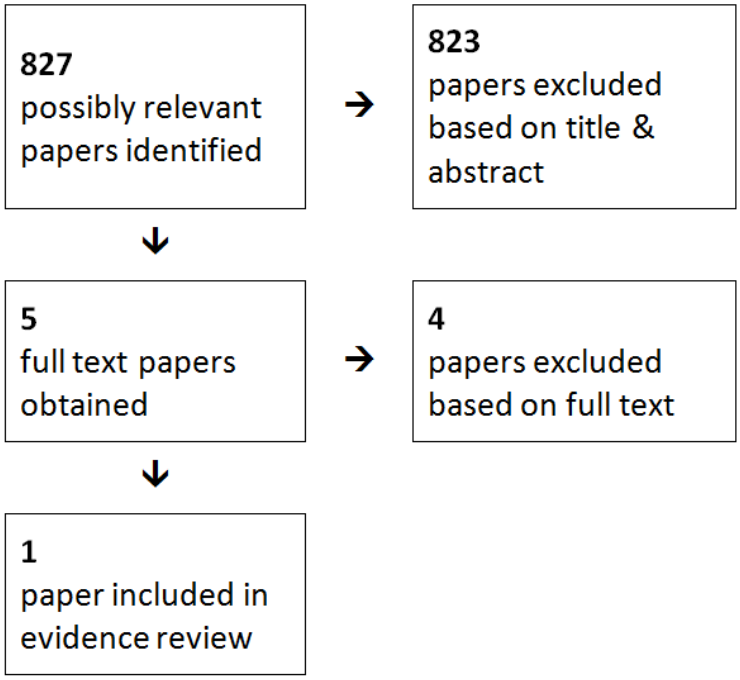
The health economist screened the literature search results obtained by the information specialist by checking the article's title and abstract for relevance to the review question. The full articles of non-excluded studies were then attained for appraisal and compared against the inclusion criteria specified above.

Results

The diagram below shows the results of the search and sifting process. It can be seen that 827 possibly relevant papers were identified. Of these, five full papers relating to this topic were obtained for appraisal. A further four papers were excluded as they were not applicable to the PICO or did not include an incremental analysis of both costs and health effects. Therefore only one paper (Stadlbauer et al. (2012)) was included in the current review of published economic evidence for this topic.

Stadlbauer et al. 2012 considered a German and Austrian health care setting and is written in German. Typically, non-English language studies are excluded from evidence reviews but, given the paucity of economic evidence in this area, an exception was made.

Figure 8: Summary of evidence search and sifting process for this topic



Quality and applicability of the included study

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

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

Table 32. Table showing methodological quality and applicability of the included study

Methodological quality	***Applicability***	
	Directly applicable	**Partially applicable**
Minor limitations		
Potentially serious limitations		Stadlbauer et al. 2012
Very serious limitations		

Modified GRADE table

The primary results of the analysis by Stadlbauer et al. 2012 are summarised in the modified GRADE table below.

Table 33. Modified GRADE table showing the included evidence (Stadlbauer et al. 2012) comparing methods of clinical staging

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

Evidence statements

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

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

References

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

Full evidence table

The full details of the study included in the evidence review are presented in the evidence table below.

Table 34. Full evidence table showing the included evidence (Mowatt et al. 2013) comparing subsequent investigation methods following an initial negative biopsy

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Study 1						
Author: Stadlbauer et al. **Year:** 2012 **Country:** Austria and Germany	**Type of analysis:** Cost-effectiveness analysis **Model structure:** Decision analytic model (decision tree) **Cycle length:** Not reported **Time horizon:** Not reported **Perspective:** Cost-effectiveness analysis from health insurance perspective for Austria and Germany **Source of base-line data:** Clinical data were sourced from a literature review (presumably systematic). English and German studies were searched using MEDLINE. The prevalence of prostate cancer was sourced from a meta-analysis by Divrik et al. 2007. In addition, studies of localised prostate cancer patients receiving clinical staging and subsequent prostatectomy were evaluated. **Source of effectiveness data:** Sensitivity and specificity rates	**Inclusion criteria:** The studies included in the literature review had to meet the following criteria: • MRI had to be used in a staging context • Findings had to be confirmed histologically • MRI had to be carried out with an MR scanner with 1.5 or 3 Tesla, • The MR images had to be at least reviewed by an experienced radiologist, • The MRI must at least meet the standards of the conventional anatomical MRI • Parameters on diagnostic accuracy had to be reported or be calculable from the study results	A. Therapy without MR staging B. Therapy with MR staging	**Effectiveness (QALYs)** Without MR staging With MR staging Incremental **Cost per patient:** Without MR staging With MR staging Incremental **Individual ICERs** Without MR staging With MR staging **ICER (cost per QALY):** **Uncertainty:** One-way and multi-way sensitivity analyses were conducted on variables of interest to the authors. Authors present results using individual cost-effectiveness ratios for each treatment. True ICERs were not presented but have been estimated using the data presented. **Varying the prevalence of prostate cancer, which has been staged incorrectly lower.** 25% 30% 35% 40% **Varying the type of MRI used (changing sensitivity, specificity and cost)**	12.191 12.289 0.099 €18,759 €16,125 -2,635 €1,539 €1,312 Dominant **ICER (cost/QALY)** Dominant Dominant Dominant Dominant	**Funding:** Not reported No competing interests are reported. **Comments** German language paper

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	were derived from published studies in the literature (as identified in the literature search outlined above). The staging accuracy of MRI was sourced from 16 published studies. One study was used for the effectiveness of conventional anatomical MRI and nine published studies were used for the effectiveness of additional MR sequences i.e. dynamic contrast enhanced MRI (DCE-MRI), diffusion-weighted MRI (DWI) and MR spectroscopy (MRS). The probability of impotence and incontinence after prostatectomy (along with treatments for these side effects) were calculated using data from ten publications (five meta-analyses and five cohort studies) while the probability of impotence and incontinence after radiotherapy was based on three published studies. Mortality probabilities were calculated using data from four publications. Life expectancy tables were derived using a web-based tool from the Cedars-Sinai Medical Center. **Source of utility data:** Utility data for the various health states were sourced from three published studies identified in the systematic review. **Source of cost data:** The costs for Germany were sourced from the financial eco-	• At least 20 people had to be included in the study Studies that met all of these criteria were used for the calculation of the probabilities and parameters used in the model. **Exclusion criteria:** Not reported **Base case (population):** Hypothetical cohort of patients with confirmed prostate cancer **Sample size:** Not stated. Results presented per patient. **Age:** 65 years old **Gender:** Men **Subgroup analysis:** Not reported		Dynamic Contrast Enhanced (DCE) MR Spectroscopy (MRS) Diffusion Weighted Imaging (DWI) Conventional atomic MRI **Varying therapy cost** Cost of prostate surgery €6,500 €11,125 €15,750 €20,375 €25,000 Cost of hormone/ radiation therapy €3,500 €4,375 €5,250 €6,125 €7,000 Two-way sensitivity analysis was also conducted whereby both therapy costs were varied simultaneously. Net monetary benefit (based on WTP = €3,500) is graphically presented with these two variables varied. Probabilistic sensitivity analysis (PSA) was not conducted.	**ICER (cost/QALY)** Dominant Dominant Dominant Dominant **ICER (cost/QALY)** €3,245 Dominant Dominant Dominant Dominant Dominant Dominant Dominant Dominant Dominant	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	nomics department at a university hospital and a Schloss Werneck MRI centre. The costs for Austria were sourced from a survey of the relevant departments at the state hospital and St Polten Hanusch Hospital Vienna. Five additional published studies were used to estimate the costs associated with the consequences of prostate surgery, radiation and hormone therapy. **Currency unit:** Euros (€) **Cost year:** Not reported **Discounting:** Not reported					

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Is there a need for radiological imaging in men with prostate cancer who are not intended for curative treatment?

Short Summary

Searches found no direct evidence about the influence of imaging on the timing of systemic treatment or frequency of clinical follow-up in men for whom radical therapy is not intended. Small case series (Noguchi *et al.* 2003; Yamashita *et al.* 1993; Knudson *et al.* 1991) reported outcomes in men with positive bone scans at presentation. Two of these series (Noguchi *et al.* 2003; Yamashita *et al.* 1993; Knudson *et al.* 1991) found extensive disease on bone scan was an adverse prognostic factor for survival. There is observational evidence (Bayley *et al.* 2004; Venkitaraman *et al.* 2007) that extensive disease on bone scan is an independent risk factor for spinal cord compression in men without functional neurological impairment.

PICO

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Men with prostate cancer: ▪ Who present with metastatic disease ▪ For whom radical treatment is not appropriate (due to age and co- morbidity)	▪ CT ▪ Isotope Bone Scan	▪ No CT ▪ No Isotope Bone Scan	▪ Timing of systemic treatment ▪ Timing and frequency of clinical follow-up

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

Evidence Summary

Searches found no direct evidence about the influence of imaging on the timing of systemic treatment or frequency of clinical follow-up. Three small case series (Noguchi *et al.* 2003; Yamashita *et al.* 1993; Knudson *et al.* 1991) reported the use of bone scans to predict survival in men with positive bone scans at presentation.

Noguchi and co-workers (Noguchi *et al.* 2003) reported that men with more than 4.6% positive area on a bone scan (PABS) had significantly lower disease specific survival than those with less than 4.6% PABS. In a multivariate prognostic model %PABS greater than 4.6% was the only statistically significant prognostic factor for disease specific survival (relative risk ratio 2.6, p=0.016). Median disease specific survival was 29 months in men with more than 4.6% PABS and 46.4 months in those with less than 4.6% PABS.

In the series of Knudson and co-workers (Knudson *et al.* 1991) the number of areas of uptake on the bone scan was related to overall survival. Men with two or less areas of uptake had better overall survival than those with more than two areas of uptake. This finding was not supported by Yamashita and co-workers (Yamashita *et al.* 1993) who did not find extent of disease on the bone scan to be a significant prognostic factor for overall survival in their series.

There is observational evidence (Bayley *et al.* 2004; Venkitaraman *et al.* 2007) that extensive of disease on bone scan is an independent risk factor for spinal cord compression in men without functional neurological impairment (see screening MRI topic).

Evidence Tables

Retrospective case series:

(Noguchi *et al.* 2003)
Design: Retrospective case series (prognosis), evidence level: 3 Country: Japan **Inclusion criteria** Men with newly diagnosed metastatic prostate cancer with no prior treatment, at a single institution between 1994 and 2000. **Exclusion criteria** - **Population** number of patients = 56. **Interventions** Radionuclide bone scan (Tc-99m HMDP), CT or MRI of the pelvis, serum PSA measurement, and TRUS. Patients were treated with an LHRH agonist and an antiandrogen (there was variability in the specific agents used). Number of bone lesions was determined using the method of Soloway (1988) and classified on the EOD scale (1 to 4). Percentage of the positive area on the bone scan (%PABS) was determined using digital image processing of bone scan tracings. **Outcomes** Disease specific survival. **Follow up** Men were clinically evaluated monthly for the first three months and thereafter every three months. Mean follow-up was 32 months (range 4 to 50 months). There was no loss to follow-up. **Results** 28/56 men died of prostate cancer. 8/56 men died of other causes. Prognostic factors for disease specific survival on univariate regression analysis: %PABS more than 4.6% (RR=2.6, P = 0.0155) serum alkaline phosphatase more than 467 IUI (RR=2.5, P = 0.0272) more than 14 bone lesions (RR=2.2, P = 0.0388) biopsy tumour grade (RR=2.1, P = 0.044) On multivariate analysis only %PABS > 4.6% was a significant prognostic factor (relative risk ratio =2.6, P=0.016) Median disease specific survival was 29 months in men with more than 4.6% PABS and 46.4 months in those with less than 4.6% PABS. **General comments** Continuous variables were dichotomised for analysis using cut-off values, unclear how these cut-offs were chosen. Small series with too few events for the number of prognostic variables examined.

(Knudson *et al.* 1991)
Design: Retrospective case series (prognosis), evidence level: 3 Country: United States **Inclusion criteria** Men with histologic diagnosis of prostate cancer, and bone metastases at initial bone scan, before any therapy. Unclear how the patients were selected. **Exclusion criteria** - **Population** number of patients = 76. **Interventions** Radionuclide bone scan (99mTc-MDP). Men were divided into 2 groups: group I was men with one or two areas of uptake on the bone scan, and group II was men with 3 or more areas of uptake. Patients received therapy although the type of therapy is not reported. **Outcomes** Progression free survival (using NCPC criteria) and overall survival, both measured from the initiation of therapy. **Follow up** The period analysis was 5 years from initiation of therapy. Unclear whether any patients were lost to follow-up, and whether all survivors were followed for 5 years. **Results** There were 31 patients in group I and 45 in group II. Z-scores were used to compare survival at 1,2,3,4 and 5 years after initiation of therapy Progression free survival: Disease progression occurred in 26/31 patients in group I and all patients in group II. Patients in group I had significantly better progression free survival than those in group II (at 2,3,4 and 5 years after therapy, $p<0.04$). Overall survival 12/31 patients in group I survived but no patients in group II survived. Patients in group I had significantly better overall survival than those in group II (at 3,4 and 5 years after therapy, $p<0.04$). **General comments** Z-scores, rather than log-rank test, used for survival analysis.

(Yamashita *et al.* 1993)
Design: Retrospective case series (prognosis), evidence level: 3 Country: Japan **Inclusion criteria** Men with newly diagnosed untreated prostate cancer with bone metastases, who presented to a single institution between 1977 and 1989. **Exclusion criteria** - **Population** number of patients = 76.

Interventions Tc-99 bone scan before treatment, and repeated every 3 to 6 months. Men were treated with variety of hormonal therapies, usually diethylstilbestrol phosphate or bilateral orchiectomy.

Outcomes Overall survival.

Follow up Median follow-up after treatment was 29 months (range 2 to 127 months).

Results Using the Japanese response criteria, 50/76 men responded to hormonal therapy. 50/76 men died of prostate cancer and 6/50 died of other causes.

For survival analysis patients were divided into groups based on the location of their bone disease: group I pelvis and lumbar spine, group II not pelvis or lumbar spine and group III had metastases in both pelvis, lumbar spine and other areas. There was no significant difference between the survival of the three groups (univariate analysis, log-rank tests).

When analysis was restricted to treatment responders patients in group I had better survival than those in groups II (p=0.017) and II (p=0.008). Survival did not differ between groups II and III.

Patients were stratified based on their EOD grade (I to IV). Log rank tests comparing EOD-I to grades II to IV combined showed no significant survival difference (p=0.154), even when analysis was restricted to treatment responders (p=0.215).

Health Economic Summary

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

Reference List

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In men with localised prostate cancer, what is the validity of published prostate cancer nomograms?

Short Summary

There is good evidence from observational studies, largely from outside the UK, that nomograms can accurately identify risks for men with prostate cancer. Most nomograms have been developed for use in men with clinically localised disease who are candidates for radical prostatectomy, and these are also the most widely validated. Although only one UK validation study was found, some nomograms have been validated in other western European countries.

PICO question

POPULATION	INTERVENTION	OUTCOMES
Men with localised prostate cancer	Published nomograms	Accuracy of prediction of: • overall survival • disease-free survival • time till next intervention • quality of life • lymph node involvement, • seminal vesicle involvement, • positive margins • PSA recurrence

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

Evidence Summary

Almost all the included studies were level 3 evidence, usually retrospective case series from academic institutions in the United States. Some authors developed multiple nomograms: M. Kattan, for example, was an author on 62% of the included papers. The most widely validated models were preoperative nomograms for men who were candidates for radical prostatectomy: the Kattan and co-workers (1998) nomogram for predicting disease recurrence and the Partin (1997, 2001) tables which predict pathological stage.

Where possible the discriminative accuracy of the nomograms was summarised using the area under the ROC curve (AUC) or concordance index (the equivalent of AUC for censored data). The AUC indicates the discriminative accuracy of the nomogram, ranging from 1 (predictions are correct every time) to 0.5 (the nomogram performs at chance level, a coin-toss). If a survival nomogram has an AUC of 0.75, for example, then for two randomly selected patients the nomogram has a 75% probability of correctly identifying which patient will survive the longest.

When the data were not censored, standard errors of AUC were calculated using the method of Hanley and McNeil (Hanley & McNeil 1982). Meta-analysis of AUC estimates for the Partin tables (Partin *et al.* 1997; Partin *et al.* 2001) was done using the method described by McClish (McClish 1992)

Abbreviations used in the tables:

ANN, artificial neural network; ASAP, atypical small acinar proliferation; CI, confidence interval; DRE, digital rectal examination; EBRT, external beam radiotherapy, 3D-CRT, three dimensional conformal radiotherapy; ECE, extracapsular extension; HGPIN, high grade prostatic intraepithelial neoplasia; LNI, lymph node involvement/invasion; OCD, organ confined disease; PCa, prostate carcinoma; PSA prostate-specific antigen; ROC receiver operating characteristic.; RP radical prostatectomy; SVI, seminal vesicle involvement;

Key to levels of nomogram validation used in the tables

A	External validation in a group of European patients by independent authors
B	External validation by independent authors
C	External validation by the nomogram developers
D	Internal validation (in the group of patients used to develop the nomogram)
–	No validation reported

Table 35. Men with raised PSA or suspicious DRE, before biopsy

Nomo-gram	Country	Disease state	Nomogram aim	Outcome	Predictors	Number of patients	Vali-dation	Accuracy
(Garzotto *et al.* 2005)	Development USA Validation USA	Men with PSA of 10 ng/ml or less, before prostate biopsy	To predict high grade PCa on biopsy	Risk of high grade PCa on biopsy	Age, DRE, PSA density	1189 patients for nomogram development and 510 for validation	C	AUC = 0.74 [cannot calculate CI]
(Karakiewicz *et al.* 2005)	Development Canada Germany Validation Germany Canada	Men with suspicious DRE and/or abnormal PSA before prostate biopsy (PSA < 50 ng/ml)	To predict presence of PCa on needle biopsy	Probability of PCa on needle biopsy.	Nomogram 1: age, DRE and PSA (ng/ml). Nomogram 2: age, DRE and PSA (ng/ml) and %fPSA	3 cohorts: 4193 in Montreal, 1762 in Hamburg and 512 in Montreal.	C	Nomogram 1: AUC = 0.69 [95% CI 0.67 – 0.71]. Nomogram 2: AUC = 0.77 [95% CI 0.75 – 0.79].
(Eastham *et al.* 1999)	Development USA	Men with raised PSA (but < 4 ng/ml) and/or suspicious DRE, before biopsy	To predict the probability of a biopsy positive for PCa	Probability of a positive biopsy	Race (African American or white), age and PSA (ng/ml)	700	D	AUC= 0.75 [95% CI 0.68 – 0.82]
(Finne *et al.* 2002)	Development Finland	Men with PSA between 4 and 30 ng/ml, before prostate biopsy	To predict the probability of prostate cancer diagnosis on biopsy	Probability of prostate cancer diagnosis on biopsy	Age, total PSA, % free PSA, prostate volume, DRE and family history of PCa	758	–	–
(Parekh *et al.* 2006)	Development USA	Men with suspicious DRE, PSA > 2.5ng/ml or first	To predict the probability of prostate cancer	Probability of prostate cancer diagnosis	Race, age, PSA level, family history of PCa, DRE result,	5519 for development	C	AUC= 0.70 in development sample

	Validation USA	degree relative with PCa, referred for biopsy	diagnosis on biopsy	on biopsy	prior negative biopsy	446 for validation		AUC= 0.66 [95% CI 0.60 –0.71] in validation sample
(Suzuki *et al.* 2006)	Development Japan Validation	Men with suspected prostate cancer, before biopsy	To predict the probability of prostate cancer diagnosis on biopsy	Probability of prostate cancer	Age, total PSA, free/total PSA ratio, prostate volume on TRUS and DRE (positive or negative).	834	C	AUC=0.82 [cannot calculate CI]
(Nam *et al.* 2006)	Development Canada Validation Canada	Men with abnormal DRE or raised PSA (>2.5 ng/ml) before prostate biopsy	To predict the probability of prostate cancer diagnosis on biopsy	Probabilities of prostate cancer, and high grade prostate cancer on biopsy	Race, age, PSA level, family history of PCa, prostate volume, prior negative biopsy, DRE result, symptoms	2637	D	AUC=0.77 [95%CI 0.76 – 0.79] for predicting PCa AUC=0.74 [95%CI 0.72 – 0.76] for predicting aggressive PCa

Table 36. Men with one or more negative prostate biopsies

Nomogram	Country	Disease state	Nomogram aim	Outcome	Predictors	Number of patients	Validation	Accuracy
(Lopez-Corona *et al.* 2003)	Development USA Validation USA	Patients with one or more negative prostate biopsies	Prediction of positive repeat biopsy	Probability of positive repeat biopsy	Age, DRE, number of negative cores taken, history of HGPIN, history of ASAP, PSA concentration, PSA slope, family history	343	C (Yanke *et al.* 2005)	AUC = 0.71 [95% CI 0.64 – 0.78]

(Chun *et al.* 2007)	Development Germany Validation Germany Italy USA	Patients with one or more negative prostate biopsies	Prediction of positive repeat biopsy	Probability of positive repeat biopsy	Age, DRE, PSA, % fPSA, previous biopsy sessions, sampling density.	721 in the development sample 361 in the validation samples	C	AUC = 0.75 in development sample AUC = 0.74 in validation sample

Table 37. Men with clinically localised prostate cancer who are candidates for brachytherapy

Nomogram	Country	Disease state	Nomogram aim	Outcome	Predictors	Number of patients	Validation	Accuracy
(Kattan *et al.* 2001)	Development USA Validation USA	Men with clinically localised PCa who are candidates for brachytherapy	To predict disease recurrence after brachytherapy	Probability of treatment failure within 5 years of brachytherapy	Pretreatment PSA, biopsy Gleason sum, clinical stage, and adjuvant EBRT.	920 in the nomogram development sample. 1827 and 765 in the validation samples.	C	AUC= 0.61 in one validation sample AUC= 0.64 in the other.
(Potters *et al.* 2002)	Development USA	Men with clinically localised PCa who are candidates for permanent prostate brachytherapy	To predict biochemical control after brachytherapy	Probability of biochemical control	The basic model contained pretreatment PSA (ng/ml), clinical stage and biopsy Gleason sum. The full model contained a further 23 variables related to the grade and distribution of cancer in the biopsy cores.	1073	D	Basic model AUC = 0.66 Full model AUC = 0.70] (AUC derived from Somers-D coefficients.)
(Kattan *et al.* 2006)	Development	Men with clinically localised PCa who are candidates for brachytherapy	To predict disease recurrence after brachytherapy	Probability of disease recurrence	Pre-treatment PSA level, biopsy Gleason sum, year of treatment, isotope and clinical stage	5889	D	AUC (c-index) =0.62

Table 38. Men with clinically localised prostate cancer who are candidates for radical prostatectomy

Nomogram	Country	Disease state	Nomogram aim	Outcome	Predictors	Number of patients	Validation	Accuracy
(Partin *et al.* 1997)	Development USA Validation USA Germany	Men with clinically localised PCa who are candidates for RP	To predict pathological stage of clinically localised cancer	Prediction of organ confined disease, capsular penetration, seminal vesicle involvement and lymph node involvement	PSA (ng/ml), TNM clinical stage and biopsy Gleason score	4133	A (Augustin *et al.* 2004; Beissner *et al.* 2002; Blute *et al.* 2000; Graefen *et al.* 2003a; Penson *et al.* 2002)	Prediction of ECE AUC=0.70 [95% CI 0.68–0.72] Prediction of SVI AUC=0.77 [95% CI 0.75–0.80] Prediction of LNI AUC=0.82 [95% CI 0.79–0.85] Prediction of OCD AUC=0.76 [95% CI 0.75–0.77]
(D'Amico *et al.* 1999)	Development USA Validation Germany	Men with clinically localised PCa, before RP or EBRT	To predict risk of disease recurrence after RP or EBRT	Probability of PSA failure within 2 years of RP or EBRT	PSA (ng/ml), biopsy Gleason score and clinical stage.	1654	A (Graefen *et al.* 2002a)	AUC=0.80
(Han *et al.* 2003)	Development USA Validation Germany	2 nomograms for men undergoing RP were developed: preoperative and post operative	To predict disease recurrence after RP	Probability of biochemical progression within 3,5,7 or 10 years of RP	The pre-op nomogram used: clinical TNM stage, biopsy Gleason score and PSA (ng/ml). The post-op nomogram used pathological stage instead of clinical stage.	2091	A (Poulakis *et al.* 2004)	AUC=0.732

Nomogram	Country	Disease state	Nomogram aim	Outcome	Predictors	Number of patients	Validation	Accuracy
(Kattan *et al.* 1998)	Development USA Validation USA Germany Australia Netherlands	Men with clinically localised PCa who are candidates for RP	To predict disease recurrence	Probability of treatment failure (disease recurrence) within 5 years of RP	PSA (ng/ml), clinical stage, and biopsy Gleason sum	983 patients for nomogram development and 168 for validation	A (Poulakis *et al.* 2004; Graefen *et al.* 2002; Bianco, Jr. *et al.* 2003; Greene *et al.* 2004; May *et al.* 2006)	AUC estimates range from 0.74 to 0.83
(Partin *et al.* 2001)	Development USA Validation Germany Turkey Japan	Men with clinically localised PCa who are candidates for RP	To predict pathological stage of clinically localised cancer	Probability of organ confined disease, capsular penetration, seminal vesicle involvement and lymph node involvement	PSA (ng/ml), TNM clinical stage and biopsy Gleason score	5079	A (Augustin *et al.* 2004; Steuber *et al.* 2005) Ayyathurai *et al.* 2006; Kuroiwa *et al.* 2007)	Prediction of ECE AUC=0.76 [95% CI 0.74–0.78] Prediction of SVI AUC=0.77 [95% CI 0.75–0.80] Prediction of LNI AUC=0.80 [95% CI 0.75–0.85] Prediction of OCD AUC=0.79 [95% CI 0.77–0.80]
(Stephenson *et al.* 2005b)	Development USA Validation	Men with clinically localised PCa who are candidates for RP.	To predict risk of disease recurrence after RP	Probability of disease recurrence within 10 years of RP	Base model: PSA (ng/ml), clinical stage, primary and secondary Gleason scores. The enhanced model also included the number of positive and negative	Development sample 1978 patients, validation sample 1545 patients	C	Base model AUC = 0.77 Full model AUC = 0.79

Nomogram	Country	Disease state	Nomogram aim	Outcome	Predictors	Number of patients	Validation	Accuracy
	USA				biopsy cores.			
(Kattan *et al.* 2003b)	Development USA Validation USA	Men with clinically localised PCa whose intended treatment is RP	To predict biochemical recurrence after RP	The probability of biochemical recurrence within 5 years of RP	Pre operative PSA (ng/ml), IL6SR (ng/ml) and TGF-beta 1; biopsy primary and secondary Gleason grade and clinical stage.	714	C	AUC = 0.83 Omitting IL6SR and TGF-beta-1 gave an AUC of 0.75.
(Stephenson *et al.* 2005c)	Development USA	Men who are candidates for RP for PCa	To predict the long term risk of metastasis after RP	Metastasis of PCa within 13 years of RP	Pre-biopsy PSA (ng/ml), primary and secondary Gleason grade, clinical stage, year of treatment and neoadjuvant hormonal therapy	4590	D	AUC= 0.79
(Cagiannos *et al.* 2003)	Development USA Germany Australia	Men with clinically localised PCa who are candidates for RP	To identify risk of positive pelvic lymph nodes	Probability of positive pelvic lymph nodes	Nomogram 1: PSA (ng/ml), clinical stage and biopsy Gleason sum. Nomogram 2 also included institutional incidence of positive lymph nodes	5510	D	Nomogram 1 AUC= 0.76 f Nomogram 2 AUC= 0.78
(Kattan *et al.* 2003a)	Development USA Germany Validation Netherlands	Men with clinically indolent cancer before RP	To predict the probability of indolent PCa	Probability of prostate confined tumour less than 5cc in volume	The basic model: PSA (ng/ml), primary and secondary biopsy Gleason grade. The full model also included: clinical T stage, prostate volume, mm of cancer and mm of non-cancer in biopsy cores.	409	C (Steyerberg *et al.* 2007)	Basic model AUC=0.64 [95%CI 0.57–0.71] Full model AUC= 0.79 [95%CI 0.73–0.85]

Nomogram	Country	Disease state	Nomogram aim	Outcome	Predictors	Number of patients	Validation	Accuracy
	Sweden Finland Belgium France Spain Italy Switzerland							
(Koh *et al.* 2003)	Development USA	Men with localised PCa who are candidates for RP	To predict seminal vesicle invasion	Probability of seminal vesicle invasion	Preoperative PSA (ng/ml). primary Gleason grade, secondary Gleason grade, clinical stage and % of cancer at the base of the prostate (in biopsy)	763	D	AUC= 0.88 [95%CI 0.83–0.94]
(Ohori *et al.* 2004)	Development USA	Men who are candidates for radical prostatectomy	To predict the probability of extra capsular extension in each lobe of the prostate	Probability of ECE in each lobe of the prostate	3 nomograms are presented, the most comprehensive requires: PSA (ng/ml), clinical T stage on each side, biopsy Gleason sum on each side, % positive cores on each side and % cancer in cores on each side.	763	D	AUC = 0.81 [95%CI 0.77–0.85] for the full model.
(Poulakis *et al.* 2004)	Development Validation	Men with clinically localised prostate cancer (but pN0) treated with RP	To predict the risk of disease recurrence after RP	Probability of biochemical recurrence within 5 years of RP	Clinical TNM stage, PSA (ng/ml), biopsy Gleason score and pMRI findings	191	D	Best ANN model AUC= 0.89 Best regression model

Nomogram	Country	Disease state	Nomogram aim	Outcome	Predictors	Number of patients	Validation	Accuracy
								AUC=0.781
(Gancarczyk *et al.* 2003)	Development USA	Men with clinically localised PCa who are candidates for RP	To predict pathological stage	Probability of organ confined disease, extracapsular extension, seminal vesicle invasion and lymph node invasion	PSA (ng/ml), Gleason score and percentage of positive biopsy cores	1510	–	–
(Martorana *et al.* 2000)	Development Italy	Men who are candidates for RP, PSA <50 ng/ml and clinical stage T3c or less	To predict pathologic stage, after RP	Probability of lymph node involvement, pT3ab, PT3c and pT4ab disease	Clinical T stage, PSA (ng/ml) and biopsy Gleason score	250	–	–
(Baccala *et al.* 2007)	Development USA Validation USA	Men with clinically localised PCa who are candidates for RP	To predict the probability of SVI after RP	Probability of SVI	Age, Pre-treatment PSA, Biopsy Gleason Score, Clinical T stage.	6740	D	AUC = 0.8 [95% CI 0.778 to 0.822]
(Stephenson *et al.* 2006)	Development USA Validation USA	Men with clinically localised PCa who are candidates for RP	To predict the likelihood of disease recurrence	Probability of disease recurrence	Pre-treatment PSA level, number of positive cores, number of negative cores, clinical stage, primary biopsy Gleason score and secondary biopsy Gleason score	3253	C	AUC (c-index) of 0.76 and 0.79 in internal and external validation groups respectively.
(Walz *et al.* 2007)	Not reported	Men with clinically localised PCa, candi-	To predict survival	Probability of survival at 10 years after	Age-at-therapy (years) and Charlston Comor-	9983	C	Accuracy was 86.6% in the external validation co-

Nomogram	Country	Disease state	Nomogram aim	Outcome	Predictors	Number of patients	Validation	Accuracy
		dates for either RP or EBRT		treatment	bidity Index			hort.
(Wang *et al.* 2007)	Development USA	Men with clinically localised PCa, candidates for RP	To predict seminal vesicle involvement in the surgical specimen	Probability of SVI	Pre-treatment PSA level, Gleason grade at biopsy, clinical stage, MRI findings and percentage of positive biopsy cores	573	D	AUC = 0.87 [95% CI 0.784 to 0.956]
(Crippa *et al.* 2006)	Development USA	Men with clinically localised PCa, candidates for RP	To predict pathological stage after RP	Probability of pathological stage T2, T3 and T4 disease	Pre-treatment PSA, biopsy Gleason score and percent of positive biopsy cores	898	D	AUC not reported.
(Joniau *et al.* 2007)	Development Belgium	Men with clinically localised PCa, candidates for RP	To predict pathological stage after RP	Probabilities of organ confined disease (OCD), seminal vesicle involvement (SVI), and extracapsular extension (ECE)	Biopsy Gleason score (3+4 or less vs. 4+3 or more) and by PSA (10 ng/ml or less, 10 to 20 ng/ml or more than 20 ng/ml)	200	D	AUC for OCD was 0.59 (95% CI 0.49 to 0.67), for ECE: 0.61 (95% CI 0.52 to 0.70), for SVI: 0.73 (95% CI 0.65 to 0.80) and for adjacent structure involvement 0.80 (95% CI 0.732 to 0.86).
(Chun *et al.* 2006)	Development USA	Men with clinically localised PCa, candidates for RP	To predict upgrading of Gleason sum between biopsy and RP	Gleason sum of the prostatectomy	Pre-operative variables: PSA, clinical stage, biopsy Gleason primary pattern, and biopsy Gleason secondary pattern	2982	D	Accuracy 80% (AUC not reported).
(Briganti *et al.* 2007)	Not reported	Men with clinically localised PCa, candidates for RP	To predict risk of nonobturator lymph node invasion (NOLNI)	Probability of NOLNI	Preoperative variables: PSA, clinical tumour stage and biopsy Gleason score	565	D	AUC = 0.8 [95% CI 0.710 to 0.890]

Nomogram	Country	Disease state	Nomogram aim	Outcome	Predictors	Number of patients	Validation	Accuracy
(Briganti *et al.* 2006a)	Not reported	Men with clinically localised PCa, candidates for RP	To predict risk of lymph node invasion (LNI)	Probability of LNI	Preoperative variables: PSA, clinical tumour stage and biopsy Gleason sum.	602	D	AUC = 0.76 [95% CI 0.690 to 0.830]
(Kuroiwa *et al.* 2007)	Development Japan	Men with clinically localised PCa, candidates for RP	To predict pathological stage after RP	Probability of OCD, LNI	Preoperative PSA, clinical stage and biopsy Gleason score.	1188	D	For OCD: AUC = 0.715 [95% CI 0.686 to 0.744] For LNI: AUC = 0.861 [95% CI 0.784 to 0.938]
(Steuber *et al.* 2006)	Development Germany	Men with clinically localised PCa, candidates for RP	To predict side specific extracapsular extension (SSECE) of prostate cancer.	Probability of SSECE	Clinical stage, pretreatment PSA, biopsy Gleason sum, percent positive cores and percent cancer in the biopsy specimen	1118	D	AUC = 0.84 [95% CI 0.814 to 0.866]
(Nakanishi *et al.* 2007)	Development USA	Men with clinically localised PCa, candidates for RP, with biopsy Gleason score ≤ 3+4	To select men for active surveillance	Probability of low volume and low grade PCa in RP specimen	Pretreatment variables: age, PSA, prostate volume, maximum tumour length in a core, and number of positive cores.	421	D	AUC = 0.839 [95% CI 0.796 to 0.882]

Table 39. Men with clinically localised prostate cancer who are candidates for radical EBRT

Nomogram	Country	Disease state	Nomogram aim	Outcome	Predictors	Number of patients	Validation	Accuracy
(Kattan *et al.* 2000)	Development USA Validation USA	Men who are candidates for 3D conformal radiotherapy for PCa	To predict the probability of disease recurrence	Probability of PSA recurrence within 5 years of 3D-CRT	Pretreatment PSA (ng/ml), clinical stage, biopsy Gleason sum, radiation dose and neoadjuvant hormone therapy	Development sample 1042, validation sample 912	C	AUC=0.76
(Kattan *et al.* 2003c)	Development USA Validation USA	Men with clinically localised PCa who are candidates for 3D conformal radiotherapy	To predict the risk of metastasis after 3D-CRT	Probability of radiologically defined metastasis within 5 years of 3D-CRT	Pretreatment PSA (ng/ml), clinical stage and biopsy Gleason sum	1677 for nomogram development and 1626 for validation	C	AUC= 0.81
(D'Amico *et al.* 1999)	Development USA	Men with clinically localised PCa, before RP or EBRT	To predict risk of disease recurrence after RP or EBRT	Probability of PSA failure within 2 years of RP or EBRT	PSA (ng/ml), biopsy Gleason score and clinical stage.	1654	D	–
(Parker *et al.* 2002)	Development UK	Men with clinically localised PCa who are candidates for neoadjuvant hormone therapy and radical radiotherapy	To predict the risk of biochemical recurrence	The probability of biochemical recurrence within 5 years of radical radiotherapy.	T stage, Gleason score and preoperative PSA (ng/ml)	517	–	–

Table 40. Men after radical prostatectomy for prostate cancer

Nomogram	Country	Disease state	Nomogram aim	Outcome	Predictors	Number of patients	Validation	Accuracy
(Han *et al.* 2003)	Development USA Validation Germany	2 nomograms for men undergoing RP were developed: preoperative and post operative	To predict the probability of disease recurrence after RP	Probability of biochemical progression within 3,5,7 or 10 years of RP	The pre-op nomogram used: clinical TNM stage, biopsy Gleason score and PSA (ng/ml). The post-op nomogram used pathological stage instead of clinical stage.	2091	A {Poulakis, 2004 17 /id	
(Kattan *et al.* 1999)	Development USA Validation USA Netherlands Australia	Men treated with RP and pelvic lymphadenectomy for PCa	To predict the probability of disease recurrence after RP	Probability of PSA recurrence within 7 years of RP	Preop. PSA, Gleason sum, prostatic capsular invasion, surgical margins, seminal vesicle invasion, and lymph node positivity	Nomogram development sample n = 996, validation sample n = 322	A (Bianco, Jr. *et al.* 2003; Graefen *et al* 2002b, RRamsden, 2004).	Estimates of AUC ranged from 0.74 to 0.85
(Stephenson *et al.* 2005a)	Development USA Validation USA	Men after RP for PCa	To predict the probability of disease recurrence after RP	Probability of disease recurrence within 10 years of RP	Year of RP, surgical margins, extracapsular extension, seminal vesicle invasion, lymph node involvement, primary and secondary Gleason score (from surgical specimen) and preoperative PSA (ng/ml)	Nomogram development sample of 1881 men, validation samples of 1782 and 1357 men	C	AUC = 0.79
(Dotan *et al.* 2005)	Development	Men rising PSA after RP	To predict bone metas-	Probability of a positive	Pre treatment PSA (ng/ml), surgical mar-	239	D	AUC = 0.93

Nomogram	Country	Disease state	Nomogram aim	Outcome	Predictors	Number of patients	Validation	Accuracy
	USA		tases	bone scan	gin (positive or negative), seminal vesicle involvement, Gleason sum of RP specimen, extracapsular extension, trigger PSA (before the bone scan), PSA slope, PSA velocity			
(Stephenson *et al.* 2007)	Development USA	Men with biochemical recurrence after RP for PCa	To predict the outcome of salvage radiotherapy (SRT)	Probability of 6 year recurrence free survival	Prostatectomy PSA, Gleason score, SVI, surgical margins, LNI, persistently elevated postoperative PSA, pre-SRT PSA, PSA-DT, neoadjuvant ADT, and radiation dose	1540	D	AUC = 0.69.
(Stephenson *et al.* 2005d)	Development USA	Men after RP for PCa	To predict the probability of disease recurrence after RP	Probability of biochemical recurrence within 7 years of RP	Clinical variables from Kattan post-op nomogram plus gene expression information (models selected up to 8 genes from a set of 46)	79	D	Gene expression model AUC = 0.75 Kattan post-op model AUC = 0.84 Combined model AUC = 0.89.

Table 41. Men with progressing prostate cancer after castration

Nomogram	Country	Disease state	Nomogram aim	Outcome	Predictors	Number of patients	Validation	Accuracy
(Smaletz *et al.* 2002)	Development USA Validation USA	Men with progressive metastatic prostate cancer, after castration	To predict survival	One and two year overall survival, median survival	Age, Karnofsky performance status, haemoglobin; levels of: prostate-specific antigen, lactate dehydrogenase , alkaline phosphatase, and albumin	409 patients for nomogram development and 433 for validation	C	AUC = 0.67
(Halabi *et al.* 2003)	Development USA Validation USA	Men with hormone refractory metastatic prostate cancer	To predict survival	Probability of surviving 1 year and 2 years. Median survival	Levels of lactate dehydrogenase, prostate-specific antigen, alkaline phosphatase, Gleason sum, Eastern Cooperative Oncology Group performance status, haemoglobin, and the presence of visceral disease	760 for nomogram development and 341 for validation	C	AUC = 0.68
(Svatek *et al.* 2006)	Development USA	Men with androgen independent prostate cancer after androgen deprivation therapy.	To predict survival	Androgen-independent-prostate-cancer-specific survival	PSA at initiation of androgen deprivation therapy (ADT), PSA doubling time after AIPC diagnosis, nadir PSA on ADT and time from ADT to AIPC.	129	D	AUC = 0.81

Table 42. Men with clinically localised prostate cancer who are candidates for primary androgen suppression therapy

Nomogram	Country	Disease state	Nomogram aim	Outcome	Predictors	Number of patients	Validation	Accuracy
(Graff *et al.* 2007)	Development USA	Men with clinically localised PCa	To estimate overall survival probability	Probability of overall survival at 5 years after diagnosis.	DRE (normal or not), Age (years), PSA (ng/ml) and biopsy Gleason score.	276	–	

Evidence Tables

Prospective case series

Finne, Auvinen, Aro, Juusela, Maattanen, Rannikko, Hakama, Tammela & Stenman. Estimation of prostate cancer risk on the basis of total and free prostate-specific antigen, prostate volume and digital rectal examination. European Urology 41[6]. 2002.

Design: Prospective case series (prognosis), evidence level: 3

Country: Finland, setting: Community

Inclusion criteria Men identified from a population screening exercise with PSA between 4 and 20 ng/ml, who underwent biopsy. Complete data on the prognostic variables were only available for 758/856 men.

Exclusion criteria -

Population number of patients = 758, age range 55 to 57 years, mean age = 62 years.

Interventions DRE, defined as positive if anything abnormal was palpated.

Total and free serum PSA were derived from frozen samples (Prostatus PSA and Hybridtech Tandem-E assays).

Prostate volume was measured using TRUS.

Sextant biopsies were performed under TRUS guidance; additional biopsies were taken from suspicious lesions identified by DRE or TRUS.

Other prognostic variables were: age and family history of prostate cancer (father or brother).

Outcomes Probability of biopsy diagnosis of prostate cancer.

Follow up Men with negative initial biopsies were re-biopsied if they had HGPIN (n=1) or serum PSA >10 ng/ml (n=?).

Results Prostate cancer was diagnosed following biopsy in 200/758 men.

The sensitivity and specificity for PCa corresponding to threshold values of nomogram PCa probability were:

PCa probability cut-off	*Sensitivity*	*Specificity*
0.06	98.5%	14%
0.09	95%	27%
0.12	92%	36%
0.15	88%	45%
0.18	84%	55%

Nomogram details	
Clinical disease state	Men with PSA between 4 and 30 ng/ml, before prostate biopsy
Nomogram aim	To predict the probability of prostate cancer diagnosis on biopsy
Outcome	Probability of prostate cancer diagnosis on biopsy
Predictors	Age, total PSA, % free PSA, prostate volume, DRE and family history of PCa
Number of patients	758
Validation	No

General comments Low rate of re-biopsy?

Garzotto, Collins, Priest, Spurgeon, Hsieh, Beer & Mori. Nomogram for the prediction of high-grade prostate cancer on ultrasound guided needle biopsy. Journal of Clinical Oncology 23[16]. 2005.

Design: Prospective case series (prognosis), evidence level: 3

Country: United States

Inclusion criteria A prospective series of men undergoing prostate biopsy, with serum PSA of 10 ng/ml or less.

Exclusion criteria -

Population number of patients = 1699.

Interventions Prognostic variables included: age, race, family history, DRE, PSA concentration, PSA density, PSA doubling time and ultrasound findings.

Prostate biopsy (at least 6 cores)

Outcomes High grade prostate cancer on biopsy.

Follow up Not reported whether there were repeat biopsies.

Results High grade PCa was diagnosed in 157 patients.

The authors developed a nomogram by entering the predictor variables into a logistic regression. It appears that only age, DRE and PSA density were used in the final nomogram.

The nomogram was validated in an independent set of 510 patients: area under the ROC curve was 0.74 for the nomogram.

Nomogram details

Clinical disease state	Men with PSA of 10 ng/ml or less, before prostate biopsy
Nomogram aim	To predict high grade PCa on biopsy
Outcome	Risk of high grade PCa on biopsy
Predictors	Age, DRE, PSA density
Number of patients	1189 patients for nomogram development and 510 for validation
Validation	Yes, 30% of the original cohort were used for validation. The nomogram was derived using the other 70%.
Accuracy measure	AUC = 0.74 [cannot calculate CI]

General comments Abstract only, limited detail about methods and participants. Continuous variables were split into categories. Some of the original predictor variables appear to have been excluded from the final nomogram. Insufficient information to calculate confidence intervals for AUC.

Retrospective case series

Yanke, Gonen, Scardino & Kattan. Validation of a nomogram for predicting positive repeat biopsy for prostate cancer. Journal of Urology 173[2]. 2005.

Design: Retrospective case series, evidence level: 3, Country: United States

Inclusion criteria Men undergoing one or more repeat biopsies (at one institution) after an initial negative biopsy, between 1993 and 2003. Indications for repeat biopsy at this institution were: HGPIN and/or ASAP, persistently increased PSA, positive DRE or PSA slope greater than 0.75 ng/ml/year.

Exclusion criteria Missing PSA values, DRE results or family history.

Population number of patients = 230, age range 38 to 81 years, mean age = 66 years.

Interventions The prognostic variables measured were: patient age, serum PSA, PSA slope (ng/ml/year), DRE and the cumulative number of previous negative cores.

All patients had either sextant biopsy (1993 to 1998) or 12 core biopsy (1999 to 2003).

Outcomes Probability of repeat biopsy positive for PCa.

Follow up The mean number of biopsy sessions was 2.56 (range 2 to 7).

Results HGPIN was present in 32/230 patients and ASAP in 71/230 patients. Prostate cancer was eventually diagnosed in 78/230 patients.

AUC = 0.71 [95% CI 0.64 - 0.78] in this validation sample. Using the predictor variables alone

was less accurate than using the combined nomogram.

Validation details	
Nomogram name	validates Lopez-Corona et al (2003)
Number of patients	230

General comments The authors state that the validation sample in this study was more heterogeneous than that used in the development sample (Lopez-Corona et al, 2005).

Stephenson, Smith, Kattan, Satagopan, Reuter, Scardino & Gerald. Integration of gene expression profiling and clinical variables to predict prostate carcinoma recurrence after radical prostatectomy. Cancer 104[2]. 2005.

Design: Retrospective case series (prognosis), evidence level:

Country: United States, setting: Tertiary care

Inclusion criteria Men with clinically localised PCa, treated with RP at Memorial Sloan-Kettering Cancer Centre between 1993 and 1999.

Exclusion criteria -

Population number of patients = 79, age range 50 to 73 years, mean age = 63 years.

Interventions Gene expression analysis using the Affymetrix U133A human gene array. The predictor variables used for the Kattan postoperative nomogram were also measured.

Outcomes Disease recurrence, defined as 3 consecutive PSA increases greater than 0.1 ng/ml.

Follow up Median follow up was 4.8 years (range 0.9 to 9 years).

Results Logistic regression models were developed for each case (n=79) and validated using "leave-one-out-cross-validation". The models included 5, 6, 7 and 8 different genes in 2, 64, 12 and 1 cases respectively. 3 genes were included in nearly all models: EI24, EPB29 and MAP4K4.

The modelling approach using gene variables alone accurately classified 59 (75%) tissue samples. However, this predictive accuracy was inferior to the nomogram (concordance index, 0.75 vs. 0.84, P = 0.01).

Models combining clinical and gene variables accurately classified 70 (89%) tissue samples and the predictive accuracy using this approach (concordance index, 0.89) was superior to the nomogram (P = 0.009) and models based on gene variables alone (P < 0.001).

Nomogram details

Clinical disease state	Men after RP for PCa
Nomogram aim	To predict risk of disease recurrence
Outcome	Biochemical recurrence within 7 years of RP
Predictors	Clinical variables from Kattan post-op nomogram plus gene expression information (models selected up to 8 genes from a set of 46)
Number of patients	79
Validation	Internal validation (leave-one-out-cross-validation)
Accuracy measure	The area under the ROC curve (the concordance index) was 0.75 for the gene expression model, 0.84 for the Kattan post-operative nomogram and 0.89 for a model combining the gene expression data with the Kattan nomogram prediction.

General comments Small number of events (37 tumour recurrences) but large number of prognostic factors (thousands of potential prognostic genes in the gene array). It was unclear whether the predictive accuracy figures for the models using genetic information, refer to a combination of all 79 models or the most accurate one.

Stephenson, Scardino, Eastham, Bianco, Dotan & Kattan. Predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy: A new preoperative nomogram. Journal of Urology 173[4]. 2005.

Design: Retrospective case series (prognosis), evidence level:

Country: United States, setting: Tertiary care

Inclusion criteria Patients with clinically localised PCa admitted with the intention to treat with RP (n=1978) by 2 surgeons at a single institution. An independent validation set of 1545 men, treated by other surgeons at the institution, was also included.

Exclusion criteria Neoadjuvant therapy, incomplete records.

Population number of patients = 3523.

Interventions Preoperative PSA test, systematic prostate biopsy (primary and secondary Gleason score, and the number of positive and negative cores are used as prognostic variables), and clinical stage. All patients

Outcomes Probability of disease progression within 10 years of RP. Authors defined disease progression as PSA level of 0.40 ng/ml and rising, clinical progression, adjuvant therapy or aborted RP due to positive lymph nodes.

Follow up Median follow up for those free of progression was 26 months for the nomogram development cohort and 38 months for the validation cohort

Results The 10 year progression free probability was 77% in the nomogram development sample (but not reported in the validation sample).

Nomogram details	
Clinical disease state	Men with clinically localised PCa who are candidates for RP.
Nomogram aim	To predict risk of disease recurrence after RP
Outcome	Probability of disease recurrence within 10 years of RP
Predictors	Base model: PSA (ng/ml), clinical stage, primary and secondary Gleason score. The enhanced model also included the number of positive and negative biopsy cores.
Number of patients	Development sample 1978 patients, validation sample 1545 patients
Validation	Internal: independent validation sample.
Accuracy measure	With the validation sample, the area under the ROC curve was 0.77 for the base model and 0.79 for the enhanced model.

General comments Abstract only. This study reports an update of the Kattan (1998) preoperative nomogram.

Kattan, Zelefsky, Kupelian, Scardino, Fuks & Leibel. Pretreatment nomogram for predicting the outcome of three-dimensional conformal radiotherapy in prostate cancer. Journal of Clinical Oncology 18[19]. 2000.

Design: Retrospective case series (prognosis), evidence level: 2+

Country: United States, setting: Tertiary care

Inclusion criteria Men treated with 3D conformal radiotherapy for histologically confirmed prostate cancer at a single institution (MSKCC) 1988-1998. A validation sample of 912 similarly treated men was drawn from another institution (Cleveland Clinic), 1986-1998.

Exclusion criteria Patients with missing data were excluded (N=38).

Population number of patients = 1042, age range 46 to 86 years, median age = 68 years.

Interventions Clinical staging, serum PSA tested used the Tosoh radioimmunoassay All patients had 3D-conformal radiotherapy (dose range 64.8 to 86 Gy, in daily dose fractionations of 1.8Gy using a dose escalation scheme). 37% of patients had neoadjuvant hormone therapy.

The nomogram variables were: clinical stage, biopsy Gleason score, pre-treatment serum PSA level, neoadjuvant hormone therapy and radiation dose.

Outcomes Treatment failure (PSA recurrence): defined as three consecutive rises of serum PSA level. The date of treatment failure was the midpoint between the last non-rising and the first rising PSA value. Follow-up examinations were performed at 3 to 6 month intervals.

Follow up The median follow-up time for the patients who did not relapse was 29 months

(range 6 to 113 months).

Results In the development of the nomogram, eight statistical prediction techniques were compared. Cox proportional hazards model (with restricted cubic splines) was the most accurate and was used for the nomogram.

The nomogram predictions were compared with those from 7 risk stratification schemes from the literature in a validation sample. Using the validation sample, from the Cleveland Clinic, the Somers' D correlation coefficient for the nomogram (0.52) was higher ($p<0.0001$) than the best risk stratification model. The Somers' D correlation ranges from 0 (no association) to 1 (perfect correlation between prediction and outcome), the nomogram performs at the centre of this scale - so this is a degree of uncertainty in its predictions.

Nomogram details	
Clinical disease state	Men who are candidates for 3D conformal radiotherapy for PCa
Nomogram aim	To predict the probability of disease recurrence
Outcome	Probability of PSA recurrence within 5 years of 3D-CRT
Predictors	Pretreatment PSA (ng/ml), clinical stage, biopsy Gleason sum, radiation dose and neoadjuvant hormone therapy
Number of patients	Development sample 1042, validation sample 912
Validation	Internal, an independent validation sample from another clinic was used
Accuracy measure	In the validation sample the nomogram had a Somers' D rank correlation between predicted and observed failure times of 0.52

General comments Nomogram is only applicable to patients who are candidates for radiotherapy. What is the definition of a candidate for RT?

(Ayyathurai *et al.* 2006)

Design: Retrospective case series (prognosis), evidence level: 3

Country: United Kingdom, setting: Tertiary care

Inclusion criteria Men treated with radical prostatectomy for T1c to T2c prostate cancer at a single institution between 1993 and 2004.

Exclusion criteria Incomplete clinical staging information. Neoadjuvant therapy.

Population number of patients = 177, age range 48 to 73 years, median age = 64 years.

Interventions All men had radical prostatectomy. Preoperatively serum PSA, clinical stage and biopsy Gleason score were all recorded.

Outcomes Predictive value of Partin (2001) tables, estimated using the area under the ROC

curve.

Results Pathological stage was: organ confined (75% of cases), extracapsular extension (14%), seminal vesicle involvement (9%), and lymph node involvement (2%).

The area under the ROC curve was 0.733 (95% CI 0.644 to 0.822) for organ confinement, 0.738 (95% CI 0.650 to 0.870) for seminal vesicle invasion and 0.780 (95% CI 0.708 to 0.908) for lymph node involvement, suggesting good predictive value.

General comments -

Augustin, Eggert, Wenske, Karakiewicz, Palisaar, Daghofer, Huland & Graefen. Comparison of accuracy between the Partin tables of 1997 and 2001 to predict final pathological stage in clinically localized prostate cancer. Journal of Urology 171[1]. 2004.

Design: Retrospective case series (prognosis), evidence level: 3

Country: Germany, setting: Tertiary care

Inclusion criteria Men treated with radical prostatectomy and staging pelvic lymphadenectomy for clinically localised PCa at University of Hamburg hospital between 1992 and 2002.

Exclusion criteria Neoadjuvant hormone therapy, missing clinical stage information, missing PSA data or missing Gleason score.

Population number of patients = 2139.

Interventions Serum PSA concentration (Axym PSA assay), DRE and TRUS guided needle biopsy. Clinical staging (AJCC 4th edition). Radical prostatectomy and staging pelvic lymphadenectomy. Lymphadenectomy was performed routinely from 1992 to 2000 but only in high risk patients from 2000 to 2002.

The surgical specimen was processed in compliance with the Stanford protocol

Outcomes Study compared nomogram predicted probabilities of organ confined disease (OC), extracapsular extension (ECE), lymph node involvement (LNI) and seminal vesicle involvement (SVI) with observed pathological stage. Separate comparisons were made for the 1997 and 2001 updates of the Partin tables.

Results OC, ECE, SVI and LNI were noted in 63.5%, 23.1%, 10.5% and 2.9% of cases, respectively.

Validation results for Partin (1997) were:

ECE, AUC = 0.728 [95% CI 0.701 to 0.755]

SVI, AUC = 0.791 [95% CI 0.755 to 0.827]

LNI, AUC = 0.799 [95% CI 0.719 to 0.879]

OCD, AUC = 0.784 [95% CI 0.765 to 0.803]

Validation results for Partin (2001) were:

ECE, AUC = 0.766 [95% CI 0.740 to 0.792]

SVI, AUC = 0.775 [95% CI 0.738 to 0.812]

LNI, AUC = 0.79 [95% CI 0.709 to 0.871]

OCD, AUC = 0.787 [95% CI 0.768 to 0.806]

Validation details	
Nomogram name	Partin (1997 and 2001) nomograms
Number of patients	2139

General comments Considerable overlap of patients between this study and Graefen et al (2003) and Steuber et al (2005)

Beissner, Stricker, Speights, Coffield, Spiekerman & Riggs. Frozen section diagnosis of metastatic prostate adenocarcinoma in pelvic lymphadenectomy compared with nomogram prediction of metastasis. Urology 59[5]. 2002.

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

Country: United States, setting: Tertiary care

Inclusion criteria Patients who were treated with bilateral pelvic lymphadenectomy and radical prostatectomy for prostate cancer, at a single hospital between 1991 and 1997.

Exclusion criteria Patients with missing data needed for the nomogram (62 cases).

Population number of patients = 530.

Interventions Preoperative tests: DRE (used for clinical T staging), Gleason score (biopsy method is not described) and serum PSA concentration (Abbott total PSA procedure).

Bilateral pelvic lymphadenectomy and radical prostatectomy. Frozen section and permanent section pathological analysis of lymph nodes.

Outcomes Predicted and observed pelvic lymph node involvement. The predictions were derived from the Partin (1997) tables. The authors compared the sensitivity and specificity of frozen section analysis and nomogram predictions using permanent section analysis as the gold standard diagnosis.

Results The reported sensitivity for detecting lymph node metastasis on frozen section analysis for all risk groups was 33% (9 of 27). 67% (18 of 27) of patients with lymph node metastasis were identified as at high risk of having nodal metastasis using the Partin Tables (P = 0.04). The authors report the sensitivity of the nomogram as 67%.

The overall negative predictive value for frozen section analysis was 96.5% (503 of 521). The negative predictive value for uninvolved lymph nodes, using low and intermediate-risk groups stratified by published nomograms, was 97.9% (436 of 445)

Validation details	
Nomogram name	Partin (1997) nomogram
Number of patients	530

General comments In 9 of the included cases frozen sections were read as positive but RP was performed. What about cases where RP was abandoned because frozen section analysis was positive? Including such cases would probably increase the sensitivity estimate.

Bianco, Jr., Kattan, Scardino, Powell, Pontes & Wood, Jr. Radical prostatectomy nomograms in black American men: accuracy and applicability. Journal of Urology 170[1]. 2003.

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men treated with radical prostatectomy as monotherapy for localised prostate cancer (T1 to T2, NX, and M0) at Wayne State University between 1990 and 1999. Subgroup analysis was done for Caucasian American (n=712(and African American (n= 331) groups.

Exclusion criteria Prior radiotherapy or hormone therapy

Population number of patients = 1043.

Interventions Clinical stage (AJCC TNM 1992), PSA (Hybridtech Tandem-R assay), and prostate needle biopsy with primary and secondary Gleason grade. Radical prostatectomy and pelvic lymphadenectomy.

Outcomes Biochemical recurrence (predicted and observed). Biochemical recurrence was defined as a postoperative PSA of greater than 0.4 ng/ml and rising. None of the patients in the series had clinical recurrence before biochemical recurrence. Both the preoperative and postoperative Kattan nomograms were validated.

Follow up Follow up was a PSA test every 3 to 6 months with assessment of the patient's clinical condition. Median follow up in patients without biochemical progression was 52 months.

Results Biochemical failure occurred in 193 patients (18.5%). The Kaplan Meier estimate of recurrence free survival was 77% at 5 years and 75% at 10 years.

The calibration of the nomogram was tested by dividing the sample into quartiles based on predicted risk of biochemical recurrence and comparing the actual rates of recurrence. Visually, calibration for the preoperative nomogram seemed good, but the postoperative nomogram tended to underestimate risk of recurrence. There was no significant difference in the

concordance index between the 2 racial subgroups, suggesting that the nomogram was valid in both groups.

Validation details	
Nomogram name	Kattan (1998) nomogram
Nomogram name	Kaplan (1999) nomogram
Number of patients	1043

General comments -

Blute, Bergstralh, Partin, Walsh, Kattan, Scardino, Montie, Pearson, Slezak & Zincke. Validation of Partin tables for predicting pathological stage of clinically localized prostate cancer. [See comment]. Journal of Urology 164[5]. 2000.

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men treated with pelvic lymphadenectomy and RP for PCa at the Mayo Clinic between 1990 and 1996. For inclusion men required: preoperative serum PSA before or at least 4 weeks after biopsy, Gleason score, no preoperative hormone treatment or radiotherapy and clinical stage T1 to T3a

Exclusion criteria Missing data.

Population number of patients = 2475.

Interventions Prostate biopsy (needle or TURP, Gleason graded), preoperative serum PSA test and clinical staging.

Bilateral pelvic lymphadenectomy and RP.

Pathological staging of the surgical specimen and removed nodes.

Outcomes Nomogram predicted probability of: organ confined disease, extracapsular extension, seminal vesicle involvement and lymph node involvement.

The accuracy of the nomogram was estimated using ROC curves.

Results The Mayo validation sample appeared to have better prognosis than the cohort used to develop the Partin nomogram. There was a greater proportion of organ confined disease and tendency towards lower Gleason score, although clinical stage appeared to be comparable between the two studies.

Using the predicted probabilities of Partin et al the ROC curve area for predicted node positive disease was 0.84 for Mayo cases compared to an estimated 0. 82 in the Partin series. The ROC curve area for predicting organ confined cancer was 0.76 for the Mayo Clinic compared to an estimated 0.73 for the Partin series. The observed rates of node positive disease were similar to those predicted (Partin) based on clinical stage, PSA and Gleason score. For

organ confined disease, the Mayo rates were consistently higher than those predicted from the Partin series using a cut point of 0.50 or greater. Positive and negative predictive values were 0.83 and 0.49 versus 0.63 and 0.70 for the Mayo Clinic and Partin series.

Validation details	
Nomogram name	Partin (1997) nomogram
Number of patients	2475

General comments Only 2475/5780 patients treated with RP 1990 - 1996 met the inclusion criteria for the Partin nomogram.

Cagiannos, Karakiewicz, Eastham, Ohori, Rabbani, Gerigk, Reuter, Graefen, Hammerer, Erbersdobler, Huland, Kupelian, Klein, Quinn, Henshall, Grygiel, Sutherland, Stricker, Morash, Scardino & Kattan . A preoperative nomogram identifying decreased risk of positive pelvic lymph nodes in patients with prostate cancer. Journal of Urology 170[5]. 2003.

Design: Retrospective case series (prognosis), evidence level: 3

Country: International, setting: Tertiary care

Inclusion criteria Patients with clinically localised prostate cancer treated with RP and pelvic lymphadenectomy at 6 institutions between 1985 and 2000.

Exclusion criteria Neoadjuvant hormone therapy, incomplete clinical information, pretreatment PSA greater than 50 ng/ml

Population number of patients = 5510.

Interventions DRE and clinical stage (1992 AJCC criteria), pretreatment serum PSA (Hybridtech Tandem-R assay), prostate biopsy and Gleason sum. RP and pelvic lymphadenectomy.

Outcomes Predicted and observed probability of positive pelvic lymph nodes. Predicted probabilities were generated using multivariate logistic regression models.

Results Pelvic lymph nodes were positive in 206 / 5510 patients.

Nomogram details	
Clinical disease state	Men with clinically localised PCa who are candidates for RP
Nomogram aim	To identify risk of positive pelvic lymph nodes
Outcome	Probability of positive pelvic lymph nodes
Predictors	Nomogram 1: PSA (ng/ml), clinical stage and biopsy Gleason sum. Nomogram 2 also included institutional incidence of positive lymph

	nodes
Number of patients	5510
Validation	Internal, bootstrap resampling
Accuracy measure	The area under the ROC curve was 0.76 for the 3 variable nomogram and 0.78 for the 4 variable nomogram

General comments -

D'Amico, Whittington, Malkowicz, Fondurulia, Chen, Kaplan, Beard, Tomaszewski, Renshaw, Wein & Coleman. Pretreatment nomogram for prostate-specific antigen recurrence after radical prostatectomy or external-beam radiation therapy for clinically localized prostate cancer. Journal of Clinical Oncology 17[1]. 1999.

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men treated with RP and pelvic lymphadenectomy at University Hospital Pennsylvania, or with EBRT at the Joint Center for Radiation therapy, between 1989 and 1997. Their prostate cancer was either PSA-detected or clinically palpable.

Population number of patients = 1654.

Interventions Preoperative tests were DRE, CT or MRI of the prostate, sextant biopsy (with Gleason score) and serum PSA test. Clinical stage was determined from the DRE using the AJCC staging system.

Radical therapy was RP and pelvic lymphadenectomy or EBRT.

Outcomes Probability of treatment failure (PSA failure) within 2 years of radical therapy. The authors define PSA failure as 3 consecutive increasing post therapy PSA values, after an undetectable or nadir value.

Follow up Median follow up was 42 months for the surgical group and 38 months for the radiotherapy group. Patients were seen at 1 month post-op and then at 3 monthly intervals for 2 years, 6 monthly intervals for 5 years and annually thereafter. Follow up examinations included a PSA test and DRE.

Results Using Cox regression analysis (separately for the RP and EBRT groups), pre-therapy PSA, AJCC clinical stage, and biopsy Gleason score were independent predictors ($P < .0001$) of time to post therapy PSA failure in patients managed with either RP or RT.

Nomogram details	
Clinical disease state	Men with clinically localised PCa, before RP or EBRT
Nomogram aim	To predict risk of disease recurrence after RP or EBRT

Outcome	Probability of PSA failure within 2 years of RP or EBRT
Predictors	PSA (ng/ml), biopsy Gleason score and clinical stage.
Number of patients	1654
Validation	Internal (bootstrap validation)
Accuracy measure	No single measure of classification accuracy, 95% CI for nomogram predictions are supplied

General comments Adjuvant therapy is not reported.

Dotan, Bianco, Jr., Rabbani, Eastham, Fearn, Scher, Kelly, Chen, Schoder, Hricak, Scardino & Kattan. Pattern of prostate-specific antigen (PSA) failure dictates the probability of a positive bone scan in patients with an increasing PSA after radical prostatectomy. Journal of Clinical Oncology 23[9]. 2005.

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Patients treated with radical prostatectomy (RP) for prostate cancer at Memorial Sloan Kettering Cancer Centre (1985 to 2003), who had detectable PSA after RP.

Exclusion criteria Preoperative radiotherapy, chemotherapy or adjuvant hormone therapy before treatment failure.

Population number of patients = 239.

Interventions Radical prostatectomy. Patients were staged according to the AJCC 1992 criteria.

Technetium-99 bone scan (BS) after PSA failure (>0.4 ng/ml) or initiation of secondary treatment).

The following variables were measured and included in a predictive nomogram: preoperative PSA, time to biochemical recurrence (BCR), pathologic findings of the RP, PSA before the BS (trigger PSA), PSA kinetics (PSA doubling time, PSA slope, and PSA velocity), and time from BCR to BS.

Outcomes Predicted and observed probability of positive bone scan.

Results 155 patients had a single bone scan, 39 two bone scans, 21 three bone scans and 24 more than three scans.

Nomogram details	
Clinical disease state	Men rising PSA after RP
Nomogram aim	To predict bone metastases

Outcome	Probability of a positive bone scan
Predictors	Pre treatment PSA (ng/ml), surgical margin (positive or negative), seminal vesicle involvement, Gleason sum of RP specimen, extra-capsular extension, trigger PSA (before the bone scan), PSA slope, PSA velocity
Number of patients	239
Validation	Internal
Accuracy measure	AUC = 0.93

General comments -

Eastham, May, Robertson, Sartor & Kattan. Development of a nomogram that predicts the probability of a positive prostate biopsy in men with an abnormal digital rectal examination and a prostate-specific antigen between 0 and 4 ng/mL. Urology 54[4]. 1999.

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

Country: United States, setting: Tertiary care

Inclusion criteria Men who had TRUS guided prostate biopsy for an elevated PSA level (but less than 4 ng/ml) and/or DRE suspicious for cancer, between 1990 and 1997, at a single institution.

Exclusion criteria Serum PSA concentration greater than 4ng/ml.

Population number of patients = 700, age range 40 to 83 years.

Interventions Serum PSA level (Abbott IMx assay). A member of the Urology department performed DRE and classified examinations as normal, abnormal-benign or abnormal-suspicious for cancer. Patients were also classified into white or African American groups.

TRUS guided sextant biopsies were performed in all patients, with additional biopsies performed under digital guidance at the discretion of the doctor performing the biopsy.

If patients had multiple sets of negative biopsies, then only data from the first biopsy was included in analysis, If patients had multiple sets of biopsies and cancer was detected, then only data relating to the cancer containing biopsy was included.

Variables were entered into logistic regression analysis and a nomogram generated.

Outcomes Probability of a biopsy that was positive for PCa.

Results The proportion of patients with positive biopsies was 65 / 700 (9%). In the multivariate analysis of pre-biopsy risk factors (age, race, serum PSA), serum PSA was the only independent predictor of a positive prostate biopsy

Nomogram details

Clinical disease state	Men with raised PSA (but < 4 ng/ml) and/or suspicious DRE, before biopsy
Nomogram aim	To predict the probability of a biopsy positive for PCa
Outcome	Probability of a positive biopsy
Predictors	Race (African American or white), age and PSA (ng/ml)
Number of patients	700
Validation	Internal, bootstrap resampling
Accuracy measure	AUC= 0.75 [95% CI 0.68 to 0.82]

General comments Some men had repeated biopsies - increasing the chance of a positive biopsy. It is likely than PSA level and DRE result influenced the decision to repeat biopsies, which could inflate their significance in the analysis.

Eskicorapci, Karabulut, Turkeri, Baltaci, Cal, Toktas, Akpinar, Ozer, Sozen, Tokuc, Lekili, Soylu, Albayrak, Sahin, Alpar & Ozen . Validation of 2001 Partin tables in Turkey: a multicenter study. European Urology 47[2]. 2005.

Design: Retrospective case series (prognosis), evidence level: 3

Country: Turkey, setting: Tertiary care

Inclusion criteria Men who had RP for clinically localised PCa in 13 Turkish hospitals between 1992 and 2003.

Exclusion criteria Neoadjuvant hormone therapy; missing clinical, PSA or Gleason data.

Population number of patients = 1043, age range 45 to 74 years, median age = 60 years.

Interventions Serum PSA testing, clinical staging, biopsy, radical prostatectomy and pathological evaluation of the surgical specimen.

Outcomes Partin table (2001 update) probabilities of organ confined disease, extracapsular extension, seminal vesicle involvement and lymph node involvement. These probabilities were compared to the observed pathological stage to derive ROC curves as an accuracy measure.

Results 43% of patients had clinical stage T1c cancer . 23.4% of patients had Gleason score of 2-4 on biopsy. The percentages with organ confined disease, seminal vesicle involvement, lymph node metastases were 64.7%, 10.3%, 1.8% respectively.

Validation results were:

ECE, not reported

SVI, AUC = 0.733 [95% CI 0.677 to 0.789]

LNI, AUC = 0.759 [95% CI 0.632 to 0.886]

OCD, AUC = 0.665 [95% CI 0.632 to 0.698]

Validation details	
Nomogram name	Partin (2001) nomogram
Number of patients	1043

General comments Gleason score of 2 to 4 on prostate biopsy is no longer given in some institutions (e.g. Partin, 2001). Multi-institutional study. No description of biopsy, RP, lymphadenectomy or pathological staging.

Gancarczyk, Wu, McLeod, Kane, Kusuda, Lance, Herring, Foley, Baldwin, Bishoff, Soderdahl & Moul . Using the percentage of biopsy cores positive for cancer, pretreatment PSA, and highest biopsy Gleason sum to predict pathologic stage after radical prostatectomy: the Center for Prostate Disease Research nomograms. Urology 61[3]. 2003.

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

Country: United States, setting: Tertiary care

Inclusion criteria Patients entered into a multi-institutional Department of Defence database between 1990 and 2000. All had RP as primary therapy for PCa, following TRUS guided biopsy and pretreatment PSA test.

Exclusion criteria Neoadjuvant hormone therapy. Any missing data. Less than 6 or more than 12 biopsy cores. Clinical T3 disease.

Population number of patients = 1510.

Interventions TRUS and prostate biopsy, radical prostatectomy as primary therapy. Predictor variables were age, race, clinical stage, pretreatment PSA, biopsy Gleason sum, and percentage of biopsy cores positive for cancer (total number of cores positive for cancer divided by the total number of cores obtained). The percentages of biopsy cores positive were grouped as less than 30%, 30% to 59%, and greater than or equal to 60%.

Outcomes The three most significant predictor variables (PSA (ng/ml), Gleason sum and % of positive biopsy cores) were used to develop probability nomograms for pathologic stage.

Results On logistic regression, PSA, biopsy Gleason sum, and percentage of cores positive were the three most significant independent predictors of pathologic stage. The assigned percentage of biopsy core-positive subgroups along with pretreatment PSA and highest Gleason sum were used to develop probability nomograms for pathologic stage.

Nomogram details

Clinical disease state	Men with clinically localised PCa who are candidates for RP
Nomogram aim	To predict pathological stage
Outcome	Probability of organ confined disease, extracapsular extension, seminal vesicle invasion and lymph node invasion
Predictors	PSA (ng/ml), Gleason score and percentage of positive biopsy cores
Number of patients	1510
Validation	No
Accuracy measure	None

General comments No validation. Selection of variables for inclusion in the nomogram was based on statistical (not clinical) significance.

Graefen, Karakiewicz, Cagiannos, Klein, Kupelian, Quinn, Henshall, Grygiel, Sutherland, Stricker, de, Cangiano, Schroder, Wildhagen, Scardino & Kattan . Validation study of the accuracy of a postoperative nomogram for recurrence after radical prostatectomy for localized prostate cancer. Journal of Clinical Oncology 20[4]. 2002.

Design: Retrospective case series (prognosis), evidence level: 3

Country: International, setting: Tertiary care

Inclusion criteria Men treated with RP at one of 4 institutions in the USA, Australia and Europe.

Exclusion criteria Neoadjuvant hormone therapy, missing pretreatment PSA or Gleason score, missing pathological stage information.

Population number of patients = 2465.

Interventions Pretreatment PSA test. Radical prostatectomy. 250 men (deemed low risk) did not have pelvic lymphadenectomy, otherwise it was performed routinely. Pathological staging: level of prostatic capsule invasion, surgical margin status, seminal vesicle involvement and lymph node involvement.

Outcomes Predicted and observed probability of treatment failure within 7 years of RP. Treatment failure was defined as: biochemical failure (PSA of 0.2 to 0.4 depending upon the institution), the start of adjuvant therapy before documented biochemical failure, or clinical recurrence.

Follow up Median follow up was 2.2 years. 5% of patients were followed for 7 years or more.

Results 439 patients experienced treatment failure. The Kaplan-Meier estimate of 7 year treatment failure rate was 30% (95%CI 24 to 17%).

Validation result for Kattan (1999) nomogram, AUC = 0.8 [95% CI 0.779 to 0.821]

Validation details	
Nomogram name	Kattan (1999) nomogram
Number of patients	2465

General comments -

Graefen, Karakiewicz, Cagiannos, Quinn, Henshall, Grygiel, Sutherland, Stricker, Klein, Kupelian, Skinner, Lieskovsky, Bochner, Huland, Hammerer, Haese, Erbersdobler, Eastham, de, Cangiano, Schroder, Wildhagen, van der Kwast, Scardino & Kattan . International validation of a preoperative nomogram for prostate cancer recurrence after radical prostatectomy. Journal of Clinical Oncology 20[15]. 2002.

Design: Retrospective case series (prognosis), evidence level: 3

Country: International, setting: Tertiary care

Inclusion criteria Men treated with RP at any of 7 international institutions in USA, Europe and Australia.

Exclusion criteria Pretreatment PSA 100 ng/ml or greater. Missing PSA value, clinical stage or Gleason score.

Population number of patients = 6232.

Interventions Clinical stage (AJCC TNM classification), pretreatment PSA, prostate biopsy with Gleason score. Radical prostatectomy (the procedure was aborted in 54 men with positive lymph nodes). Some patients received neoadjuvant therapy before RP; these were treated as a separate group in the analysis. Adjuvant therapy was not standardised.

Outcomes Probability of biochemical failure within 5 years of RP. Authors defined biochemical failure as a threshold value (ranging from 0.1 to 0.4 ng/ml depending on the institution) followed by another higher value. If patients received adjuvant therapy before documented biochemical failure, it was defined as treatment failure.

Follow up Median follow up was 23.9 months, range 0.1 to 152.7 months.

Results Treatment failure was seen in 1446 / 6232 patients. Treatment failure was classified as PSA recurrence in 804 cases, adjuvant hormones in 88 cases, adjuvant radiotherapy in 496 cases, clinical recurrence in 4 cases, and aborted RP in 54 cases.

For the Kattan (1998) nomogram, AUC = 0.83 [95% CI 0.803 to 0.857]

Validation details

Nomogram name	Kattan (1998) nomogram
Number of patients	6232 patients from 7 institutions

General comments The authors claim that "the use of neoadjuvant therapy, variation in the prostate-specific antigen recurrence definitions between institutions, and minor differences in the way the Gleason grade was reported did not substantially affect the predictive accuracy of the nomogram. "

Graefen, Karakiewicz, Cagiannos, Hammerer, Haese, Palisaar, Fernandez, Noldus, Erbersdobler, Huland, Scardino & Kattan . A validation of two preoperative nomograms predicting recurrence following radical prostatectomy in a cohort of European men. Urologic Oncology 7[4]. 2002.

Design: Retrospective case series (prognosis), evidence level: 3

Country: Germany, setting: Tertiary care

Inclusion criteria Men admitted to the University Hospital with the intention to treat their clinically localised PCa with RP.

Exclusion criteria Neoadjuvant hormone therapy, missing pretreatment PSA values, Gleason score or clinical stage. The study excluded patients with pretreatment PSA greater than 100 ng/ml from the Kattan (1998) nomogram validation. The study excluded patients with pretreatment PSA greater than 50 ng/ml, or clinical T1a/b or T3 disease from the D'Amico(1999) nomogram validation

Population number of patients = 1003.

Interventions Clinical stage (using 1992 AJCC TNM classification), prostate biopsy with Gleason score and PSA concentration (Immulite DPC assay). Radical prostatectomy (RP was abandoned in 34 men due to positive lymph nodes, these cases were classified as immediate treatment failures).

Outcomes Probability of biochemical recurrence within 2 and 5 years of RP. The definition of biochemical recurrence was a PSA level of 0.1 ng/ml and rising. Adjuvant therapy was never started before documented biochemical recurrence in this series.

Follow up Median follow up was 25.6 months.

Results The overall 2 and 5 year biochemical recurrence rates were 22% and 42% respectively. For the D'Amico nomogram: AUC = 0.8, for the Kattan nomogram: AUC = 0.81

Validation details	
Nomogram name	Kattan (1998) nomogram
Nomogram name	D'Amico (1999) nomogram
Number of patients	1003 for the Kattan (1998) nomogram

Number of patients	932 for the D'Amico (1999) nomogram

General comments Not much detail on biopsy, lymphadenectomy or pathological staging. The D'Amico (1999) nomogram predicts probability of recurrence within 2 years of RP whereas the Kattan (1998) nomogram predicts within 5 years.

Graefen, Augustin, Karakiewicz, Hammerer, Haese, Palisaar, Blonski, Fernandez, Erbersdobler & Huland . Can predictive models for prostate cancer patients derived in the United States of America be utilized in European patients? A validation study of the Partin tables.[see comment]. European Urology 43[1]. 2003.

Design: Retrospective case series (prognosis), evidence level: 3

Country: Germany, setting: Tertiary care

Inclusion criteria Men who underwent RP for clinically localised PCa at a single Hamburg hospital between 1992 and 2000.

Exclusion criteria Neoadjuvant hormone therapy, missing information on clinical stage, missing biopsy Gleason score, missing PSA test results

Population number of patients = 1131.

Interventions PSA test (Immulite DPC assay), prostate needle biopsy. All RP specimens were processed according to the Stanford protocol.

Outcomes Receiver operating characteristic (ROC) curve analysis was performed to compare observed and predicted Partin rates for each pathologic stage.

Results The rate for organ confinement was 56% in Hamburg patients compared to 48% in the Partin study. The rates of Hamburg patients for extracapsular extension without seminal vesicle or lymph node involvement were 25%, for seminal vesicle without lymph node involvement 14% and for lymph node metastases 5%. The corresponding rates of the Partin study were 40, 7 and 5%, respectively.

Validation results:

ECE, not reported

SVI, AUC = 0.793 [95% CI 0.750 to 0.836]

LNI, AUC = 0.807 [95% CI 0.738 to 0.876]

OCD, AUC = 0.817 [95% CI 0.793 to 0.841]

Validation details

Nomogram name	Partin (1997) nomogram

Number of patients	1131

General comments The accuracy of Partin table predictions was high in this European cohort suggesting comparable accuracy to that reported for validation studies in American patients.

Incomplete information about biopsy technique and pelvic lymphadenectomy .

Greene, Meng, Elkin, Cooperberg, Pasta, Kattan, Wallace & Carroll . Validation of the Kattan preoperative nomogram for prostate cancer recurrence using a community based cohort: results from cancer of the prostate strategic urological research endeavor (capsure). Journal of Urology 171[6 Pt 1]. 2004.

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Community

Inclusion criteria Men enrolled in the CaPSURE registry with clinically localised PCa (cT3a or less and N0M0) treated with RP between 1989 and 2000.

Exclusion criteria Neoadjuvant or adjuvant therapy. More than one missing prognostic variable.

Population number of patients = 1701.

Interventions Pre-operative tests included PSA concentration, clinical staging (AJCC TNM 1997 classification), and prostate biopsy with Gleason score. All men had RP (the rate of pelvic lymphadenectomy is not reported).

Outcomes Probability of treatment failure within 5 years of RP. Treatment failure was defined as consecutive PSA values of 0.2 ng/ml or greater after RP, or the initiation of adjuvant therapy in the absence of documented biochemical failure.

Follow up Median follow up in men with recurrence was 2.3 years compared to 2.9 years in those without recurrence.

Results Treatment failure was seen in 413/1701 patients. Validation: AUC = 0.8

Validation details	
Nomogram name	Kattan (1998) nomogram
Number of patients	1701

General comments -

Halabi, Small, Kantoff, Kattan, Kaplan, Dawson, Levine, Blumenstein & Vogelzang . Prognostic model for predicting survival in men with hormone-refractory metastatic prostate cancer. J Clin Oncol 21[7]. 2003.

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria The data from 6 clinical trials (1992 to 1998) were pooled for this analysis. All patients had progressive metastatic prostate cancer, and had failed both androgen ablation and antiandrogen withdrawal. For entry into the clinical trials patients required ECOG performance status of 0 to 2, and adequate haematological renal and hepatic function.

Exclusion criteria -

Population number of patients = 1101.

Interventions The prediction variables included in the nomogram were: levels of lactate dehydrogenase, prostate-specific antigen, and alkaline phosphatase; Gleason sum, Eastern Cooperative Oncology Group performance status, haemoglobin, and the presence of visceral disease.

Outcomes Overall survival, defined as the time between randomisation and death. The nomogram predicted 1 and 2 year survival probability and median survival time.

Follow up Median follow up among surviving patients was 37 months.

Results Data from 760 patients were used to develop the nomogram and data from the remaining 341 were used to validate the model. Median overall survival was 13 months in the nomogram development sample and 17 months in the validation sample.

Nomogram details	
Clinical disease state	Men with hormone refractory metastatic prostate cancer
Nomogram aim	To predict survival
Outcome	Probability of surviving 1 year and 2 years. Median survival
Predictors	Levels of lactate dehydrogenase, prostate-specific antigen, alkaline phosphatase, Gleason sum, Eastern Cooperative Oncology Group performance status, haemoglobin, and the presence of visceral disease
Number of patients	760 for nomogram development and 341 for validation
Validation	Independent validation sample
Accuracy measure	AUC = 0.68

General comments -

Han, Partin, Zahurak, Piantadosi, Epstein & Walsh . Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. Journal of Urology 169[2]. 2003.

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men with clinically localised PCa who had RP and staging pelvic lymphadenectomy at a single institution between 1982 and 1999.

Exclusion criteria Insufficient follow up (not defined); T1a, T1b or T3a disease; Gleason score less than 5, Jewitt clinical stage D0 or D2, preoperative or immediate postoperative radiotherapy, and neoadjuvant or immediate postoperative hormone therapy.

Population number of patients = 2091, age range 33 to 76 years, mean age = 58 years.

Interventions Clinical staging (AJCC 1992), PSA test (Hybridtech Tandem-R and E assays), needle biopsy with Gleason score. Radical retropubic prostatectomy and pelvic lymphadenectomy.

Outcomes Probability of biochemical recurrence within 10 years of radical retropubic prostatectomy. Biochemical recurrence was defined as PSA of 0.2 ng/ml or more. Multivariate regression (Cox proportional hazards) was used to develop a nomogram.

Follow up Follow up consisted of DRE and PSA measurement every 3 months for the first post operative year, every 6 months for the next year and yearly thereafter. Median follow up was 5.9 years (range 1 to 17 years).

Results 360 / 2091 men (17%) had biochemical recurrence.

Nomogram details	
Clinical disease state	2 nomograms for men undergoing RP were developed: preoperative and post operative
Nomogram aim	To predict disease recurrence after RP
Outcome	Probability of biochemical progression within 3,5,7 or 10 years of RP
Predictors	The pre-op nomogram used: clinical TNM stage, biopsy Gleason score and PSA (ng/ml). The post-op nomogram used pathological stage instead of clinical stage.
Number of patients	2091
Validation	None reported - 95% confidence intervals are supplied for each predicted probability. External validation by Poulakis (2004).

General comments -

Karakiewicz, Benayoun, Kattan, Perrotte, Valiquette, Scardino, Cagiannos, Heinzer, Tanguay, Aprikian, Huland & Graefen . Development and validation of a nomogram predicting the outcome of prostate biopsy based on patient age, digital rectal examination and serum prostate specific antigen. Journal of Urology 173[6]. 2005.

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

Country: International, setting: Secondary care

Inclusion criteria The study used 3 cohorts of men who were evaluated with sextant biopsy of the prostate and whose presenting PSA was 50 ng/ml or less. 4193 men who had sextant prostate biopsy in Montreal between 1990 and 1998. 514 patients who had sextant prostate biopsy in Montreal 1998 to 1999. 1762 men who had sextant prostate biopsy at one German hospital between 1992 and 2000.

Exclusion criteria -

Population number of patients = 6469, age range 17 to 88 years, mean age = 64 years.

Interventions Data from 4,193 men from Montreal, Canada were used to develop a nomogram based on age, digital rectal examination (DRE) and serum PSA.

External validation was performed on 1,762 men from Hamburg, Germany. Data from these men were subsequently used to develop a second nomogram in which percent free PSA (%fPSA) was added as a predictor.

External validation was performed using 514 men from Montreal. Both nomograms were based on multivariate logistic regression models.

TRUS guided sextant biopsies were used

Outcomes Presence of prostate cancer on needle biopsy.

Follow up Repeat biopsies are not reported.

Results PCa was detected in 1,477 (35.2%) men from Montreal, 739 (41.9%) men from Hamburg and 189 (36.8%) men from Montreal.

In both models, all predictor variables were significant at 0.05. The predictive accuracy was evaluated with areas under the receiver operating characteristic curve and graphically with loess smoothing plots. Using age, DRE and PSA, external validation AUC was 0.69. Using age, DRE, PSA and %fPSA, external validation AUC was 0.77.

Nomogram details	
Clinical disease state	Men with suspicious DRE and/or abnormal PSA before prostate biopsy (PSA < 50 ng/ml)
Nomogram aim	To predict presence of PCa on needle biopsy
Outcome	Probability of PCa on needle biopsy.
Predictors	Nomogram 1: age, DRE and PSA (ng/ml). Nomogram 2: age, DRE and PSA (ng/ml) and %fPSA

Number of patients	3 cohorts: 4193 in Montreal, 1762 in Hamburg and 512 in Montreal.
Validation	Yes, external validation
Accuracy measure	External validation: Montreal nomogram AUC = 0.69. Hamburg nomogram (using %fPSA) AUC = 0.77

General comments -

Kattan, Eastham, Stapleton, Wheeler & Scardino . A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. Journal of the National Cancer Institute 90[10]. 1998.

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men admitted to the Methodist Hospital, Houston (between 1983 and 1996) with the intention to treat their localised PCa with RP.

Exclusion criteria Initial treatment with radiotherapy or cryotherapy. Missing follow up data. Missing PSA values (n=75) or Gleason scores (n=16) were imputed statistically.

Population number of patients = 983, age range 31 to 81 years, median age = 63 years.

Interventions Preoperative interventions: clinical stage, PSA test (Tandem-R PSA assay) and prostate biopsy with Gleason score. Radical prostatectomy and pelvic lymphadenectomy. 55 men who had nodal metastases did not have RP, but were included in the analysis.

Outcomes Predicted and observed probability of treatment failure.

Treatment failure was defined as either the earliest date that postoperative PSA level rose to 0.4 ng/ml or higher, or the earliest date of clinical evidence of cancer in men with undetectable PSA concentration.

Follow up Patients without treatment failure had a median follow-up of 30 months (range, 1-146 months).

Results Treatment failure was seen in 196 of the 983 men, The 5-year probability of freedom from failure for the cohort was 73% (95% CI = 69%-76%).

Nomogram details	
Clinical disease state	Men with clinically localised PCa who are candidates for RP
Nomogram aim	To predict disease recurrence
Outcome	Probability of treatment failure (disease recurrence) within 5 years of RP

Predictors	PSA (ng/ml), clinical stage, and biopsy Gleason sum
Number of patients	983 patients for nomogram development and 168 for validation
Validation	Yes: internal (bootstrap resampling) and independent validation sample. External validation (Poulakis, 2004; Graefen et al 2002; Bianco et al, 2003).
Accuracy measure	The area under the ROC curve (for the independent validation sample) was 0.79

General comments Limited description of measurement of prognostic variables.

Kattan, Wheeler & Scardino . Postoperative nomogram for disease recurrence after radical prostatectomy for prostate cancer. Journal of Clinical Oncology 17[5]. 1999.

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Patients treated with radical prostatectomy by a single surgeon between 1983 and 1997 were eligible for inclusion (N=1145). 996 patients were included for the development of the nomogram. A further 322 men treated at the same institution by other surgeons were included as the nomogram validation sample.

Exclusion criteria Men whose prostatectomy was aborted (positive intraoperative histopathology of the pelvic lymph nodes; N=32). Men treated with definitive radiotherapy (N=56), hormone therapy (N=43), cryotherapy (N=3) or other radiotherapy (N=3). Men without follow-up information (N=12)

Population number of patients = 996, age range 38 to 81 years, median age = 63 years.

Interventions Prognostic variables were: pretreatment serum PSA level, Gleason sum in the surgical specimen, prostatic capsular invasion, surgical margin status, seminal vesicle invasion and lymph node status.

Pretreatment PSA was measured using the Hybridtech Tandem-R assay. A single pathologist measured the histological parameters using the whole mounted, sectioned surgical specimen

Outcomes The nomogram was developed to predict the probability of treatment failure within the 7 years after prostatectomy. Treatment failure was defined as postoperative serum PSA greater than 0.4 ng/ml or clinical evidence of cancer recurrence in men with undetectable (or unmeasured) serum PSA. Men who started on radiotherapy or hormone therapy, before documented disease recurrence, were also considered as treatment failures.

Follow up For patients without disease recurrence the median follow up was 37 months (range 1 to 168 months)

Results 189/996 of the patients in the first group had evidence of recurrence after prostatectomy. 20/322 of the validation group had evidence of recurrence.

Nomogram details	
Clinical disease state	Men treated with RP and pelvic lymphadenectomy for PCa
Nomogram aim	To predict the probability of disease recurrence after RP
Outcome	Probability of PSA recurrence within 7 years of RP
Predictors	Preop. PSA, Gleason sum, prostatic capsular invasion, surgical margins, seminal vesicle invasion, and lymph node positivity
Number of patients	Nomogram development sample n = 996, validation sample n = 322
Validation	Internal, bootstrap resampling and with independent validation sample. External: (Bianco et al, 2003: Graefen et al, 2002; Ramsden, 2004).
Accuracy measure	The area under the ROC curve was 0.88 for bootstrap validation and 0.89 for the independent validation sample

General comments The nomogram was developed using Cox proportional hazards regression. No "cut-off" probabilities quoted to stratify risk (e.g. at what probability of recurrence adjuvant therapy should be considered?) . The purpose of the nomogram is to counsel patients about their risk of recurrence.

Kattan, Potters, Blasko, Beyer, Fearn, Cavanagh, Leibel & Scardino . Pretreatment nomogram for predicting freedom from recurrence after permanent prostate brachytherapy in prostate cancer. Urology 58[3]. 2001.

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Patients treated with permanent brachytherapy for clinically localised PCa, between 1992 and 2000. The nomogram development sample came from Memorial Sloan Kettering Cancer Center, with 2 validation samples drawn from the Seattle Prostate Institute and Arizona Oncology services.

Exclusion criteria Neoadjuvant hormone therapy. Stage T1a, T1b or T3 cancers (1997 TNM system). Biopsy Gleason sum greater than 8.

Population number of patients = 3512.

Interventions Pretreatment PSA test, biopsy with Gleason score, clinical T stage (1997 TNM system). Permanent brachytherapy.

Outcomes Probability of treatment failure within 5 years of treatment. Treatment failure was defined as biochemical recurrence, the initiation of androgen therapy or clinical relapse. A modification of the ASTRO (1997) definition of biochemical recurrence after EBRT was used. Biochemical recurrence was the midpoint in time between the post treatment nadir and the first

of 3 PSA rises.

Cox proportional hazards analysis was used to create a nomogram from pretreatment variables.

Follow up Median follow up was 2.4 years for the nomogram development sample and 2.8 and 1.8 years for the validation samples.

Results The overall recurrence rate was 124/920 in the nomogram development sample, compared with 205/1827 and 187/765 in the validation samples.

The calibration graphs suggested good accuracy in the Seattle validation set, but the nomogram tended to underestimate the risk of treatment failure in the Arizona validation set.

Nomogram details	
Clinical disease state	Men with clinically localised PCa who are candidates for brachytherapy
Nomogram aim	To predict disease recurrence after brachytherapy
Outcome	Probability of treatment failure within 5 years of brachytherapy
Predictors	Pretreatment PSA, biopsy Gleason sum, clinical stage, and adjuvant EBRT.
Number of patients	920 in the nomogram development sample. 1827 and 765 in the validation samples.
Validation	Independent validation samples from other institutions
Accuracy measure	The concordance index (similar to AUC) was 0.61 in one validation sample and 0.64 in the other.

General comments No details of brachytherapy, was treatment standardised?

Kattan, Zelefsky, Kupelian, Cho, Scardino, Fuks & Leibel . Pretreatment nomogram that predicts 5-year probability of metastasis following three-dimensional conformal radiation therapy for localized prostate cancer. Journal of Clinical Oncology 21[24]. 2003.

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men with histologically confirmed, clinically localised PCa, treated at Memorial Sloan Kettering Cancer Center between 1988 and 2001, treated with 3D conformal radiotherapy. A validation sample was drawn from a similar group treated at the Cleveland Clinic between 1986 and 2001.

Exclusion criteria -

Population number of patients = 3303, age range 45 to 86 years, median age = 69 years.

Interventions Clinical staging (AJCC 2002 system), pretreatment PSA test (Tosoh radioimmunoassay) and biopsy (with Gleason score).

Outcomes Predicted and observed probability of developing metastasis within 5 years after 3D conformal radiation therapy. Metastasis was defined radiologically as the definitive onset of visceral metastatic lesions and/or bony osteoblastic lesions.

Follow up Median follow up was 3.2 years. Every 3 to 6 months patients received periodic bone scans, CT scans and MRI when indicated, depending on biochemical failure.

Results 159 / 1677 patients in the MSKCC series developed metastasis. At 5 years, 11% of patients experienced metastasis by cumulative incidence analysis (95% CI, 9% to 13%).

Nomogram details	
Clinical disease state	Men with clinically localised PCa who are candidates for 3D conformal radiotherapy
Nomogram aim	To predict the risk of metastasis after 3D-CRT
Outcome	Probability of radiologically defined metastasis within 5 years of 3D-CRT
Predictors	Pretreatment PSA (ng/ml), clinical stage and biopsy Gleason sum
Number of patients	1677 for nomogram development and 1626 for validation
Validation	The authors used an independent sample from another institution to validate the nomogram.
Accuracy measure	The concordance index for the validation sample was 0.81

General comments The authors used a proportional hazards model to construct the nomogram. 127 patients in the MSKCC series received salvage hormone therapy, but this was not incorporated into the nomogram.

Kattan, Eastham, Wheeler, Maru, Scardino, Erbersdobler, Graefen, Huland, Koh, Shariat, Slawin & Ohori . Counseling men with prostate cancer: a nomogram for predicting the presence of small, moderately differentiated, confined tumors. Journal of Urology 170[5]. 2003.

Design: Retrospective case series (prognosis), evidence level: 3

Country: International, setting: Tertiary care

Inclusion criteria Men treated with RP at one of 2 institutions, between 1986 and 2000. All men had histologically confirmed PCa.

Exclusion criteria Any features inconsistent with indolent cancer: pretreatment PSA greater than 20 ng/ml, primary or secondary Gleason grade 4 or 5 cancer in biopsy, total cancer in biopsy cores greater than 20 mm or benign tissue in all cores less than 40 mm.

Population number of patients = 409.

Interventions Ultrasound measurement of prostate volume (calculated using ellipsoid formula). Clinical staging (1992 TNM system). Serum PSA (Hybridtech Tandem-R or DPC Immulite assay). Systematic biopsy of 6 or more cores, with Gleason score. Retropubic radical prostatectomy. Pathological processing of the surgical specimen involved whole mount transverse serial sections of the prostate. Indolent cancer was defined as total tumour volume less than 0.5cc, confined to the prostate and no Gleason pattern 4 or 5.

Outcomes Predicted and observed risk of indolent prostate cancer. Data was analysed using logistic regression. Several models were considered, ranging from the base model with 3 variables to the full model with 7 variables.

Results 80 /409 (20%) of the patients had indolent cancer. Calibration of the models appeared reasonable: predicted and observed probabilities of indolent cancer were similar, at least for probabilities less than 0.50.

Nomogram details	
Clinical disease state	Men with clinically indolent cancer before RP
Nomogram aim	To predict the probability of indolent PCa
Outcome	Probability of prostate confined tumour less than 5cc in volume
Predictors	The basic model: PSA (ng/ml), primary and secondary biopsy Gleason grade. The full model also included: clinical T stage, prostate volume, mm of cancer and mm of non-cancer in biopsy cores.
Number of patients	409
Validation	Internal validation (bootstrap and jack-knife resampling)
Accuracy measure	The area under the ROC curve ranged from 0.64 for the basic model to 0.79 for the full model

General comments -

Kattan, Shariat, Andrews, Zhu, Canto, Matsumoto, Muramoto, Scardino, Ohori, Wheeler & Slawin . The addition of interleukin-6 soluble receptor and transforming growth factor beta1 improves a preoperative nomogram for predicting biochemical progression in patients with clinically localized prostate cancer.[see comment]. Journal of Clinical Oncology 21[19]. 2003.

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Patients admitted to the Methodist Hospital, Houston with the intention to treat their localised PCa with radical retropubic prostatectomy.

Exclusion criteria Men treated with definitive radiotherapy or cryotherapy, or with neoadjuvant

hormone therapy. Missing data on PSA, Gleason grade or clinical stage.

Population number of patients = 714, age range 40 to 81 years, median age = 62 years.

Interventions Pretreatment PSA test (Hybridtech Tandem-R assay).

TRUS guided needle biopsy of the prostate with Gleason score. Clinical stage was assigned using the according to the 1992 TNM classification. Pretreatment plasma levels of interleukin-6 soluble receptor (IL6SR) and transforming growth factor beta1 (TGF-beta1) were also obtained.

Radical retropubic prostatectomy in all but 2 of the included patients. The rate of lymphadenectomy is not reported.

Outcomes Probability of biochemical progression. Biochemical progression was defined as the earliest date, after RP, that serum PSA exceeded 0.2ng/ml, or the patient received hormone therapy.

Follow up For patients without disease progression the median follow up was 4.6 years (maximum 8 years).

Results 86 / 714 patients experienced biochemical progression, and 7 received hormone therapy without evidence of biochemical progression.

In a multivariate Cox regression model, PSA (P =.004), IL6SR (P <.001), TGF-beta1 (P <.001), primary Gleason grade (P <.002), and secondary Gleason grade (P =.029) were associated with PSA progression, whereas clinical stage (P =.696) was not.

Nomogram details	
Clinical disease state	Men with clinically localised PCa whose intended treatment is RP
Nomogram aim	To predict biochemical recurrence after RP
Outcome	The probability of biochemical recurrence within 5 years of RP
Predictors	Pre operative PSA (ng/ml), IL6SR (ng/ml) and TGF-beta 1; biopsy primary and secondary Gleason grade and clinical stage.
Number of patients	714
Validation	Internal (bootstrap resampling)
Accuracy measure	The area under the ROC curve was 0.83. Omitting IL6SR and TGF-beta-1 gave an AUC of 0.75.

General comments Relatively low number of events (86 biochemical progressions) to build a model with 6 predictor variables.

Koh, Kattan, Scardino, Suyama, Maru, Slawin, Wheeler & Ohori . A nomogram to predict seminal vesicle invasion by the extent and location of cancer in systematic biopsy results. Journal of Urology 170[4 Pt 1]. 2003.

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Patients treated with pelvic lymphadenectomy and radical prostatectomy for clinically localised prostate cancer at either of 2 institutions between 1989 and 2000. Diagnosis by systematic biopsy (6 or more cores)

Exclusion criteria Androgen deprivation therapy or radiotherapy before RP.

Population number of patients = 763, age range 38 to 77 years, mean age = 61 years, median age = 61 years.

Interventions Systematic needle biopsy of the prostate (6 or more cores), Gleason score, DRE, clinical T stage and pretreatment PSA (ng/ml).

Pelvic lymphadenectomy and radical prostatectomy

Outcomes Predicted and observed seminal vesicle invasion (SVI) SVI was predicted using a multivariate logistic regression model, which was also used to generate the nomograms.

Results 60 /763 patients (7.9%) had SVI.

Nomogram details	
Clinical disease state	Men with localised PCa who are candidates for RP
Nomogram aim	To predict seminal vesicle invasion
Outcome	Probability of seminal vesicle invasion
Predictors	Preoperative PSA (ng/ml). primary Gleason grade, secondary Gleason grade, clinical stage and % of cancer at the base of the prostate (in biopsy)
Number of patients	763
Validation	Internal validation, bootstrap resampling
Accuracy measure	The area under the ROC curve was 0.883

General comments Same cohort as Ohori (2005).

Lopez-Corona, Ohori, Scardino, Reuter, Gonen & Kattan . A nomogram for predicting a positive repeat prostate biopsy in patients with a previous negative biopsy session.[erratum appears in J Urol. 2004 Jan;171(1):360-1]. Journal of Urology 170[4 Pt 1]. 2003.

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria All patients with an initially negative biopsy at a single institution, between 1999 and 2001. The study included 32 patients initially biopsied elsewhere.

Exclusion criteria -

Population number of patients = 343, age range 38 to 81 years, mean age = 62 years.

Interventions The initial biopsy was usually a sextant biopsy. All repeat biopsies included 2 transition zone biopsies. The number of cores obtained in repeat biopsies ranged from 6 to 22. For analysis each core was classified as normal, with HGPIN and/or ASAP, or with prostate cancer.

The following clinical variables were assessed:

serum PSA (Hybridtech assay), PSA slope ng/ml/year, PSA density, DRE, patient age and family history of prostate cancer, cumulative number of negative cores obtained previously and history of HGPIN and ASAP.

Outcomes Probability of a positive prostate biopsy following a previous negative biopsy.

Follow up A mean of 2.9 biopsies per patient were performed. Each patient had at least 2 biopsies, 47% had 3 and 45% had 4 or more.

Results 1004 biopsies were performed in the 343 patients, of which 661 were repeat biopsies. The cancer detection rate was 19.5% in the second biopsy, decreasing to 13.5% after 5 or more biopsies

Nomogram details	
Clinical disease state	Patients with one or more negative prostate biopsies
Nomogram aim	Prediction of positive repeat biopsy
Outcome	Probability of positive repeat biopsy
Predictors	Age, DRE, number of negative cores taken, history of HGPIN, history of ASAP, PSA concentration, PSA slope, family history
Number of patients	343
Validation	Internal validation (jack nife resampling), external validation: Yanke et al (2005)
Accuracy measure	Concordance index = 0.70

General comments PSA density was not available for many patients and for practical reasons

was left out of the nomogram. Not much detail on the calibration of the model: jack-knife re-sampling was used.

Martorana, Bertaccini, Viaggi & Belleli . An innovative tool for predicting the pathologic stage of prostate cancer. Prostate Journal 2[4]. 2000.

Design: Retrospective case series (prognosis), evidence level: 3

Country: Italy, setting: Tertiary care

Inclusion criteria Men treated with radical prostatectomy between 1995 and 1997 were selected from a multi-institutional prostate cancer database. PSA <50 ng/ml. Clinical stage T3c or less

Exclusion criteria Missing Gleason score or missing surgical specimen.

Population number of patients = 250, age range 45 to 80 years, mean age = 65 years.

Interventions Serum PSA test, clinical staging, prostate biopsy with Gleason score. Radical prostatectomy.

9% of patients had neoadjuvant hormone therapy.

PSA, Gleason score and clinical stage were entered into multivariate logistic regression model for nomogram development.

Outcomes Pathologic stage. Separate nomograms predicted the probability of lymph node involvement, stage pT3ab disease, stage pT3c disease or stage pT4ab disease

Results -

Nomogram details	
Clinical disease state	Men who are candidates for RP, PSA <50 ng/ml and clinical stage T3c or less
Nomogram aim	To predict pathologic stage, after RP
Outcome	Probability of lymph node involvement, pT3ab, PT3c and pT4ab disease
Predictors	Clinical T stage, PSA (ng/ml) and biopsy Gleason score
Number of patients	250
Validation	None reported

General comments Results poorly described, the number of men with each pathologic stage is not reported. It is not possible to judge the appropriateness of the methods.

Mitchell, Cooperberg, Elkin, Lubeck, Mehta, Kane & Carroll . Ability of 2 pretreatment risk assessment methods to predict prostate cancer recurrence after radical prostatectomy: data from CaPSURE. Journal of Urology 173[4]. 2005.
Design: Retrospective case series (prognosis), evidence level: 3 Country: United States, setting: Community **Inclusion criteria** Men entered into the CaPSURE prostate cancer registry, who had RP performed between 1989 and 2002 for clinically localised PCa (T1-T3a). Men with some missing data were included (29% of cases). **Exclusion criteria** Neoadjuvant therapy or therapy within 6 months of RP. Men with multiple missing variables were excluded. **Population** number of patients = 1701, age range 39 to 79 years, mean age = 63 years. **Interventions** Preoperative PSA test, prostate biopsy and Gleason score, clinical stage (1997 AJCC), RP. **Outcomes** Probability of treatment failure within years of RP. Treatment failure was defined as biochemical recurrence (post-op serum PSA greater than 0.2 ng/ml on consecutive tests) or the initiation of adjuvant therapy (more than 6 months after RP). **Follow up** Not described **Results** Treatment failure occurred in 413/1701 patients (24%). Treatment failure was classified as biochemical progression in 248 cases and the start of adjuvant therapy in 165 cases. Based on the D'Amico classification 671 cases (39%) were classified as low risk, 446 (26%) were intermediate risk and 584 (34%) were high risk. Five-year freedom from progression (FFP) was 78%, 63% and 60% in the low, intermediate and high risk groups (HR 1.00, 1.87 and 2.32 respectively, p <0.0001). Mean 5-year FFP predicted by the Kattan nomogram in these risk groups was 91%, 74% and 69%, respectively, somewhat higher than the observed values. **General comments** The same patient cohort is used to validate Kattan (1998) in the paper by Greene et al (2004). The present study does not properly evaluate the Kattan (1998) nomogram, it compares the predicted and observed outcomes of patients grouped by D'Amico (1999) classification. Area under the ROC curve would have been a useful measure, but it is not reported. Men with therapy within 6 months of RP were excluded, this is inconsistent with the nomogram criteria.

Ohori, Kattan, Koh, Maru, Slawin, Shariat, Muramoto, Reuter, Wheeler & Scardino . Predicting the presence and side of extracapsular extension: a nomogram for staging prostate cancer. Journal of Urology 171[5]. 2004.
Design: Retrospective case series (diagnosis, screening), evidence level: 3 Country: United States, setting: Tertiary care

Inclusion criteria Men treated with pelvic lymphadenectomy and radical prostatectomy between 1989 and 2000 at two institutions. Histologically confirmed prostate cancer.

Exclusion criteria Androgen deprivation therapy or radiotherapy before RP.

Population number of patients = 763, age range 38 to 77 years, median age = 61 years.

Interventions Systematic needle biopsy of the prostate (6 or more cores), Gleason score was calculated for each side of the prostate, DRE (recorded for each side of the prostate) and pretreatment PSA (ng/ml).

Pelvic lymphadenectomy and radical prostatectomy

Outcomes Extra capsular extension (ECE) in each lobe of the prostate. ECE was predicted using multivariate logistic regression models, which were also used to generate the nomograms.

Results 30% of the patients and 17% of 1526 prostate lobes (left or right) had ECE. The calibration plot of predicted versus observed probability of ECE suggested good nomogram accuracy, at least in internal validation.

Nomogram details	
Clinical disease state	Men who are candidates for radical prostatectomy
Nomogram aim	To predict the probability of extra capsular extension in each lobe of the prostate
Outcome	Probability of ECE in each lobe of the prostate
Predictors	3 nomograms are presented, the most comprehensive requires: PSA (ng/ml), clinical T stage on each side, biopsy Gleason sum on each side, % positive cores on each side and % cancer in cores on each side.
Number of patients	763
Validation	Internal, bootstrap resampling
Accuracy measure	The area under the ROC curve was 0.806 for the most comprehensive nomogram.

General comments -

Parker, Norman, Huddart, Horwich & Dearnaley . Pre-treatment nomogram for biochemical control after neoadjuvant androgen deprivation and radical radiotherapy for clinically localised prostate cancer. British Journal of Cancer 86[5]. 2002.

Design: Retrospective case series (prognosis), evidence level: 3

Country: United Kingdom, setting: Tertiary care

Inclusion criteria Men with histologically proven, clinically localised prostate cancer treated with radical EBRT and neoadjuvant androgen deprivation at the Royal Marsden Hospital between 1988 and 1998.

Exclusion criteria Significant co-morbidity, life expectancy less than 5 years.

Population number of patients = 517, age range 49 to 83 years, median age = 69 years.

Interventions Pretreatment prognostic factors included in the nomogram were: serum PSA concentration, T stage, Gleason score (from sextant biopsy or TURP).

Neoadjuvant deprivation was achieved by an initial course of cyproterone acetate, together with monthly leuprorelin or goserelin starting one week after cyproterone and continuing until the competition of radiotherapy.

Radiotherapy was delivered using an anterior field and 2 wedged lateral or postero-lateral fields, using 6 to 10 MV photons. The planned dose was 64 Gy, delivered in 2 Gy fractions 5 times a week.

Outcomes Biochemical failure within 5 years of radical radiotherapy with neoadjuvant hormones. The definition of biochemical failure was consecutive rises in PSA greater than 2 ng/ml. or the start of androgen deprivation therapy.

Follow up Follow up included serum PSA measurement and clinical examination. Men were seen 6 weeks after starting neoadjuvant hormones and on alternate weeks during radiotherapy. They were then seen at 2 to 3 monthly intervals for the next 2 years, and from then on annually.

Results 233 / 517 men developed biochemical failure. Overall freedom from biochemical failure was 68%, 56% and 41% at 2, 3 and 5 years respectively.

Nomogram details	
Clinical disease state	Men with clinically localised PCa who are candidates for neoadjuvant hormone therapy and radical radiotherapy
Nomogram aim	To predict the risk of biochemical recurrence
Outcome	The probability of biochemical recurrence within 5 years of radical radiotherapy.
Predictors	T stage, Gleason score and preoperative PSA (ng/ml)
Number of patients	517
Validation	None reported
Accuracy measure	95% confidence intervals are supplied for nomogram predictions

General comments -

Partin, Kattan, Subong, Walsh, Wojno, Oesterling, Scardino & Pearson. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer. A multi-institutional update. JAMA 277[18]. 1997.

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

Country: United States, setting: Tertiary care

Inclusion criteria Men with clinically localised prostate cancer who had staging lymphadenectomy and radical prostatectomy in any of 3 institutions, between 1982 and 1996. Men had to have a pre-operative PSA level collected within 4 weeks of prostate needle biopsy or TURP. A preoperative Gleason score. 75 men with grossly positive lymph nodes at time of surgery did not have a prostatectomy.

Exclusion criteria Preoperative hormonal therapy or radiotherapy.

Population number of patients = 4113.

Interventions Preoperative serum PSA test, histological grade (based on needle biopsy, TURP or both), staging lymphadenectomy and radical prostatectomy.

Pre-operative PSA level, clinical stage and biopsy histological Gleason score were combined in nomogram tables to predict pathological stage.

Outcomes Pathological stage. The four categories were defined as: organ confined, capsular penetration, positive seminal vesicle involvement and lymph node involvement.

Follow up Complete - all included men had pathological staging.

Results The nomogram was developed using multinomial log-linear regression, and validated using bootstrap resampling. In the validation analysis 72.4% of the time, the nomograms correctly predicted the probability of a pathological stage to within 10%. The authors presented the sensitivity, specificity, PPV and NPV of the nomogram predictions for organ confined disease and lymph node involvement using a range of probability cut-offs from 0.1 to 0.9).

Nomogram details	
Clinical disease state	Men with clinically localised PCa who are candidates for RP
Nomogram aim	To predict pathological stage of clinically localised cancer
Outcome	Prediction of organ confined disease, capsular penetration, seminal vesicle involvement and lymph node involvement
Predictors	PSA (ng/ml), TNM clinical stage and biopsy Gleason score
Number of patients	4133
Validation	Yes, internal validation (bootstrap resampling); external validation (Boote et al, 2000; Graefen et al, 2003; Augustin et al 2004; Beiss-

	ner et al 2002).
Accuracy measure	Classification accuracy: 74% of the time the nomogram predicted pathological stage to within 10%

General comments Not enough detail about the pathological processing of the surgical specimen and lymph nodes (was it the same for all patients?); unclear whether the pathologists were blind to the clinical stage of the patients. PSA is treated as a 4-level categorical (rather than continuous) variable in the nomogram - unclear how the 4 category bins were decided, possible loss of prognostic Bootstrap validation only (resampling of the original sample not validation in a new group of patients).

Partin, Mangold, Lamm, Walsh, Epstein & Pearson. Contemporary update of prostate cancer staging nomograms (Partin Tables) for the new millennium. Urology 58[6]. 2001.

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men treated with RP and staging lymphadenectomy for clinically localised prostate cancer between 1994 and 2000 at the Johns Hopkins Hospital. All men had preoperative PSA test, biopsy histologic grade and clinical stage

Exclusion criteria Men were excluded if there was any missing data of if they received neoadjuvant hormone therapy. Men with grossly positive lymph nodes, who did not have RP, were also excluded.

Population number of patients = 5079, age range 42 to 74 years, mean age = 58 years.

Interventions Preoperative serum PSA level, prostate needle biopsy, clinical staging (AJCC-TNM, 1992), RP and staging lymphadenectomy.

The surgical specimen and any removed pelvic lymph nodes were sectioned and examined to establish pathological stage.

Outcomes Probability of: organ confined disease, extraprostatic extension, seminal vesicle or lymph node involvement. Multinomial log-linear regression analysis was used to derive these probabilities.

Results The final pathologic stage showed 64%, 30%, 4% and 2% had organ confined disease, extraprostatic extension, seminal vesicle involvement or lymph node involvement, respectively.

Nomogram details	
Clinical disease state	Men with clinically localised PCa who are candidates for RP
Nomogram aim	To predict pathological stage of clinically localised cancer
Outcome	Probability of organ confined disease, capsular penetration, seminal vesicle involvement and lymph node involvement

Predictors	PSA (ng/ml), TNM clinical stage and biopsy Gleason score
Number of patients	5079
Validation	Yes, internal. Bootstrap resampling was done to obtain 95% confidence intervals. External validation by Augustin et al (2004) and Steuber et al (2005).
Accuracy measure	None reported

General comments The measurement of the predictor variables is poorly described. Not reported whether pathological staging was done "blind". The updated nomogram stratifies the predictor variables into more categories than the original 1997 version, which should improve accuracy.

The data for the original Partin nomograms were collected from men treated between 1982 and 1996. This study is an update: the stage at presentation shifted in the years following the original nomogram, with more men presenting with Stage T1c, Gleason score 5 to 6, and serum PSA levels less than 10.0 ng/mL.

Penson, Grossfeld, Li, Henning, Lubeck & Carroll . How well does the Partin nomogram predict pathological stage after radical prostatectomy in a community based population? Results of the cancer of the prostate strategic urological research endeavor. Journal of Urology 167[4]. 2002.

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Community

Inclusion criteria Men entered into the CaPSURE prostate cancer registry between 1995 and 1999. Men were treated at any of 30 institutions with radical prostatectomy and bilateral pelvic lymphadenectomy. Clinical stage T1 to T3a disease.

Exclusion criteria Missing pathological outcome data. Neoadjuvant hormone therapy

Population number of patients = 1162.

Interventions Preoperative serum PSA test, clinical T staging and biopsy with Gleason score available. Radical prostatectomy and bilateral pelvic lymphadenectomy. Pathological results of RP were assessed from the surgical pathology report. Each report was read independently by 2 clinicians blinded to the patient's clinical information.

Outcomes Predicted and observed lymph node involvement, seminal vesicle involvement, extra capsular extension and organ confined disease. Predictions were calculated using the Partin (1997) nomogram.

Results 860 (74%) men had organ confined disease, 179 (15%) had established capsular penetration, 95 (8%) had seminal vesicle involvement and 37 (3%) had lymph node involvement.

Validation results:

ECE, AUC = 0.614 [95% CI 0.567 to 0.661]

SVI, AUC = 0.726 [95% CI 0.666 to 0.786]

LNI, AUC = 0.766 [95% CI 0.675 to 0.857]

OCD, AUC = 0.684 [95% CI 0.652 to 0.716]

Validation details	
Nomogram name	Partin (1997) nomogram
Number of patients	1162

General comments The discriminative ability of the Partin tables was lower than in previously published reports.

Potters, Purrazzella, Brustein, Fearn, Leibel & Kattan . A comprehensive and novel predictive modeling technique using detailed pathology factors in men with localized prostate carcinoma. Cancer 95[7]. 2002.

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Patients treated with permanent prostate brachytherapy for histologically confirmed and clinically localised prostate cancer, at the Memorial Sloan Kettering Cancer Center between 1992 and 1999.

Exclusion criteria -

Population number of patients = 1073, age range 43 to 84 years, median age = 70 years.

Interventions Sextant prostate biopsy with Gleason score. Clinical staging according to AJCC 1997 criteria. TRUS assessment of prostate volume.

Permanent prostate brachytherapy, either I-125 or Pd-103 prescribed to 144 Gy or 140 Gy, respectively. Patients with prostates greater than 60 cc had neoadjuvant hormone therapy. Patients with PSA greater than 10 ng/ml, Gleason sum 7 to 10 or clinical stage 2b were usually offered a combination of EBRT and brachytherapy.

Outcomes Treatment failure following brachytherapy. Treatment failure was defined as biochemical recurrence, clinical recurrence or the initiation of adjuvant hormone therapy. Biochemical recurrence was defined using a modification of the American Society for Therapeutic Radiology and Oncology (ASTRO) criteria.

Follow up Median follow up was 3 years for censored patients, range 0.5 to 7.6 years. Follow up started at 5 weeks after treatment and then 3 to 4 monthly for the next 2 years, and then at 6 monthly intervals.

Results 104 / 1073 patients experienced treatment failure. The pretreatment variables were

incorporated into nomograms of varying complexity (from 3 to 26 variables).

Nomogram details	
Clinical disease state	Men with clinically localised PCa who are candidates for permanent prostate brachytherapy
Nomogram aim	To predict biochemical control after brachytherapy
Outcome	Probability of biochemical control
Predictors	The basic model contained pretreatment PSA (ng/ml), clinical stage and biopsy Gleason sum. The full model contained a further 23 variables related to the grade and distribution of cancer in the biopsy cores.
Number of patients	1073
Validation	Internal validation, bootstrap resampling.
Accuracy measure	The Somers D rank correlation coefficient ranged from 0.32 (for the base model) to 0.39 for the full model. Converting to area under the ROC curve gives values of 0.66 to 0.70

General comments -

Poulakis, Witzsch, de, Emmerlich, Meves, Altmannsberger & Becht . Preoperative neural network using combined magnetic resonance imaging variables, prostate-specific antigen, and Gleason score for predicting prostate cancer biochemical recurrence after radical prostatectomy. Urology 64[6]. 2004.

Design: Retrospective case series (prognosis), evidence level: 3

Country: Germany, setting: Tertiary care

Inclusion criteria Patients who had preoperative pelvic coil MRI before retropubic radical prostatectomy and staging lymphadenectomy for localised PCa.

Exclusion criteria Men with lymph node metastasis in the final histologic examination (n=36) and those who were lost to follow up (n=2).

Population number of patients = 191, age range 47 to 79 years, median age = 65 years.

Interventions The preoperative predictive variables included clinical TNM stage, serum PSA level, biopsy Gleason score, and pMRI findings. Retropubic radical prostatectomy.

Outcomes Artificial neural network (ANN) and logistic regression (LR) predictions for biochemical recurrence. Biochemical recurrence was defined as any detectable PSA level (0.1 ng/ml or greater). The predictions were compared to those of the Kattan (1998) and Han (1992) nomograms. The ANN, LR and nomograms were validated using an internal 4-way cross validation method.

Follow up Patients were evaluated 1 month after RP, every 3 months for 2 years and then every 6 months thereafter. Median follow up was 62 months (range 4 to 92 months).

Results 57 / 191 patients, 57 (30%) developed disease progression at a median follow-up of 64 months (mean 61, range 2 to 86). For Han (2003) AUC = 0.732, for Kattan (1998) AUC = 0.737.

Nomogram details	
Clinical disease state	Men with clinically localised prostate cancer (but pN0) treated with RP
Nomogram aim	To predict the risk of disease recurrence after RP
Outcome	Probability of biochemical recurrence within 5 years of RP
Predictors	Clinical TNM stage, PSA (ng/ml), biopsy Gleason score and pMRI findings
Number of patients	191
Validation	Internal (4 cross validation sub samples)
Accuracy measure	Area under ROC curve was 0.89 for the best ANN model and 0.781 for the best logistic regression model
Validation details	
Nomogram name	Kattan (1998) nomogram
Nomogram name	Han (2003) nomogram
Number of patients	For Kattan (1998) validation, n=191
Number of patients	For Han (2003) nomogram validation, n = 191

General comments All biopsy and histologic specimens were reviewed by one pathologist who was blinded to the clinical variables. This study also validates the Kattan (1998) and Han (2002) nomograms (which use slightly different definitions of biochemical recurrence).

Ramsden & Chodak . An analysis of risk factors for biochemical progression in patients with seminal vesicle invasion: validation of Kattan's nomogram in a pathological subgroup.[see comment]. BJU International 93[7]. 2004.

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men with seminal vesicle involvement after radical prostatectomy, treated by one surgeon between 1984 and 2000.

Exclusion criteria Patients with positive lymph nodes, adjuvant radiotherapy or hormone

therapy were excluded.

Population number of patients = 42, mean age = 65 years.

Interventions Preoperative variables: PSA level, biopsy Gleason score, and clinical stage. Radical prostatectomy. Post operative variables: pathological Gleason score, margin status, capsular invasion, seminal vesicle involvement and lymph node involvement.

Outcomes Predicted and observed probability of biochemical recurrence within 7 years of RP. Biochemical recurrence was defined as one measurement of PSA of 0.4 ng/ml or more.

Follow up Median follow up was 2.6 years.

Results 22/42 men experienced biochemical recurrence. Kaplan Meier plots were used to derive the observed probabilities of recurrence. AUC = 0.739 [95% CI 0.589 to 0.889]

Validation details	
Nomogram name	Kattan (1999) nomogram
Number of patients	42

General comments Very small study

Slaton, Schwartz, Wasserman & Mian . Validation of the Kattan nomogram for predicting cancer on repeat prostate biopsy after an initial biopsy that was negative for cancer. Journal of Urology 173[4]. 2005.

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

Country: United States, setting: Tertiary care

Inclusion criteria Patients undergoing repeat prostate biopsy following an initial negative biopsy at 2 institutions. Indications for repeat biopsy at these hospitals are not reported.

Exclusion criteria -

Population number of patients = 310.

Interventions Validation of Lopez-Corona et al (2003) nomogram

Outcomes Probability of repeat prostate biopsy positive for PCa.

Results The patients were stratified into 4 groups based on risk predictions from the nomogram. The observed risk of prostate cancer in each group tended to be slightly lower than the range predicted by the nomogram.

General comments Abstract only, limited details of methods and patients.

Smaletz, Scher, Small, Verbel, McMillan, Regan, Kelly & Kattan . Nomogram for overall survival of patients with progressive metastatic prostate cancer after castration. Journal of Clinical Oncology 20[19]. 2002.

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Patients treated on one of 19 clinical trials at Memorial Sloan Kettering Cancer Center between 1989 and 2000. Entry onto 15 of the trials was restricted to men with prostate cancer with castrate metastatic progression.

Exclusion criteria Non-castrate disease (testosterone levels more than 50 ng/dL). No metastases on scan. Missing data for the prognostic variables.

Population number of patients = 842.

Interventions The prognostic factors included in the model were: age, Karnofsky performance status (KPS), haemoglobin (HGB), prostate-specific antigen (PSA), lactate dehydrogenase (LDH), alkaline phosphatase (ALK), and albumin.

Outcomes Overall survival. The nomogram generated predictions of 1 year and 2 year survival probability, as well as median survival.

Results Median survival was 15.8 months for patients in the nomogram development sample, and 10.3 months for the validation sample. There were 357 deaths (87%) in the nomogram development sample compared to 395 deaths (91%) in the validation sample

Nomogram details	
Clinical disease state	Men with progressive metastatic prostate cancer, after castration
Nomogram aim	To predict survival
Outcome	One and two year overall survival, median survival
Predictors	age, Karnofsky performance status (KPS), haemoglobin (HGB), prostate-specific antigen (PSA), lactate dehydrogenase (LDH), alkaline phosphatase (ALK), and albumin
Number of patients	409 patients for nomogram development and 433 for validation
Validation	Independent validation set
Accuracy measure	AUC = 0.67

General comments -

Stephenson, Scardino, Eastham, Bianco, Jr., Dotan, DiBlasio, Reuther, Klein & Kattan . Post-operative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. Journal of Clinical Oncology 23[28]. 2005.

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria The nomogram was developed using data from men who underwent RP for clinically-localized prostate cancer by two high-volume surgeons at Memorial Sloan Kettering Cancer Center (MSKCC) between 1983 and 2003. The model was validated separately on two independent groups of patients: group 1 were treated by other surgeons at MSKCC and group 2 were treated at the Cleveland Clinic Foundation (1999 to 2000).

Exclusion criteria Missing values for the predictor variables. Patients whose RP was aborted due to intraoperative identification of positive lymph nodes were excluded.

Population number of patients = 5021, age range 37 to 81 years, mean age = 66 years.

Interventions Preoperative tests: PSA concentration, prostate needle biopsy and Gleason score, clinical staging

Radical prostatectomy. Pathological staging and Gleason score

Outcomes Predicted and observed disease progression within 10 years of RP. Progression was defined as: biochemical recurrence (PSA 0.4 ng/ml and rising), biopsy confirmed local recurrence, distant metastases, cancer specific mortality or the initiation of adjuvant therapy except for EBRT at PSA levels of less than 0.2ng/ml).

Follow up In most cases patients were followed up with PSA test and clinical examination every 3 months for the first 3 years, every 6 months in years 4 and 5, and then yearly thereafter. Median follow up was 2.08 years for the modelling set, and 3.33 years and 4.42 years for the two modelling sets.

Results Using Kaplan-Meier method the 10-year progression-free probability for the modelling set was 79% (95% CI, 75% to 82%). In the validation sets, the 10-year progression-free probability was 70% (95% CI, 64% to 75%) for MKSCC and 67% (95% CI, 63% to 71%).

Nomogram details	
Clinical disease state	Men after RP for PCa
Nomogram aim	To predict the probability of disease recurrence
Outcome	Probability of disease recurrence within 10 years of RP
Predictors	Year of RP, surgical margins, extracapsular extension, seminal vesicle invasion, lymph node involvement, primary and secondary Gleason score (from surgical specimen) and preoperative PSA (ng/ml)
Number of patients	Nomogram development sample of 1881 men, validation samples of 1782 and 1357 men
Validation	Internal - jack-knife method and independent validation samples
Accuracy measure	The area under the ROC curve was 0.81 and 0.79 for the develop-

ment and validation samples respectively.
General comments Update of Kattan (1999) nomogram to allow 10 year predictions.

Stephenson, Scardino, Eastham, Bianco & Kattan . Pretreatment nomogram predicting the long-term risk of metastatic progression of prostate cancer after radical prostatectomy. Journal of Clinical Oncology 23[16]. 2005.

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men treated with radical prostatectomy between 1983 and 2002 (not stated where patients were treated, but probably at the Memorial Sloan Kettering Cancer Center and the Cleveland Clinic).

Exclusion criteria -

Population number of patients = 4590.

Interventions Preoperative tests included: pre-biopsy PSA, primary and secondary Gleason grade, clinical stage.

Radical prostatectomy. Some patients (16%) had neoadjuvant androgen deprivation therapy.

Outcomes Long term risk of metastatic progression of prostate cancer after RP. A nomogram to predict metastatic progression was developed by entering pretreatment variables into a Cox proportional hazards model.

Follow up Median follow up for patients free of metastases was 5.1 years.

Results 209 patients developed metastasis. The overall 13 year metastasis free survival probability was 88%. The authors report that the nomogram was accurate, but there is limited detail in this abstract.

Nomogram details	
Clinical disease state	Men who are candidates for RP for PCa
Nomogram aim	To predict the long term risk of metastasis after RP
Outcome	Metastasis of PCa within 13 years of RP
Predictors	Pre-biopsy PSA (ng/ml), primary and secondary Gleason grade, clinical stage, year of treatment and neoadjuvant hormone therapy
Number of patients	4590
Validation	Internal, bootstrap resampling
Accuracy measure	Area under the ROC curve was 0.79

General comments Abstract only

Steuber, Karakiewicz, Augustin, Erbersdobler, Lange, Haese, Chun, Walz, Graefen & Huland . Transition zone cancers undermine the predictive accuracy of Partin table stage predictions. Journal of Urology 173[3]. 2005.

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

Country: Germany, setting: Tertiary care

Inclusion criteria Patients with biopsy confirmed clinically localised PCa who underwent RP and staging lymphadenectomy at one German hospital between 1994 and 2002.

Exclusion criteria Neoadjuvant endocrine therapy, clinical stage T1a or T1b and patients in whom RP was abandoned because of positive lymph nodes.

Population number of patients = 1990.

Interventions PSA concentration (AxSym PSA assay), DRE and TRUS guided biopsy. Clinical stage was defined using the AJCC 4th edition criteria.

Pelvic lymph node dissection (PLND) was performed universally in the early years of the study but only for high risk patients in the later years. Risk was defined using an algorithm based on biopsy characteristics.

Tumour areas in the RP specimen were mapped and tumours were classified as TZ cancers when more than 70% of the tumour volume was within the TZ.

Outcomes The predictive accuracy of the Partin (2001) nomogram for organ confined disease (OC), seminal vesicle invasion (SVI), lymph node invasion (LNI) and extra capsular extension (ECE). Subgroup analysis of TZ and PZ cancers was conducted.

Results There were 222 TZ cancers and 1,768 PZ cancers.

The 1,990 radical retropubic prostatectomy specimens demonstrated ECE in 689 cases (34.6%) (TZ in 58 or 27.1% and PZ in 631 or 35.8%) and SVI in 224 (TZ in 13 or 6.1% and PZ in 211 or 11.9%). The 1,320 lymphadenectomy specimens demonstrated LNI in 56 cases (TZ in 2 or 0.9% and PZ in 54 or 4.6%). OC was found in 784 cases (59.4%) (TZ in 95 or 69.9% and PZ in 689 or 58.2%).

Validation:

ECE, AUC = 0.76 [95% CI 0.737 to 0.783]

SVI, AUC = 0.78 [95% CI 0.743 to 0.817]

LNI, AUC = 0.81 [95% CI 0.741 to 0.879]

OCD, AUC = 0.79 [95% CI 0.766 to 0.814]

Validation details

Nomogram name	Partin (2001) nomogram
Number of patients	1990

General comments The accuracy of the Partin (2001) nomogram pathological stage predictions was less for TZ PCa than for PZ PCa. It appears that the Partin nomogram tended to underestimate OC for TZ PCa and overestimate ECE for TZ PCa.

Svatek, Karakiewicz, Shulman, Karam, Perrotte & Benaim . Pre-Treatment Nomogram for Disease-Specific Survival of Patients with Chemotherapy-Naive Androgen Independent Prostate Cancer. European Urology [Jan 6]. 2006.

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Patients with untreated androgen independent prostate cancer (AIPC), diagnosed at a single institution between 1989 and 2002.

Exclusion criteria Missing data from medical records. Treatment with cytotoxic chemotherapy.

Population number of patients = 129, median age = 69 years.

Interventions The following variables were measured: PSA at initiation of androgen deprivation therapy (ADT), PSA doubling time after AIPC diagnosis, nadir PSA on ADT and time from ADT to AIPC. The variables were used in a Cox regression model to develop a nomogram.

AIPC was defined as two consecutive increases in PSA values above the nadir value, each of which was greater than 25% of the nadir value.

Outcomes Overall survival, AIPC specific survival and other cause survival.

Follow up Of the original 129 patients, 106, 82, 65, 44, and 28 remained at risk at 1, 2, 3, 4 and 5 years respectively.

Results AIPC-specific mortality was recorded in 74 of 129 patients (57.4%). Other-cause mortality was recorded in 7 men (5.4%). Median overall survival was 52 months (mean, 36.0 months; range 3 to 107 months) and median AIPC-specific survival was 54 months (mean, 35 months; range 3 to 107 months).

Nomogram details	
Clinical disease state	Men with androgen independent prostate cancer after androgen deprivation therapy.
Nomogram aim	To predict survival
Outcome	Androgen-independent-prostate-cancer-specific survival

Predictors	PSA at initiation of androgen deprivation therapy (ADT), PSA doubling time after AIPC diagnosis, nadir PSA on ADT and time from ADT to AIPC.
Number of patients	129
Validation	Internal, bootstrap resampling
Accuracy measure	The concordance index (AUC for censored data) was 0.809

General comments -

Schwarzer & Schumacher . Artificial neural networks for diagnosis and prognosis in prostate cancer. Semin. Urol. Oncol 20[2]. 2002.

Design: Review (diagnosis, screening), evidence level: 3

Country: International, setting: Other

Inclusion criteria Studies reporting feed-forward artificial neural networks (FFNN) for diagnosis and prognosis in prostate cancer. English language, published between 1999 and 2001, and indexed on MEDLINE

Exclusion criteria -

Population -

Interventions FFNNs for diagnosis and prognosis in prostate cancer. 10 studies used FFNNs to predict the diagnosis of prostate cancer or the stage of the disease. 4 studies used FFNNs to predict prognosis.

In 11 studies, the predictions made by the FFNNs were compared with those using statistical methods (usually logistic regression).

Outcomes Accuracy of prediction.

Results The review does not report the accuracies of the predictions, but in 8 studies, the FFNNs were considered more accurate than the statistical methods, in 2 studies, the statistical methods were more accurate, and in one study, the techniques were equally accurate.

The methods were often poorly reported and 9/14 studies had poor methodology (no validation of network, overoptimistic assessment of its performance or inappropriate use of an FFNN with censored data).

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General comments FFNNs are essentially non-linear regression models.

Retrospective cohort studies

(Graff *et al.* 2007)
Design: Retrospective cohort study (prognosis), evidence level: 2+ Country: United States, setting: Community **Inclusion criteria** Men with clinically localised (T1 or T2) prostate cancer in the Prostate Cancer Outcomes Study cohort who were treated with primary hormonal therapy. **Exclusion criteria** - **Population** number of patients = 276. **Interventions** All men had primary hormonal therapy (medical or surgical castration with or without non-steroidal antiandrogens). **Outcomes** Overall survival. **Follow up** Median follow-up for censored patients was 7.6 years (range 1.1 to 8.1 years). **Results** The risk of death at 5 years was 9%. A nomogram was developed for 5 year overall survival but no validation was available. The pretreatment prognostic factors included were: DRE (normal or not), Age (years) PSA (ng/ml) and biopsy Gleason score. - **General comments** See prognostic factors section for further appraisal of this paper.

Prospective case series

(Finne *et al.* 2002)
Design: Prospective case series (prognosis), evidence level: 3 Country: Finland, setting: Community **Inclusion criteria** Men identified from a population screening exercise with PSA between 4 and 20 ng/ml, who underwent biopsy. Complete data on the prognostic variables were only available for 758/856 men. **Exclusion criteria** -

Population number of patients = 758, age range 55 to 57 years, mean age = 62 years.

Interventions DRE, defined as positive if anything abnormal was palpated.

Total and free serum PSA were derived from frozen samples (Prostatus PSA and Hybridtech Tandem-E assays).

Prostate volume was measured using TRUS.

Sextant biopsies were performed under TRUS guidance, additional biopsies were taken from suspicious lesions identified by DRE or TRUS.

Other prognostic variables were: age and family history of prostate cancer (father or brother).

Outcomes Probability of biopsy diagnosis of prostate cancer.

Follow up Men with negative initial biopsies were re-biopsied if they had HGPIN (n=1) or serum PSA >10 ng/ml (n=?).

Results Prostate cancer was diagnosed following biopsy in 200/758 men.

The sensitivity and specificity for PCa corresponding to threshold values of nomogram PCa probability were:

PCa probability cut-off	Sensitivity	Specificity
0.06	98.5%	14%
0.09	95%	27%
0.12	92%	36%
0.15	88%	45%
0.18	84%	55%

-

General comments Low rate of re-biopsy?

(Garzotto *et al.* 2005)

Design: Prospective case series (prognosis), evidence level: 3

Country: United States

Inclusion criteria A prospective series of men undergoing prostate biopsy, with serum PSA of 10 ng/ml or less.

Exclusion criteria -

Population number of patients = 1699.

Interventions Prognostic variables included: age, race, family history, DRE, PSA concentration, PSA density, PSA doubling time and ultrasound findings.

Prostate biopsy (at least 6 cores)

Outcomes High grade prostate cancer on biopsy.

Follow up Not reported whether there were repeat biopsies.

Results High grade PCa was diagnosed in 157 patients.

The authors developed a nomogram by entering the predictor variables into a logistic regression. It appears that only age, DRE and PSA density were used in the final nomogram.

The nomogram was validated in an independent set of 510 patients : area under the ROC curve was 0.74 for the nomogram.

General comments Abstract only, limited detail about methods and participants. Continuous variables were split into categories. Some of the original predictor variables appear to have been excluded from the final nomogram. Insufficient information to calculate confidence intervals for AUC.

Retrospective case series

(Steuber *et al.* 2006)

Design: Retrospective case series, evidence level: 3

Country: Germany, setting: Tertiary care

Inclusion criteria Men with biopsy confirmed, clinically localised prostate cancer, who were treated with RP at a single institution.

Exclusion criteria Neoadjuvant of adjuvant hormonal therapy. Adjuvant radiotherapy.

Population number of patients = 1118.

Interventions All men were received radical prostatectomy, some received pelvic lymphadenectomy. Extracapsular extension was determined using serial transverse sections at 3mm of the prostatectomy specimen according to the Stanford protocol.

A nomogram was developed using multivariate analysis of the following pre-operative variables: clinical stage, pretreatment PSA, biopsy Gleason sum, percent positive cores and percent cancer in the biopsy specimen.

Outcomes Side specific extracapsular extension of prostate cancer. erapy.20

Follow up Outcomes measured using prostatectomy specimen.

Results ECE was seen in 303/1118 men (27%). SS-ECE was seen in 385/2236 prostate

lobes (17%). Using bootstrap re-sampling the AUC for the nomogram was estimated as 0.84.

General comments -

(Ayyathurai *et al.* 2006)

Design: Retrospective case series (prognosis), evidence level: 3

Country: United Kingdom, setting: Tertiary care

Inclusion criteria Men treated with radical prostatectomy for T1c to T2c prostate cancer at a single institution between 1993 and 2004.

Exclusion criteria Incomplete clinical staging information. Neoadjuvant therapy.

Population number of patients = 177, age range 48 to 73 years, median age = 64 years.

Interventions All men had radical prostatectomy. Preoperatively serum PSA, clinical stage and biopsy Gleason score were all recorded.

Outcomes Predictive value of Partin (2001) tables, estimated using the area under the ROC curve.

Results Pathological stage was: organ confined (75% of cases), extracapsular extension (14%), seminal vesicle involvement (9%), and lymph node involvement (2%).

The area under the ROC curve was 0.733 (95% CI 0.644 to 0.822) for organ confinement, 0.738 (95% CI 0.650 to 0.870) for seminal vesicle invasion and 0.780 (95% CI 0.708 to 0.908) for lymph node involvement, suggesting good predictive value.

General comments -

(Baccala *et al.* 2007)

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men who had undergone RP for prostate cancer, at any of 3 hospitals.

Exclusion criteria Adjuvant radiotherapy, neoadjuvant hormone therapy.

Population number of patients = 6740, median age = 61 years.

Interventions Radical prostatectomy with complete resection of the seminal vesicles. Pathologic analysis of the surgical specimen was done using serial step sectioning.

A nomogram for the prediction of SVI was developed using Cox Regression of the following preoperative variables: Age, PSA, Biopsy Gleason Score, and Clinical T stage.

Outcomes Seminal vesicles positive for prostate cancer.

Follow up Outcome was determined postoperatively.

Results 566 (8%) men had seminal vesicle involvement.

Using internal validation (bootstrap re-sampling) the nomogram gave an AUC of 0.80, for the prediction of SVI.

General comments -

(Briganti *et al.* 2006b)

Design: Retrospective case series (prognosis), evidence level: 3

Country: , setting: Tertiary care

Inclusion criteria Men with clinical stage T1c to T3 prostate cancer treated with RP at a single institution between 2002 and 2005.

Exclusion criteria Incomplete clinical information, no pelvic lymph node dissection or PSA > 50 ng/ml

Population number of patients = 602, age range 45 to 85 years, mean age = 66 years.

Interventions Retropubic radical prostatectomy with pelvic lymph node dissection, between 10 and 40 (median 16) nodes removed. A nomogram to predict lymph node invasion was developed using the following preoperative variables: PSA, clinical tumour stage and biopsy Gleason sum.

Outcomes Lymph node invasion.

Follow up No follow-up beyond post operative pathology

Results LNI was detected in 66/602 men (11%). The AUC of the nomogram for the prediction of LNI was 0.76. Bootstrap resampling was used for the nomogram validation.

General comments -

(Briganti *et al.* 2007)

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

Country: Germany, setting: Tertiary care

Inclusion criteria Men treated with radical prostatectomy (RP) and extended pelvic lymph node dissection (ePLND) at a single institution between 2002 and 2005.

Exclusion criteria -

Population number of patients = 565, age range 42 to 82 years, mean age = 66 years.

Interventions All men received radical prostatectomy with ePLND. All ePLND specimens were mapped according to their anatomic location (obturator, external iliac, internal iliac lymph nodes). A multivariate logistic regression-based nomogram predicting nonobturator lymph node involvement was developed using the following preoperative variables: PSA, clinical tumour stage and biopsy Gleason score.

Outcomes Anatomic location-specific rate of LNI, specifically the rate of nonobturator lymph node involvement (NOLNI).

Follow up Outcomes measured using the surgical specimen (no further follow-up)

Results LNI was detected in 63/565 men (11%). NOLNI was detected in 35/63 cases of LNI (56%). Exclusive NOLNI was detected in 21/63 cases of LNI (35%).

The AUC for the nomogram predictions of NOLNI was 0.80 (internal validation using boot-strap resampling).

General comments -

(Chun *et al.* 2006)

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

Country: Germany, setting: Tertiary care

Inclusion criteria Men treated with RP for histologically confirmed prostate cancer at a single institution between 1992 and 2004.

Exclusion criteria Missing data.

Population number of patients = 2982.

Interventions Radical prostatectomy. Prostatectomy specimens were assessed according to the Stanford protocol and graded using the Gleason system.

A nomogram to predict upgrading from biopsy to RP specimen was developed using the following pre-operative variables: PSA, clinical stage, biopsy Gleason primary pattern, and biopsy Gleason secondary pattern.

Outcomes Gleason grade of the prostatectomy specimen and the initial prostate biopsy.

Follow up Outcomes determined using prostatectomy specimen (no further follow-up)

Results Upgrading of the Gleason score from biopsy to RP specimen happened in 875/2982 cases (29%). The accuracy of the nomogram was estimated at 80%, using internal validation with bootstrap re-sampling.

General comments -

(Crippa *et al.* 2006)

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

Country: Brazil, setting: Tertiary care

Inclusion criteria Men with clinically localised prostate cancer, treated with radical retropubic prostatectomy at a single institution between 1988 and 2002.

Exclusion criteria Missing clinical information, neoadjuvant therapy or diagnosis through TURP

Population number of patients = 898, age range 40 to 83 years, mean age = 63 years, median age = 64 years.

Interventions Radical retropubic prostatectomy. Pathological staging of the surgical specimen.

A nomogram to predict pathological stage was developed using the following preoperative variables: PSA, biopsy Gleason score and percent of positive biopsy cores

Outcomes Pathological stage.

Results The rates of pathological T2, T3 and T4 disease were 66.7%, 33.0% and 0.3% respectively. Internal validation using bootstrap resampling suggested that 87% of the time the nomogram correctly predicted the probability of a given pathological stage to within 10%. AUC was not reported.

General comments -

(Joniau *et al.* 2007)
Design: Retrospective case series (diagnosis, screening), evidence level: 3 Country: Belgium, setting: Tertiary care **Inclusion criteria** Men with clinical T3a prostate cancer treated with radical prostatectomy **Exclusion criteria** Bilateral clinical T3a disease, neoadjuvant therapy **Population** number of patients = 200, age range 41 to 79 years, mean age = 63 years. **Interventions** All men were treated with retropubic radical prostatectomy. In 184/200 cases a bilateral non-nerve sparing procedure was performed. The prostatectomy specimen was serially sectioned at 4mm intervals, and assigned a pathological stage. The last PSA before surgery and the biopsy Gleason score were used to develop probability tables for pathological tumour stage. Six risk groups were defined by biopsy Gleason score (3+4 or less vs. 4+3 or more) and by PSA (10 ng/ml or less, 10 to 20 ng/ml or more than 20 ng/ml) **Outcomes** Pathological stage: pT2 to pT4: organ confined disease, extraprostatic extension, seminal vesicle involvement and adjacent structure involvement. **Results** The rates of pT2, pT3a, pT3b and p4 disease were 23.5%, 56.5%, 16% and 8% respectively. 8.5% of men had positive lymph nodes and 33.5% had positive surgical margins. The AUC for the table predictions of organ confined disease was 0.59 (95% CI 0.49 to 0.67), for the prediction of extraprostatic extension 0.61 (95% CI 0.52 to 0.70), for the prediction of seminal vesicle involvement 0.73 (95% CI 0.65 to 0.80) and for adjacent structure involvement 0.80 (95% CI 0.732 to 0.86).

(Kattan *et al.* 2006)
Design: Retrospective case series (), evidence level: 3 Country: United States, setting: Tertiary care **Inclusion criteria** Men treated with permanent prostate brachytherapy at any of 6 centres **Exclusion criteria** - **Population** number of patients = 5889. **Interventions** All men were treated with permanent prostate brachytherapy. A nomogram to predict disease recurrence was developed using the following variables: pre-treatment PSA level, biopsy Gleason sum, year of treatment, isotope and clinical stage. **Outcomes** Prostate cancer recurrence.

Follow up Censored follow-up was 4.6 years (range 1 month to 14.5 years). The mean number of follow-up PSA tests per patient was 6.3 (range 2 to 22).

Results At 9 years recurrence free survival was 82% (95% CI 79% to 84%). The concordance index of the nomogram was 0.62.

General comments -

(Kuroiwa *et al.* 2007)

Design: Retrospective case series (prognosis), evidence level: 3

Country: Japan, setting: Tertiary care

Inclusion criteria Men treated with radical prostatectomy for prostate cancer between 1997 and 2005.

Exclusion criteria -

Population number of patients = 1188, median age = 66 years.

Interventions Radical prostatectomy. Pathological slides were reviewed by two pathologists. A nomogram was developed using logistic regression of the following preoperative variables: PSA, clinical stage and Gleason score.

Outcomes Pathology of the surgical specimen: organ confined disease (OCD), extracapsular extension (ECE), seminal vesicle involvement (SVI) and lymph node involvement (LND)

Results 70% of the men had T1c disease. Overall 67%, 26%, 5% and 3% had OCD, ECE, SVI and LNI respectively.

The AUC values for the prediction of OCD were 0.72 and 0.70 were for the nomogram and Partin tables respectively. The AUC values for the prediction of LNI were 0.86 and 0.79 were for the nomogram and Partin tables respectively.

General comments -

(May *et al.* 2006)

Design: Retrospective case series (prognosis), evidence level: 3

Country: Germany, setting: Tertiary care

Inclusion criteria Men with prostate cancer (clinical stage T1 to T3a), presenting with PSA

levels between 20.1 and 100 ng/ml, treated with RP between 1992 and 2003 at one of 4 hospitals.

Exclusion criteria -

Population number of patients = 191, age range 46 to 74 years, median age = 64 years.

Interventions All men were treated with radical prostatectomy. 15% had adjuvant hormonal therapy, 2% adjuvant radiotherapy and 0.5% adjuvant chemotherapy.

Outcomes Biochemical recurrence (PSA 0.1 ng/ml or more and rising)

Follow up Mean follow up was 5.9 years, median 5.7 years (range 1 month to 12.8 years).

Results Biochemical recurrence free survival was 79% at 1 year, 67% at 2 years, 46% after 5 years and 36% after 8 years. The Kattan (1998) nomogram for disease recurrence was validated in this cohort: the area under the curve was 0.66 (95% C.I. 0.57 to 0.75].

General comments -

(Nakanishi *et al.* 2007)

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Multi-institutional case series (no further details) of men treated with RP for prostate cancer.

Exclusion criteria Neoadjuvant therapy.

Population number of patients = 421.

Interventions Men were all treated with RP for prostate cancer. All were diagnosed using extended (10 or 11 core) prostate biopsy.

A nomogram for the prediction of indolent cancer (diagnosed using the prostatectomy specimen) was developed using the following pretreatment variables: age, PSA, prostate volume, maximum tumour length in a core, and number of positive cores.

Outcomes Low volume and low grade cancer (diagnosed after prostatectomy).

Results 150/421 (36%) men had low volume/ low grade cancer. The AUC value for the nomogram was 0.86, for the nomogram development sample.

General comments -

(Stephenson *et al.* 2006)
Design: Retrospective case series (prognosis), evidence level: 3 Country: United States, setting: Tertiary care **Inclusion criteria** Men with clinical tumour stage T1 to T3 prostate cancer, treated with RP by one of two surgeons between 1983 and 2003. **Exclusion criteria** - **Population** number of patients = 3523. **Interventions** All men were scheduled to receive radical prostatectomy (although some procedures were aborted due to lymph node metastases). A nomogram was developed using data from 1978 men and validated in another group of 1545 men. The following preoperative variables were included in the nomogram: PSA level, number of positive cores, number of negative cores, clinical stage, primary biopsy Gleason score and secondary biopsy Gleason score. **Outcomes** Disease progression at 1 to 10 years after surgery. Progression was defined as: PSA of 4 ng/ml or more, secondary therapy, clinical recurrence or aborted RP due to LNI. **Results** Disease progression was seen in 220/1978 men in the nomogram development group, and the 10 year progression free survival rate was 77%. The nomogram had concordance indices of 0.76 and 0.79 in internal and external validation groups respectively. **General comments** Update of Kattan (1998) nomogram for predicting recurrence after RP.

(Stephenson *et al.* 2007)
Design: Retrospective case series (prognosis), evidence level: 3 Country: United Kingdom, setting: Tertiary care **Inclusion criteria** Men from 17 hospitals treated with salvage radiotherapy (SRT) for biochemical failure after radical prostatectomy. Biochemical recurrence was defined as PSA 0.2 ng/ml or more and rising, or a single value of 0.5 ng/ml or higher. **Exclusion criteria** Adjuvant hormonal therapy after SRT (before or during SRT was acceptable). **Population** number of patients = 1540. **Interventions** Salvage radiotherapy (not specified in detail). A nomogram to predict disease progression was developed using the following pre-SRT variables: prostatectomy PSA, Gleason score, SVI, surgical margins, LNI, persistently elevated postoperative PSA, pre-SRT

PSA, PSA-DT, neoadjuvant ADT, and radiation dose.

Outcomes Disease progression after SRT, defined as serum PSA of 0.2 ng/ml or more above the post SRT nadir followed by another higher value, continued rise in PSA, initiation of systemic therapy or clinical recurrence.

Follow up Median follow-up 7.5 years

Results 866/1540 (56%) of the men experienced disease progression after SRT.

Six year progression free probability was 32% (95% CI 28% to 35%). The nomogram for the prediction of six year progression free probability was validated internally using bootstrap re-sampling. The concordance index (similar to the area under the ROC curve - but for censored outcomes) was 0.69.

The authors also tested the concordance index of other published nomograms for outcome after SRT in this cohort. Indices were 0.56 for Pound et al (1999) and 0.59 for Freedland et al (2005).

General comments -

(Suzuki *et al.* 2006)

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

Country: Japan, setting: Secondary care

Inclusion criteria Men biopsied for suspected prostate cancer at either of two hospitals between 2000 and 2003.

Exclusion criteria Less than 6 biopsy cores, missing data.

Population number of patients = 834, mean age = 70 years.

Interventions TRUS guided systematic prostate biopsy (at least six peripheral and two transition zone cores). A nomogram was developed using the following pre-biopsy variables: age, total PSA, free/total PSA ratio, prostate volume on TRUS and DRE (positive or negative). 80% of patients were chosen at random as the nomogram development cohort and the remainder were the validation set.

Outcomes Biopsy positive for prostate cancer.

Follow up Not applicable

Results 241/834 men (29%) had biopsy positive for prostate cancer. In the validation set, the nomogram gave an area under the curve value of 0.818.

General comments -

(Walz *et al.* 2007)
Design: Retrospective case series (prognosis), evidence level: 3 Country: International, setting: Tertiary care **Inclusion criteria** Men treated for prostate cancer with radical prostatectomy, who did not receive any further therapy for prostate cancer. **Exclusion criteria** - **Population** number of patients = 9983, mean age = 67 years. **Interventions** Radical prostatectomy (n=6179) or EBRT (n=3804). The cohort was split into two equally sized groups: one for nomogram development and one for validation. A nomogram for 10 year life expectancy was developed using Cox Regression of age-at-therapy (years) and Charlston Comorbidity Index. **Outcomes** 10 year life expectancy. Nomogram accuracy **Follow up** Median follow-up was 5.9 years (range 0.1 to 15.5 years) **Results** Median actuarial survival was 13.8 years (RP not reached, EBRT 4.7 years). Nomogram accuracy for the prediction of 10 year life expectancy was reported as 86.6% in the external validation cohort. The negative predictive value was 91.1%, using a nomogram probability cut-off of 50%. **General comments** It was unlikely that prostate cancer was a competing cause of mortality in this group (since none had any secondary therapy). The authors suggest nomogram would be useful for selecting patients with sufficient life expectancy to benefit from radical therapy.

(Wang *et al.* 2007)
Design: Retrospective case series (diagnosis, screening), evidence level: 3 Country: United States, setting: Tertiary care **Inclusion criteria** Men with prostate cancer referred for MRI before radical retropubic prostatectomy and pelvic lymphadenectomy at a single institution between 2000 and 2003 **Exclusion criteria** Lack of biopsy cores at the base of the prostate, neoadjuvant therapy. **Population** number of patients = 573. **Interventions** All men had MRI before radical retropubic prostatectomy, pelvic lymphadenectomy and pathological staging. MR imaging was performed using a whole body 1.5T using the body coil for excitation and a pelvic phased array coil in combination with an endorectal bal-

loon.

A nomogram for the prediction of pathologic stage was developed using the following preoperative variables: PSA level, Gleason grade at biopsy, clinical stage, MRI findings and percentage of positive biopsy cores.

Outcomes Pathological stage (in particular seminal vesicle invasion - SVI), MRI stage.

Results At surgical histopathologic analysis 28/573 (28%) of men had evidence of SVI. The Kattan nomogram plus endorectal MR imaging (0.87) had a significantly larger (P<.05) AUC than either endorectal MR imaging alone (0.76) or the Kattan nomogram alone (0.80).

General comments Modification of the Kattan 2003 nomogram (Koh et al 2003) to include MRI stage.

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 Localised Prostate Cancer

3.1 Predictive factors and risk groups

In men with clinically localised prostate cancer what are the pretreatment risk factors for prostate cancer mortality, lymph node involvement and treatment failure?

Short Summary

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

PICO question

POPULATION	Prognostic Factors	Outcomes
Men with histological diagnosis of prostate cancer and apparently localised disease	• PSA level • Histological features	The independent prognostic importance of each factor for: • disease specific mortality • lymph node involvement • treatment failure

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

Pretreatment prognostic factors for prostate cancer mortality in men with clinically localised prostate cancer

Evidence

The evidence came from observational studies, usually institutional case series. Albertsen and co-workers (2005) and Johansson and co-workers (2004) reported prostate cancer mortality (PCM) in population based cohorts of men with clinically localised prostate cancer. Aus and co-workers (2005) included men non-metastatic disease.

Papers published before 2000 were excluded, due to the large volume of published case series and the issue of stage migration. However, due to the extended follow-up needed to report survival outcomes, in some of the series the men were diagnosed as far back as the 1970s or 1980s. This limits the applicability to current populations.

Reporting of the prognostic models was often poor; some studies did not report individual hazard ratios or event rates associated with prognostic variables. Other studies used cut-points to group continuous variables (pretreatment PSA or age) into categories.

Biopsy Gleason score (see Table 45 and Table 46, and Figure 9 and Figure 10)

Biopsy Gleason score (or biopsy tumour grade) was included in all of the prognostic models. Increased biopsy Gleason score (or tumour grade) was associated with greater risk of prostate cancer mortality in radical prostatectomy case series, radiotherapy case series and in men treated with watchful waiting

Clinical tumour stage (see Table 47 and Table 48, and Figure 11)

Clinical tumour stage (or DRE findings) was included in most of the prognostic models. Clinical tumour stage was not consistently significant predictor of prostate cancer mortality (PCM) in studies restricted to men with clinical T1–T2 disease. In the majority of these studies, however, the risk of PCM was higher in men with T2 disease than with those with T1 disease. Clinical stage T3 disease was an adverse prognostic factor for PCM in two of three studies.

Age at diagnosis (see Table 49 and Table 50)

The majority of studies did not find age at diagnosis to be a statistically significant independent predictor of PCM. Albertsen and co-workers (Albertsen *et al.* 2005), however, incorporated age into their prognostic model for prostate cancer death.

Pretreatment PSA level (see Table 51 and Table 52, and Figure 12)

Higher pretreatment PSA level was consistently associated with significantly greater risk of PCM.

Comorbidity (see Table 53 and Table 54, and Figure 13)

Only one of the seven relevant studies reported an association between Charlson comorbidity score and risk of PCM.

Other predictors of prostate cancer mortality:

Other variables were considered in one or two studies only, but were reported to be significant independent predictors of prostate cancer mortality: pretreatment PSA velocity (D'Amico *et al.* 2004; D'Amico *et al.* 2005), income (Tewari *et al.* 2006), year of diagnosis (Tewari *et al.* 2006), radical treatment vs. watchful waiting (Tewari *et al.* 2006; Aus *et al.* 2005), years of follow-up (Johansson *et al.* 2004), clinical lymph node classification (Aus *et al.* 2005), ploidy (Adolfsson *et al.* 2007), marital status(Graff *et al.* 2007) and education(Graff *et al.* 2007).

Table 43. Study Characteristics

Study	Country	No. of patients	Year of PCa diagnosis	Follow-up	PCa mortality rate (%)	Inclusion criteria	Exclusion criteria
(Albertsen *et al.* 2005)	USA	767	1971–1984	Median 24 years	222 (29%)	Men with clinically localised PCa from a population based registry. Symptomatic progression was treated with AD.	RP, RT or metastatic disease. Concomitant cancer. Survival <6 months after diagnosis.
(Roach *et al.* 2007)}	USA	912	Treated 1987–1998	Median 5.75 for survivors	5 year estimate: AJCC II 4%, AJCC III 17%.	Men with clinically localised PCa treated with EBRT at either of two institutions	Missing data, clinical stage T1, AAD, NAD or metastases
(Johansson *et al.* 2004)	Sweden	223	1977–1984	21 years for all survivors	35 (16%)	Men with clinically localised PCa from a population based registry. Symptomatic progression was treated with AD.	Age >75 years
(D'Amico *et al.* 2004)	USA	1095	Treated 1989–2002	Median 5.1 years	84 (8%)	Men enrolled in a screening study, treated with RP for clinically localised PCa at a single institution	AAD
(D'Amico *et al.* 2005)	USA	358	Treated 1989–2002	Median 4.0 years	30 (8%)	Men treated with EBRT for clinically localised PCa at a single institution	NAD or AAD
(Adolfsson *et al.* 2007)	Sweden	119	1978–1982	Median 24 years	42 (38%)	Men with clinically localised PCa, managed with WW. Eventually 40% had AD, 13% RT and 3% RP.	
(Barry *et al.* 2001)	USA	2311	1971–1984	10 year survival reported		Men with clinically localised PCa included in the Connecticut tumour registry 1971 to 1984	Missing data
(Aus *et al.* 2005)	Sweden	2098	1987–1999	Median 6.7 years for	10 year mortality approx. 20%	Men younger than 75 with non-metastatic PCa at diagnosis.	

Study	Country	No. of patients	Year of PCa diagnosis	Follow-up	PCa mortality rate (%)	Inclusion criteria	Exclusion criteria
				survivors		Treatment was WW (36%), RP (26%), RT (14%) and AD (18%)	
(de Vries *et al.* 2007)	Netherlands	1014	1993–2000	Median 4.6 years	20 (2%)	Men diagnosed with PCa during the first round of a PCa screening study. Treatment was RP (39%), RT (48%), WW (10%) and AD (2%).	Cases where biopsy was refused or contra-indicated
(Tewari *et al.* 2006)	USA	3159	1980–1997	Mean 6 years	385 (11%)	Men with clinically localised PCa treated with WW (42%), EBRT (28%) or RP (30%) in one health organisation	Missing data, age > 75, and race not black or white.
(Graff *et al.* 2007)	USA	276	1994–1995	Median 7.6 years for survivors	5 year esti-mate: 9%	Men with clinically localised PCa (diagnosed 1994-95) treated with primary AD, entered in the SEER database.	

AD, androgen deprivation; AAD, adjuvant androgen deprivation; BT, brachytherapy; EBRT, external beam radiotherapy; NAD, neoadjuvant androgen deprivation; 3D-CRT, three dimensional conformal radiotherapy;, lymph node; LN+, lymph node positive for cancer; RP, radical prostatectomy; RT, radiotherapy; PCa, prostate cancer; WW, watchful waiting.

Table 44. Variables included in the prognostic models for prostate cancer mortality. The models were derived from Cox regression except in Johansson (2004) Albertsen (2005) which used Poisson regression.

Study	Number of variables included	Biopsy Gleason score or tumour grade	Clinical T stage	Age at diagnosis	PSA	Pretreatment PSA velocity	Race	Hormonal therapy	Comorbidity score	Radical treatment type	Clinical lymph node stage	D'Amico (1998) risk group	Marital status	Insurance	Income	Education	Employment	Year of diagnosis	Year of follow-up	Ploidy
Albertsen *et al.* (2005)	3	•		•															•	
Roach *et al.* (2007)	3	•	•		•															
Johansson *et al.* (2004)	4	•	•	•															•	
D'Amico *et al.* (2004)	4	•	•		•	•														
D'Amico *et al.* (2005)	4	•	•		•	•														
Adolfsson *et al.* (2007)	4	•		•					•											•
Barry *et al.* (2001)	5	•	•	•				•	•											
Aus *et al.* (2005)	5	•	•		•					•	•									
de Vries *et al.* (2007)	5	•	•	•	•							•								
Tewari *et al.* (2006)	7	•		•			•		•	•					•			•		
Graff *et al.* (2007)	12	•	•	•	•		•		•				•	••	•	•	•			

Table 45. Adjusted hazard ratios for prostate cancer mortality in men grouped by biopsy Gleason score or biopsy tumour grade

Study	Gleason score grouping or tumour grade	Adjusted HR (95% CI) of prostate cancer mortality	Comments
(Albertsen *et al.* 2005) WW	2–4, 5, 6, 7 and 8–10	Not reported	The authors used Gleason score in estimates of prostate cancer mortality.
(Roach *et al.* 2007) RT	2–6, 7 and 8–10	Not reported	Gleason score was an independent predictor of mortality in men with AJCC stage II or III disease.
(Johansson *et al.* 2004) WW	Tumour grade 1,2 or 3	2 vs. 1, RR=3.4 (1.6–7.3) 3 vs. 1, RR=46.6 (12.3–177.4)	
(D'Amico *et al.* 2004) RP	≤6, 7 and 8–10	7 vs. ≤6 HR=2.1 (0.7–5.8) 8–10 vs. ≤6 HR=3.4 (1.2–9.8)	
(D'Amico *et al.* 2005) EBRT	≤6, 7 and 8–10	7 vs. ≤6 HR=3.1 (1.2–8.4) 8–10 vs. ≤6 HR=10.8 (3.3–35.0)	
(Adolfsson *et al.* 2007) WW	Tumour grade 1 or 2–3	2–3 vs. 1, HR=0.94 (0.42–2.10)	
(Barry *et al.* 2001) WW	Categorical variable, 2–10	RR=1.6 (1.5–1.8) per unit increase	Subgroup of 880 men managed with watchful waiting
(Barry *et al.* 2001) RT	Categorical variable, 2–10	RR=1.5 (1.3–1.7) per unit increase	Subgroup of 368 men managed with radiotherapy
(Barry *et al.* 2001) RP	Categorical variable, 2–10	RR=1.7 (1.5–1.9) per unit increase	Subgroup of 1063 men managed with prostatectomy
(Aus *et al.* 2005) RP, RT or WW	Tumour grade 1,2 or 3	2 vs. 1, HR=2.47 (1.73–3.53) 3 vs. 1, HR=4.9 (3.33–7.22)	
(de Vries *et al.* 2007) RP, RT, AD or WW	≤3+3 and ≥ 4+4	≥ 4+4 vs. ≤3+3, HR=7.0 (1.3–37.7)	HRs between other Gleason groups were not statistically significant and not reported
(Tewari *et al.* 2006) RP, RT or WW	Tumour grade 1,2 or 3	2 vs. 1, HR=1.86 (1.65–2.1) 3 vs. 1, HR=3.46 (2.72–4.41)	
(Graff *et al.* 2007) AD	<7 or ≥7	≥7 vs. <7, HR=5.06 (1.36–18.8)	

Abbreviations: AD, treatment with primary androgen deprivation; WW, watchful waiting; RT, radiotherapy; RP, radical prostatectomy; HR, hazard ratio; RR, relative risk.

Figure 9. Adjusted hazard ratios (and 95% confidence intervals) for prostate cancer mortality in men with biopsy Gleason 7 versus Gleason 6 tumours. The hazard ratio from Graff et al (2007) is Gleason ≥7 versus ≤6. In D'Amico (2004, 2005) the hazard ratio is Gleason 7 versus ≤6.

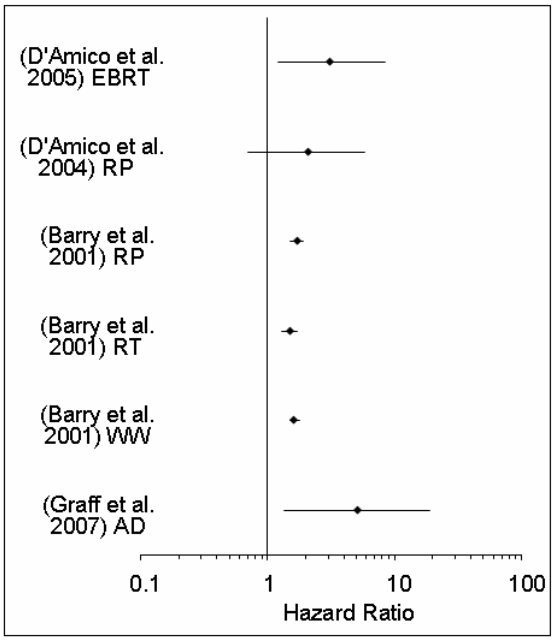
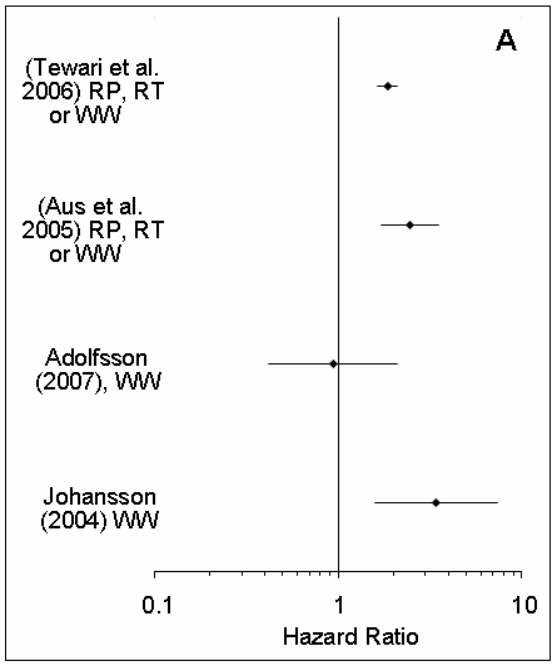


Figure 10. Adjusted hazard ratios (and 95% confidence intervals) for prostate cancer mortality in men with biopsy grade 2 versus grade 1 tumours (Figure 10A) and in men with biopsy grade 3 versus grade 1 tumours (Figure 10B).



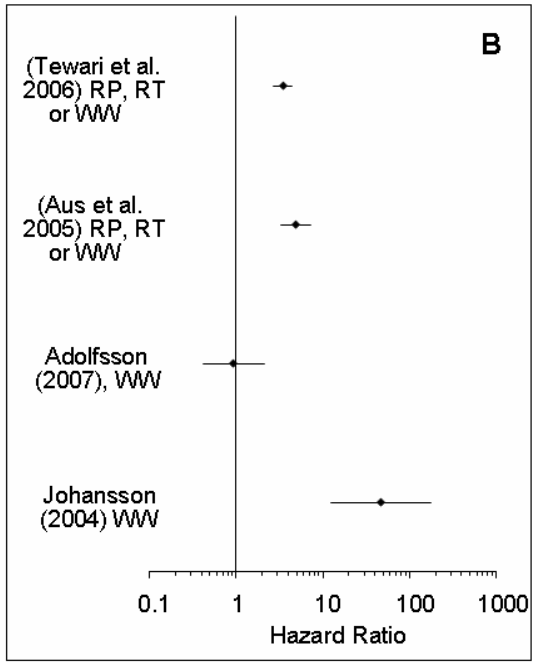


Table 46. Rate of prostate cancer mortality by biopsy Gleason score and tumour grade

	Biopsy Gleason score				
Study	**2–4**	**5**	**6**	**7**	**8–10**
(Albertsen *et al.* 2005)	10/138 (7%)	16/118 (14%)	81/294 (28%)	62/137 (45%)	53/80 (66%)
(D'Amico *et al.* 2004)	14/916 (2%)			6/133 (5%)	7/46 (15%)
(D'Amico *et al.* 2005)	8/192 (4%)			13/137 (9%)	9/29 (31%)
	Tumour grade				
	1	**2**		**3**	
(Johansson *et al.* 2004) WW	14/148 (9%)	16/66 (24%)		5/9 (56%)	
(Aus *et al.* 2005)	37/463 (8%)	208/1285 (16%)		107/339 (32%)	
(Tewari *et al.* 2006) WW	92/601 (15%)	88/562 (16%)		85/205 (42%)	
(Tewari *et al.* 2006) RT	23/237 (10%)	28/554 (5%)		23/141 (16%)	
(Tewari *et al.* 2006) RP	4/157 (3%)	13/643 (2%)		16/124 (13%)	

Table 47. Adjusted hazard ratios for prostate cancer mortality in men grouped by clinical tumour stage.

Study	T stage grouping	Adjusted HR (95% CI) of prostate cancer mortality	Comments
(Roach *et al.* 2007) RT	T1, T2 and T3	Not reported. Survival was significantly better with T1–T2 than with T3.	
(Johansson *et al.* 2004) WW	T1–T2, T0d, T01	T0d vs. T01, RR=0.7 (0.2–2.1) T1–T2 vs. T01, RR=0.7 (0.3–1.6)	
(D'Amico *et al.* 2004) RP	T1c,T2	T2 vs. T1c HR=7.4 (2.4–22.4)	
(D'Amico *et al.* 2005) EBRT	T1c,T2	T2 vs. T1c HR=1.2 (0.5–3.2)	
(Barry *et al.* 2001) WW	DRE: normal, suspicious-confined, suspicious-throughout capsule or suspicious-unknown.	DRE suspicious vs. normal: confined RR=1.3 (0.9–2.0); throughout capsule RR=1.9 (1.1–3.3); unknown, RR=1.4 (1.0–1.9)	Subgroup of 880 men managed with watchful waiting
(Barry *et al.* 2001) RT	DRE: normal, suspicious-confined, suspicious-throughout capsule	DRE suspicious vs. normal: confined, RR=1.1 (0.5–2.3) throughout capsule, RR=1.9 (0.9–3.8)	Subgroup of 368 men managed with radiotherapy
(Barry *et al.* 2001) RP	DRE: normal, suspicious-confined, suspicious-throughout capsule	DRE suspicious vs. normal: confined, RR=0.7 (0.4–1.1) throughout capsule, RR=0.7 (0.4–1.3)	Subgroup of 1063 men managed with prostatectomy
(Aus *et al.* 2005) RP, RT or WW	T1, T2, T3	T2 vs. T1, HR=1.51 (1.09–2.09) T3 vs. T1, HR=2.77 (1.99–3.85)	
(de Vries *et al.* 2007) RP, RT, AD or WW	T4, T3, T2, T1c	HR not statistically significant, figures not reported	
(Graff *et al.* 2007) AD	DRE normal or abnormal	DRE abnormal vs. normal, HR=1.67 (0.54–5.17)	

Figure 11. Adjusted hazard ratios (and 95% confidence intervals) for prostate cancer mortality in men with clinical T2 versus T1 (or suspicious/abnormal DRE versus normal DRE).

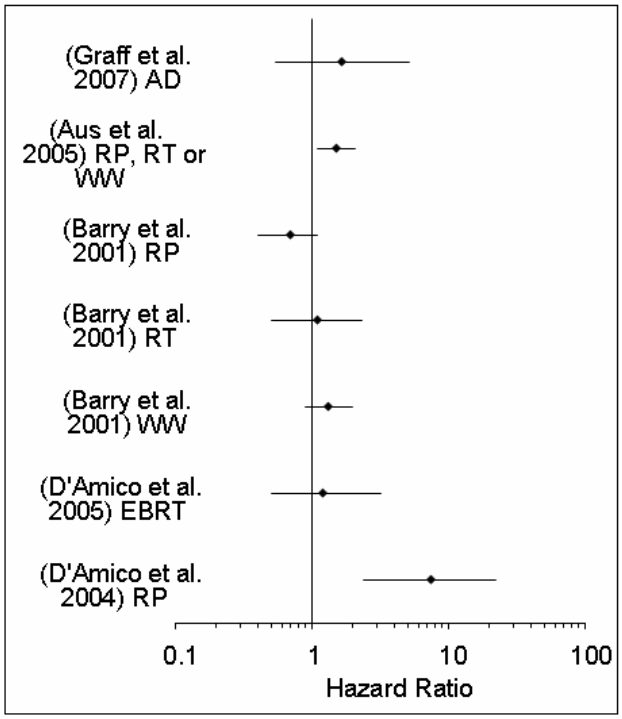


Table 48. Rate of prostate cancer mortality by clinical tumour stage

Study	T0	T1	T1b	T1c	T2a	T2b	T2c	T3
(Johansson *et al.* 2004)	18/106 (17%)	17/117 (15%)						–
(D'Amico *et al.* 2004)				4/779 (1%)	23/316 (7%)			
(D'Amico *et al.* 2005)				6 /157 (4%)	24/201 (12%)			
(Adolfsson *et al.* 2007)								
(Aus *et al.* 2005)		49/516 (9%)			154/1131 (14%)			149/440 (34%)

Table 49. Adjusted hazard ratios for prostate cancer mortality in men grouped by age at diagnosis.

Study	Age groups	Adjusted HR (95% CI) of prostate cancer mortality	Comments
(Albertsen *et al.* 2005) WW	55–59, 60–64, 65–69, 70–74 yrs	not reported	The authors used age in their prognostic model of prostate cancer mortality.
(Johansson *et al.* 2004) WW	<70 and ≥70 yrs	≥70 vs. <70, RR = 0.7 (0.3–1.6)	
(Adolfsson *et al.* 2007) WW	<70 and ≥70 yrs	≥70 vs. <70, HR = 1.15 (0.51–2.62)	
(Barry *et al.* 2001) WW	Continuous variable	RR=1.2 (0.9–1.7) per 10 year increase	Subgroup of 880 men managed with watchful waiting
(Barry *et al.* 2001) RT	Continuous variable	RR=0.9 (0.6–1.2) per 10 year increase	Subgroup of 368 men managed with radiotherapy
(Barry *et al.* 2001) RP	Continuous variable	RR=0.9 (0.7–1.3) per 10 year increase	Subgroup of 1063 men managed with prostatectomy
(de Vries *et al.* 2007) RP, RT, AD or WW	Continuous variable	HR not statistically significant, figures not reported	
(Tewari *et al.* 2006) RP, RT or WW	Continuous variable	HR=1.03 (1.01–1.05) per year increase	
(Graff *et al.* 2007) AD	<74 and ≥75 yrs	≥75 vs. <74 yrs, HR = 1.69 (0.78–3.7)	

Table 50. Rate of prostate cancer mortality by age at diagnosis

Study	≤54	55–59	60–64	65–69	70–74	75–79	≥80
(Albertsen *et al.* 2005)		11/54 (20%)	48/141 (34%)	65/242 (27%)	98/330 (30%)		
(Johansson *et al.* 2004)	3/13 (23%)		19/86 (22%)		12/96 (12%)		1/28 (4%)

Table 51. Adjusted hazard ratios for prostate cancer mortality in men grouped by pre-treatment PSA

Study	PSA grouping	Adjusted HR (95% CI) of prostate cancer mortality	Comments
(Roach *et al.* 2007) RT	0–10, 10–20, ≥20 ng/ml	Not reported.	PSA >20 ng/ml was a significant independent predictor of prostate cancer mortality
(D'Amico *et al.* 2004) RP	Continuous variable	Per unit increase HR = 1.06 (1.02–1.10)	
(D'Amico *et al.* 2005) RT	Continuous variable	Per unit increase HR = 1.01 (1.01–1.03)	
(Aus *et al.* 2005) RP, RT or WW	0–10, 10–0,20–50 ng/ml or PSA missing	10–20 vs. 0–10 ng/ml, HR = 1.16 (0.67–2.01) 20–50 vs. 0–10 ng/ml, HR = 1.39 (0.83–2.33) PSA missing vs. 0–10 ng/ml, HR=1.9 (1.27–2.85)	
(de Vries *et al.* 2007) RP, RT, AD or WW	0–4, 4–10 and >10 ng/ml	HR not statistically significant, figures not reported	
(Graff *et al.* 2007) AD	<20 and ≥20 ng/ml	≥20 vs. <20 ng/ml, HR = 3.12 (1.27–7.65)	

Figure 12. Adjusted hazard ratios (and 95% confidence intervals) for prostate cancer mortality in men with pretreatment PSA level of 20 ng/ml versus 10 ng/ml. The studies by D'Amico et al treated PSA as a continuous variable, whereas Aus et al and Graff et al categorised men into three and two PSA groups respectively.

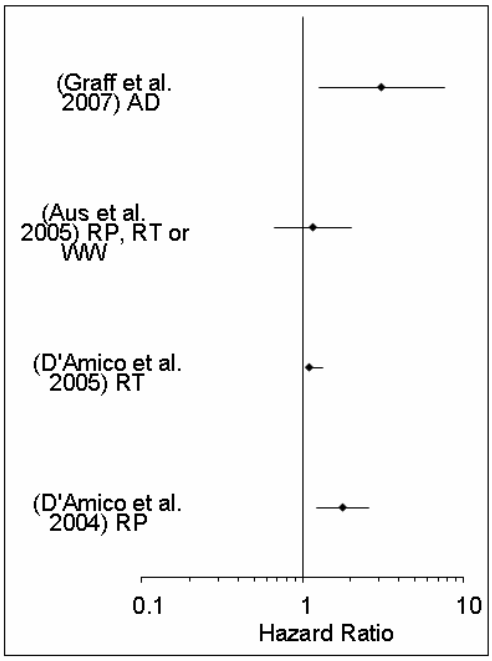


Table 52. Rate of prostate cancer mortality by pretreatment PSA

Study	<10	≥10 – <20	≥20 – <50
(Aus *et al.* 2005)	27/417 (6%)	25/316 (8%)	33/265 (12%)

Table 53. Adjusted hazard ratios for prostate cancer mortality in men grouped by Charlson comorbidity score

Study	Comorbidity grouping	Adjusted HR (95% CI) of prostate cancer mortality	Comments
(Adolfsson *et al.* 2007) WW	Charlson 0–1 and ≥2	2 vs. 0–1, HR=1.99 (0.82–4.84)	
(Barry *et al.* 2001) WW	Charlson 0, 1 and ≥2	1 vs. 0, RR=0.8 (0.6–1.1) ≥2 vs. 0, RR= 1.1 (0.8–1.6)	Subgroup of 880 men managed with watchful waiting
(Barry *et al.* 2001) RT	Charlson 0, 1 and ≥2	1 vs. 0, RR=1.2 (0.8–1.8) ≥2 vs. 0, RR= 0.7 (0.3–1.5)	Subgroup of 368 men managed with radiotherapy
(Barry *et al.* 2001) RP	Charlson 0, 1 and ≥2	1 vs. 0, RR=1.3 (1.0–1.8) ≥2 vs. 0, RR= 1.2 (0.8–2.0)	Subgroup of 1063 men managed with prostatectomy
(de Vries *et al.* 2007) RP, RT, AD or WW	Charlson 0,1 and ≥2	HR not statistically significant, figures not reported	
(Tewari *et al.* 2006) RP, RT or WW	Charlson 0–1 and ≥2	≥2 vs. 0–1, HR=1.04 (0.90–1.21)	
(Graff *et al.* 2007) AD	Charlson 0–1 and ≥2	≥2 vs. 0–1, HR=0.35 (0.15–0.78)	

Figure 13. Adjusted hazard ratios (and 95% confidence intervals) for prostate cancer mortality in men with pretreatment Charlson score ≥2 versus 0 or 1.

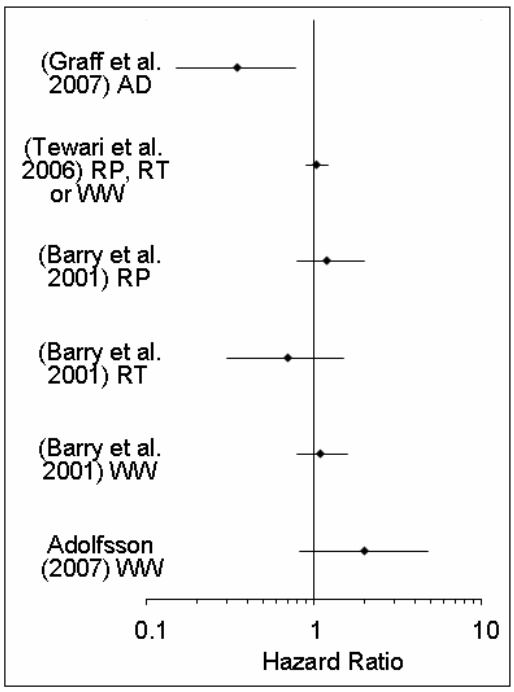


Table 54 Rate of prostate cancer mortality by comorbidity score

Study	0	1	≥2
(Tewari *et al.* 2006)	62/1353 (5%)		323/2018 (16%)

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.

Reference List

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Prognostic factors for lymph node involvement (LNI) in men with clinically localised prostate cancer

Evidence summary

Evidence comes from radical prostatectomy and pelvic lymphadenectomy case series, and so applicability is limited to men who are candidates for prostatectomy. Lymph node involvement was uncommon in these series, occurring at a rate of about 4% (probably due to careful case selection for surgery); this limited the number of prognostic variables that could be tested in any given study. The logistic regression models used in the studies were often poorly reported, and individual odds ratios associated with each prognostic factor were often not available.

Biopsy Gleason score (see Table 57 and Table 58)

Gleason score was a significant independent predictor of lymph node involvement in all studies that reported it. Rates of lymph node involvement in men with biopsy Gleason 8–10 tumours were between 11% and 22% compared with 3% for men with biopsy Gleason 6 tumours (Han *et al.* 2001; Gancarczyk *et al.* 2003).

Clinical tumour stage (see Table 59 and Table 60)

Clinical tumour stage appeared to be associated with risk of lymph node involvement, although the odds ratios between clinical T stage groups were poorly reported. One study reported that the odds of lymph node involvement in men with T2 disease were more than twice those in men with T1c disease (Chun *et al.* 2007). Another study estimated that the odds of LNI increased by a factor of 1.5 for each increase in clinical T stage category (Martorana *et al.* 2000). Gancarczyk and co-workers (Gancarczyk *et al.* 2003), however, did not find clinical T stage an independent predictor of lymph node involvement.

Pretreatment PSA (see Table 61 and Table 62)

Increased pretreatment PSA was consistently associated with a greater risk of lymph node involvement. Studies that treated PSA as a continuous variable estimated that the odds of lymph node involvement increased by a factor of between 3 and 7% with each ng/ml increase in PSA (Chun *et al.* 2007; Martorana *et al.* 2000).

Table 55. Study Characteristics

Study	Country	No. of patients	Year of radical prostatectomy	No. LN+	Inclusion criteria	Exclusion criteria
(Partin *et al.* 2001)	USA	5079	1982–1996	102 (2%)	Men treated with RP and staging lymphadenectomy	Missing pre-operative data. Men with grossly positive LN who did not have RP.
(Han *et al.* 2001)	USA	5744	1985–1988	271 (4.7%)	Men treated with RP and staging lymphadenectomy	
(Chun *et al* 2007)	Europe and USA	5921	1992–2005	293 (4.9%)	Men treated with RP for localised prostate cancer	Any missing data
(Martorana *et al.* 2000)	Italy	250	1995–1997	Not reported	Men treated with RP, clinical stage T3c or less, preop-erative PSA < 50 ng/ml	Any missing data
(Cagiannos *et al.* 2003)	International	5510	1985–2000	206 (3%)	Men treated with RP, preoperative PSA < 50 ng/ml	Neoadjuvant therapy, any missing data
(Gancarczyk *et al.* 2003)	USA	1510	1990–2000	43 (2.8%)	Men treated with RP	Missing pre-operative data

LN, lymph node; LN+, lymph node positive for cancer; RP, radical prostatectomy.

Table 56. Variables included in the prognostic models. Models were derived using logistic regression, except the Han et al (2001) artificial neural network (ANN) model and Partin (2001) which used log-linear regression.

Study	Number of variables included	PSA	Clinical stage	Biopsy Gleason score	Age	Percent positive cores	Race
Partin *et al.* (2001)	3	•	•	•			
Han *et al.* (2001)	4	•	•	•	•		
Han *et al.* (2001) ANN	4	•	•	•	•		
Chun *et al* (2007)	3	•	•	•			
Martorana *et al.* (2000)	3	•	•	•			
Cagiannos *et al.* (2003)	3	•	•	•			
Gancarczyk *et al.* (2003) model 2	3	•		•		•	
Gancarczyk *et al.* (2003) model 1	6	•	•	•	•	•	•

Table 57. Adjusted odds ratios for lymph node involvement in men grouped by biopsy Gleason score or tumour grade

Study	Gleason score grouping	Adjusted OR (95% CI) of LNI	Comments
(Partin *et al.* 2001)		not reported	Gleason score was a significant independent predictor of LNI.
(Han *et al.* 2001)	Continuous variable	not reported	
(Chun *et al* 2007)	7–10 vs. 6 or less	11.11	Subgroup of 1538 men diagnosed in 2004–2005
(Martorana *et al.* 2000)	Continuous variable	1.363 (1.181–1.573)	
(Cagiannos *et al.* 2003)	Continuous variable	not reported separately	Gleason score was a significant independent predictor of LNI.
(Gancarczyk *et al.* 2003) model 1	8–10 vs. 7 vs. 5–6 vs. 2–4	not reported separately	Gleason score was a significant independent predictor of pathological stage

Table 58. Rate of positive lymph node involvement by biopsy Gleason score

	Biopsy Gleason score				
Study	**2–4**	**5**	**6**	**7**	**8–10**
(Han *et al.* 2001)	1/154 (1%)	9/600 (2%)	95/3687 (3%)	113/1060 (11%)	53/243 (22%)
(Gancarczyk *et al.* 2003)	4/330 (1%)	24/820 (3%)		11/287 (4%)	8/76 (11%)

Table 59. Adjusted odds ratios for lymph node involvement in men grouped by clinical tumour stage

Study	Clinical stage groups	Adjusted OR (95% CI) of LNI	Comments
(Partin *et al.* 2001)	T2c, T2b, T2a, T1c	not reported	Clinical stage was an independent predictor of LNI.
(Han *et al.* 2001)	T3a, T2a, T2b, T2c, T1c, T1b, T1a	not reported	
(Chun *et al* 2007)	T2, T1c	2.14	Subgroup of 1538 men diagnosed in 2004–2005
(Martorana *et al.* 2000)	T3c, T3ab, T2abc, T1c, T1ab	1.484 (1.022–2.154)	
(Cagiannos *et al.* 2003)	T3, T2c, T2b, T2a, T1c, T1ab	not reported separately	Clinical stage was included in the final prognostic model and nomogram.
(Gancarczyk *et al.* 2003) model 1	T2, T1c	not reported separately	Clinical T stage was not an independent significant predictor of pathological stage

Table 60. Rate of positive lymph node involvement by clinical T stage

Study	T1a	T1b	T1c	T2a	T2b	T2c	T3a
(Han *et al.* 2001)	1/53 (2%)	5/123 (4%)	55/2639 (2%)	54/1544 (3%)	94/987 (10%)	39/300 (13%)	23/98 (23%)
(Gancarczyk *et al.* 2003)			12/770(2%)	29/684 (4%)			

Table 61. Adjusted odds ratios for lymph node involvement in men grouped by pretreatment PSA level

Study	PSA groups	Adjusted OR (95% CI) of LNI	Comments
(Partin *et al.* 2001)	0–2.5, 2.6–4.0, 4.1–6.0, 6.1–10.0 and >10 ng/ml	not reported	PSA was an independent predictor of LNI.
(Han *et al.* 2001)	Continuous variable	not reported	
(Chun *et al* 2007)	Continuous variable	1.07	Subgroup of 1538 men diagnosed in 2004–2005
(Martorana *et al.* 2000)	Continuous variable	1.029 (1.006–1.053)	
(Cagiannos *et al.* 2003)	Continuous variable, ln(PSA)	not reported	PSA was included in the prognostic model and nomogram.
(Gancarczyk *et al.* 2003) model 1 and 2	≤4, 4–10, 10–20 and >20 ng/ml	not reported separately	PSA was an independent predictor of pathological stage

Table 62. Rate of positive lymph node involvement by pretreatment PSA level

	Pretreatment PSA level (ng/ml)						
Study	**0–4**	**4–10**	**10–20**	**20–30**	**30–40**	**40–50**	**>50**
(Han *et al.* 2001)	15/1221 (1%)	88/3035 (3%)	105/1139 (9%)	33/218 (15%)	13/69 (19%)	6/33 (18%)	11/29 (38%)
(Gancarczyk *et al.* 2003)	5/244 (2%)	20/975 (2%)	9/223 (4%)	9/68 (13%)			

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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Pretreatment factors that predict treatment failure in men with clinically localised prostate cancer

Evidence came from radical prostatectomy or radiotherapy case series published from 2000 onwards. Treatment failure was usually biochemical recurrence, defined depending on radical treatment. Some studies used a composite endpoint of biochemical recurrence, clinical recurrence or initiation of androgen deprivation. Yoon and co-workers (2005) included some men with clinical T4 disease.

Clinical tumour stage (see Table 65 and Table 66, and Figure 14)

Men with clinical T2 tumours were at consistently higher risk of treatment failure than men with T1 tumours, although the difference was of borderline statistical significance. Studies which included men with clinical T3 and T4 tumours reported clinical T stage as a significant independent predictor of treatment failure.

Biopsy Gleason score (see Table 67 and Table 68, and Figure 15)

Greater biopsy Gleason score was consistently associated with an increased risk of treatment failure.

Perineural invasion

Systematic reviews of observational studies have considered other prognostic factors potentially available at biopsy (Harnden *et al.* 2007c; Harnden *et al.* 2007b). In subgroups of patients defined by PSA and Gleason score, perineural invasion in prostate biopsy cores was associated with an increased risk of treatment failure (Harnden *et al.* 2007b). In prostatectomy specimens, the presence of a tertiary grade was associated with an increased risk of biochemical recurrence (Harnden *et al.* 2007c).

Volume of cancer on biopsy

A systematic review of observational studies (Harnden *et al.* 2007a) examined treatment failure in men with a small volume (microfocal) of prostate cancer on biopsy. The estimated risk of biochemical failure after prostatectomy in this group was 8.6% (range 6.1 to 12.1%), and after external beam radiotherapy ranged from 0% to 20%. The maximum reported rate of clinical progression after prostatectomy or radiotherapy was 2%.

Pretreatment PSA (see Table 69 and Table 70, and Figure 16)

Increased pretreatment PSA level was consistently associated with an increased risk of treatment failure. Estimates suggested that risk of treatment failure increased by a factor of 1 to 2% with each ng/ml increase in PSA level.

Age at treatment

Age at treatment was not a prognostic factor for treatment failure in most of the studies that considered it.

Table 63. Study Characteristics

Study	Country	No. of patients	Year of radical therapy	Follow up	Recurrence rate (%)	Inclusion criteria	Exclusion criteria	Definition of treatment failure
(Kattan *et al.* 2001)	USA	920	1992–2000	Median > 2 years	353 (38%)	Men treated with brachytherapy	Clinical stage T1a, T1b or T3. Gleason score 8 or more. PSA > 112 ng/ml.	ASTRO (1997) definition
(Kattan *et al.* 2000)	USA	1042	1988–1998	Median 2.9 years	not reported	Men treated with 3D-CRT at a single institution	Any missing data	ASTRO (1997) definition
(Parker *et al.* 2002)	UK	517	1988–1998	Median 3.7 years	233 (45%)	Men with clinically localised disease treated with NAD and radiotherapy at a single institution		Consecutive rises in PSA >2 ng/ml or the start of AD
(Kattan *et al.* 2003)	USA	1677	1988–2000	Median 3.2 years	At 10 years 470 (28%)	Men treated with 3D-CRT		Visceral or bony metastatic lesions
(Yoon *et al.* 2006)	Canada	181	1992–1996	Median 6.5 years	ASTRO 104 (57%), Houston 82 (45%),	Men without evidence of metastases treated with radical radiotherapy.	Missing data	Clinical or biochemical failure (ASTRO 2003; HOUSTON) or start of AD
(D'Amico *et al.* 2004)	USA	1095	1989–2002	Median 5.1 years	366 (33%)	Men enrolled in a screening study, treated with RP for clinically localised PCa at a single institution	AAD	Biochemical recurrence: consecutive PSA values > 0.2 ng/ml
(D'Amico *et al.* 2005)	USA	358	1989–2002	Median 4.0 years	160 (45%)	Men treated with EBRT for clinically localised PCa at a single institution	NAD or AAD	Biochemical recurrence: ASTRO-1997
(Han *et al.* 2003)	USA	2091	1982–1999	Median 5.9 years	360 (17%)	Men treated with RP for clinically localised PCa at a single institution.	Adjuvant EBRT, NAD, or AAD. Clinical stage T1a/b or T3 disease. Gleason	Biochemical recurrence: PSA ≥ 0.2 ng/ml

Study	Country	No. of patients	Year of radical therapy	Follow up	Recurrence rate (%)	Inclusion criteria	Exclusion criteria	Definition of treatment failure
							score < 5.	
(Poulakis *et al.* 2004)	Germany	210	1995–1999	Median 5 years	73 (35%)	Men treated with RP for clinically localised PCa at a single institution.	NAD, AAD or adjuvant EBRT before disease recurrence	Biochemical recurrence: PSA ≥ 0.1 ng/ml
(Freedland *et al.* 2004)	USA	459	1990–2002	Mean 3.2 years	118 (26%)	Men treated with RP for clinically localised PCa at 5 institutions	NAD or neoadjuvant EBRT	Biochemical recurrence: PSA ≥ 0.2 ng/ml
(Kupelian *et al.* 2004)	USA	2991	1990–1998	Median 4.7 years	At 7 years 28%	Men treated with RP, EBRT or BT for clinically localised PCa at 2 institutions	Less than 1 year follow-up, missing data, AAD or adjuvant EBRT	Biochemical recurrence: For radiotherapy patients ASTRO 1997; for RP patients consecutive PSA > 0.2 ng/ml
(Krygiel *et al.* 2005)	USA	1939	1989–1999	Median 5.1 years	339 (17%)	Men with clinically localised PCa detected in a screening study. 50 years or older, (40 yrs for high risk men). All were treated with RP or radiotherapy.	Missing data, refusal to participate in the study	Biochemical recurrence: RT, ASTRO-1997; RP, PSA > 0.2 ng/ml.
(Roach *et al.* 2007)}	USA	912	1987–1998	Median 5.75 for survivors	5 year estimate: AJCC II 46%, AJCC III 82%.	Men with clinically localised PCa treated with EBRT at either of two institutions	Missing data, clinical stage T1, AAD, NAD or metastases	Biochemical recurrence (ASTRO-1997); clinical recurrence, PCa death or initiation of AD

AD, androgen deprivation; AAD, adjuvant androgen deprivation; BT, brachytherapy; EBRT, external beam radiotherapy; NAD, neoadjuvant androgen deprivation; 3D-CRT, three dimensional conformal radiotherapy;, lymph node; LN+, lymph node positive for cancer; RP, radical prostatectomy; RT, radiotherapy; PCa, prostate cancer.

Table 64. Variables included in the prognostic models. All models were constructed using Cox proportional hazards regression.

Study	Number of variables included	Clinical stage	Biopsy Gleason score	Pre-treatment PSA	Age	External beam radiotherapy	Radiotherapy dose	Adjuvant hormonal therapy	ECE on TRUS	Pretreatment PSA velocity	Pelvic MRI stage	% biopsy tissue with cancer	Type of radical therapy	Year of therapy
(Kattan *et al.* 2001)	4	•	•	•		•								
(Kattan *et al.* 2000)	5	•	•	•			•	•						
(Parker *et al.* 2002)	4	•	•	•	•									
(Kattan *et al.* 2003)	3	•	•	•										
(Yoon *et al.* 2006) ASTRO	4	•		•				•	•					
(Yoon *et al.* 2006) HOUSTON	3		•	•				•	•					
(D'Amico *et al.* 2004)	4	•	•	•						•				
(D'Amico *et al.* 2005)	4	•	•	•						•				
(Han *et al.* 2003)	3	•	•	•										
(Poulakis *et al.* 2004)	4	•	•	•							•			
(Freedland *et al.* 2004)	3		•	•								•		
(Kupelian *et al.* 2004)	6	•	•	•				•					•	•
(Krygiel *et al.* 2005)	6	•	•	•	•								•	•
(Roach *et al.* 2007)	3	•	•	•										

Abbreviations: TRUS, transrectal ultrasound; ECE, extracapsular extension;

Table 65. Adjusted hazard ratios for treatment failure in men grouped by clinical tumour stage

Study	Clinical stage groups	Adjusted HR (95% CI) of disease recurrence	Comments
(Kattan *et al.* 2001) BT	T1c, T2a and T2b	not reported	Clinical T stage was not a significant independent predictor of disease recurrence, but was included in the nomogram.
(Kattan *et al.* 2000) RT	T1c, T2a, T2b, T2c, T3ab and T3c	not reported	Clinical T stage was included in the nomogram for PSA recurrence
(Parker *et al.* 2002) RT	T1–T2 and T3–T4	T3–T4 vs. T1–T2, HR=1.65 (1.19–2.28)	
(Kattan *et al.* 2003) RT	T1c, T2a, T2b, T2c, T3ab and T3c	not reported	Clinical T stage was included in the nomogram for metastasis prediction
(Yoon *et al.* 2006) RT - ASTRO	T1, T2, T3 and T4	HR = 1.63 (1.00–2.66) for unit increase in T stage	Using the ASTRO definition of PSA failure.
(Yoon *et al.* 2006) RT - HOUSTON	T1, T2, T3 and T4	not reported	Using the Houston definition, clinical stage was not a significant independent prognostic factor for PSA failure
(D'Amico *et al.* 2004) RP	T1c and T2	T2 vs. T1c, HR = 1.0 (0.8–1.3)	
(D'Amico *et al.* 2005) RT	T1c and T2	T2 vs. T1c, HR = 1.3 (0.9–1.8)	
(Han *et al.* 2003) RP	T1c, T2a and T2bc	not reported	The study presents tables showing risk of biochemical recurrence by biopsy Gleason score, PSA and clinical T stage.
(Poulakis *et al.* 2004) RP	T1a, T1b, T1c, T2a, T2b, and T3	not reported	Clinical stage was a significant independent predictor of PSA failure
(Freedland *et al.* 2004) RP	T1, T2 and T3	not reported	Clinical stage was not a significant independent predictor of PSA failure
(Kupelian *et al.* 2004) RP & RT	T1a, T1b, T1c, T2a and T2b	RR=1.11 (0.99–1.25) for a unit increase in tumour stage	
(Krygiel *et al.* 2005) RP & RT	T1 and T2	T2 vs. T1, HR=1.20 (0.94–1.53)	
(Roach *et al.* 2007)} RT	RTOG risk groups	HR = 1.62 (1.36–1.93) for a unit increase in	RTOG risk group incorporates both Gleason score and clinical

Study	Clinical stage groups	Adjusted HR (95% CI) of disease recurrence	Comments
	1,2,3 and 4	RTOG risk group	stage

Figure 14. Adjusted hazard ratios (and 95% confidence intervals) for biochemical recurrence in men with clinical stage T2 vs. T1 tumours.

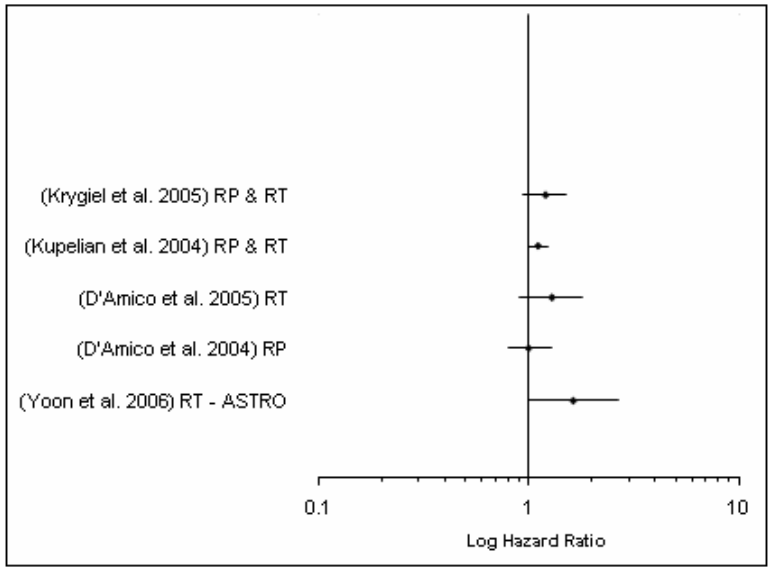

Table 66. Rate of treatment failure by clinical tumour stage

	Clinical tumour stage							
Study	**T1a**	**T1b**	**T1c**	**T2a**	**T2b**	**T2c**	**T3**	**T4**
(Parker *et al.* 2002) RT	18% at 3 years			33% at 3 years			54% at 3 years	45% at 3 years
(D'Amico *et al.* 2004) RP			255/768 (33%)	111/295 (38%)				
(D'Amico *et al.* 2005) RT			61/157 (39%)	99/201 (49%)				
(Poulakis *et al.* 2004) RP	0/2 (0%)	1/4 (25%)	13/34 (38%)	25/84 (30%)	25/71 (35%)		9/15 (60%)	
(Krygiel *et al.* 2005) RP & RT	155/1159 (13%)			184/780 (24%)				

Table 67. Adjusted hazard ratios for treatment failure in men grouped by biopsy Gleason score

Study	Gleason score grouping or tumour grade	Adjusted HR (95% CI) of prostate cancer recurrence	Comments
(Kattan *et al.* 2001) BT	Categorical, 2 to 8	not reported	Biopsy Gleason sum was a significant independent predictor of disease recurrence and used in the nomogram for PSA recurrence
(Kattan *et al.* 2000) RT	Categorical, 2 to 10	not reported	Gleason sum was used in the nomogram for PSA recurrence
(Parker *et al.* 2002) RT	2–4, 5–7 and 8–10	5–7 vs. 2–4, HR=1.87 (1.06–3.17) 8–10 vs. 2–4, HR= 3.89 (1.80–5.65)	
(Kattan *et al.* 2003) RT	Categorical, 2 to 10	not reported	Gleason sum was used in the nomogram for metastasis prediction
(Yoon *et al.* 2006) RT –	Categorical, 5 to 10	not reported	Biopsy Gleason sum was not a significant independent predictor of

Study	Gleason score grouping or tumour grade	Adjusted HR (95% CI) of prostate cancer recurrence	Comments
ASTRO			PSA recurrence using the ASTRO definition
(Yoon *et al.* 2006) RT - HOUSTON	Categorical, 5 to 10	HR=1.88 (1.14–3.12) for a unit increase in Gleason score	
(D'Amico *et al.* 2004) RP	≤6, 7 and 8–10	7 vs. ≤6, HR = 1.4 (1.0–1.9) 8–10 vs. ≤6, HR = 1.9 (1.2–3.0)	
(D'Amico *et al.* 2005) RT	≤6, 7 and 8–10	7 vs. ≤6, HR = 1.2 (0.8–1.7) 8–10 vs. ≤6, HR = 2.9 (1.8–4.6)	
(Han *et al.* 2003) RP	5, 6, 3+4, 4+3 and 8–10	not reported	Biopsy Gleason sum was used in the probability tables for the prediction of PSA failure
(Poulakis *et al.* 2004) RP	2–4, 5, 6, 7 and 8–10	not reported	Biopsy Gleason sum was a significant independent predictor of PSA failure
(Freedland *et al.* 2004) RP	2–6, 3+4 and ≥4+3	≥4+3 vs. 3+4 vs. 2–6, HR= 1.51 (1.17–1.97)	
(Kupelian *et al.* 2004) RP & RT	Continuous variable	RR=1.33 (1.23–1.44) for a unit increase in Gleason score	
(Krygiel *et al.* 2005) RP & RT	2–4, 5–6, 7 and 8–10	5–6 vs. 2–4, HR = 1.97 (1.43–2.71) 7 vs. 2–4, HR = 4.98 (3.22–7.69) 8–10 vs. 2–4, HR = 4.41 (2.77–7.04)	
(Roach *et al.* 2007)} RT	RTOG risk groups 1,2,3 and 4	HR = 1.62 (1.36–1.93) for a unit increase in RTOG risk group	RTOG risk group incorporates both Gleason score and clinical stage

Figure 15. Adjusted hazard ratios (and 95% confidence intervals) for biochemical recurrence in men with biopsy Gleason 7 vs. 6 tumours.

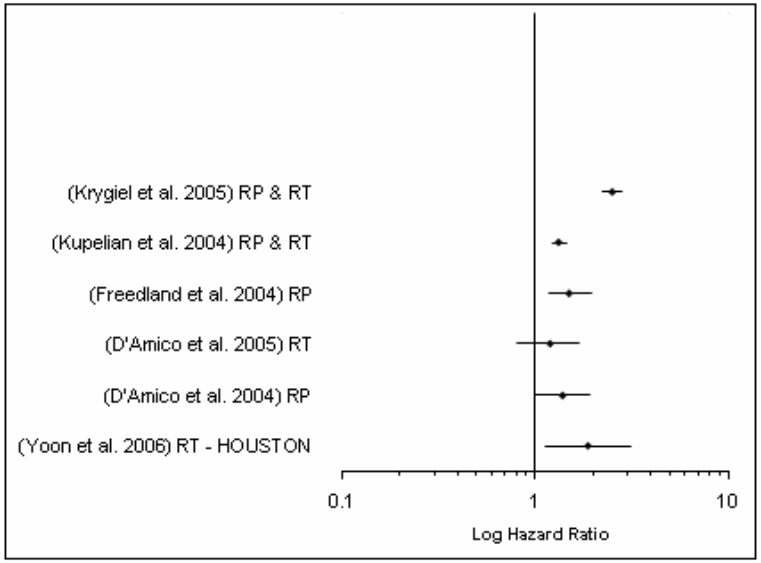

Table 68. Rate of treatment failure by biopsy Gleason score

	Biopsy Gleason Score				
Study	**2–4**	**5**	**6**	**7**	**8–10**
(Parker *et al.* 2002) RT	25% at 3 years	40% at 3 years		77% at 3 years	
(D'Amico *et al.* 2004) RP	292/891 (33%)			49/126 (39%)	25/46 (54%)
(D'Amico *et al.* 2005) RT	80/192 (42%)			57/137 (64%)	23/29 (79%)
(Poulakis *et al.* 2004) RP	1/19 (5%)	9/53 (17%)	28/81 (35%)	17/33 (52%)	18/24 (75%)
(Krygiel *et al.* 2005) RP & RT	70/557 (13%)	164/1097 (15%)		62/162 (38%)	35/89 (39%)

Table 69. Adjusted hazard ratios for treatment failure in men grouped by pre-treatment PSA level

Study	PSA groups	Adjusted HR (95% CI) of prostate cancer recurrence	Comments
(Kattan *et al.* 2001) BT	Continuous variable (ng/ml)	not reported	Pretreatment PSA was a significant independent predictor of disease recurrence, and used in the nomogram
(Kattan *et al.* 2000) RT	Continuous variable (ng/ml)	not reported	Pretreatment PSA was used in the nomogram for prediction of PSA recurrence
(Parker *et al.* 2002) RT	<10, 10–20, 20–50 and >50 ng/ml	10–20 vs.<10 ng/ml, HR=1.25 (0.76–2.05) 20–50 vs.<10 ng/ml, HR=1.88 (1.2–2.94) >50 vs.<10 ng/ml, HR=4.20 (2.64–6.08)	
(Kattan *et al.* 2003) RT	Continuous variable (ng/ml)	not reported	Pretreatment PSA was used in the nomogram for prediction of metastasis
(Yoon *et al.* 2006) RT – ASTRO	Continuous variable (ng/ml)	HR = 1.01 (1.00–1.01) for a unit increase in PSA	
(Yoon *et al.* 2006) RT -	Continuous variable (ng/ml)	HR = 1.01 (1.00–1.02) for a unit increase in PSA	
(D'Amico *et al.* 2004) RP	Continuous variable (ng/ml)	HR = 1.03 (1.00–1.05) for a unit increase in PSA	
(D'Amico *et al.* 2005) RT	Continuous variable (ng/ml)	HR = 1.03 (1.02–1.04) for a unit increase in PSA	
(Han *et al.* 2003) RP	0–4, >4–10, >10–20 and >20 ng/ml	not reported	The study presents tables showing risk of biochemical recurrence by biopsy Gleason score, PSA and clinical T stage.
(Poulakis *et al.* 2004) RP	0–4, >4–10, >10–20 and >20 ng/ml	not reported	PSA was a significant independent predictor of PSA failure
(Freedland *et al.* 2004) RP	<10, 10–20 and >20 ng/ml	>20 vs. 10–20 vs. <10 ng/ml, HR=1.51 (1.71-1.97)	
(Kupelian *et al.*	Continuous variable	RR= 1.01 (1.01–1.01) for each 1 ng/ml in-	

Study	PSA groups	Adjusted HR (95% CI) of prostate cancer recurrence	Comments
2004) RP & RT		crease in PSA	
(Krygiel *et al.* 2005) RP & RT	Continuous variable	HR= 1.02 (1.01–1.02) for each 1 ng/ml in-crease in PSA	
(Roach *et al.* 2007)} RT	<10, 10–20 and >20 ng/ml	10–20 vs. <10 ng/ml, HR = 2.40 (1.63–3.54) >20 vs.10–20 ng/ml, HR = 2.40 (1.63–3.54)	

Figure 16. Adjusted hazard ratios for treatment failure for each 1 ng/ml increase in pretreatment PSA level

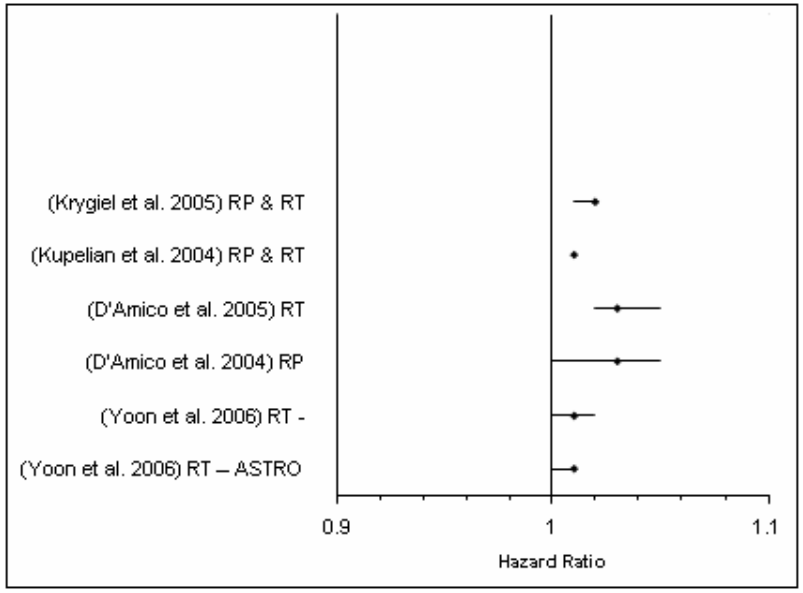

Table 70. Rate of treatment failure by pretreatment PSA level

Study	0–4 ng/ml	>4–10 ng/ml	>10–20 ng/ml	>20–50 ng/ml	>50 ng/ml
(Parker *et al.* 2002) RT	30% at 3 years		30% at 3 years	44% at 3 years	76% at 3 years
(Poulakis *et al.* 2004) RP	1/15 (7%)	20/95 (21%)	30/67 (45%)	22/32 (69%)	
(Krygiel *et al.* 2005) RP & RT	45/565 (8%)	294/1374 (21%)			

Table 71. Adjusted hazard ratios for treatment failure in men grouped age at treatment

Study	Age groups	Adjusted HR (95% CI) of prostate cancer recurrence	Comments
(Parker *et al.* 2002) RT	<69 and ≥69 years	<69 vs. ≥69, HR=1.47 (1.10–1.97)	
(Han *et al.* 2003) RP	Continuous	not reported	Age was not used in the final probability tables
(Poulakis *et al.* 2004) RP	10 year age groups from 41 to 80 years	not reported	Age was not a significant independent predictor of PSA failure
(Freedland *et al.* 2004) RP	Continuous	not reported	Age was not a significant independent predictor of PSA failure
(Krygiel *et al.* 2005) RP & RT	Continuous	HR = 0.97 (0.92–1.03) per additional year	
(Roach *et al.* 2007)} RT	≤ 75 and >75 years	Not reported	Age was not a significant independent predictor of biochemical failure or disease progression.

Table 72 Rate of treatment failure by age at treatment

Study	<50	51–60	61–70	71–80	>80
(Parker *et al.* 2002) RT	49% at 3 years			40% at 3 years	
(Poulakis *et al.* 2004) RP	1/2 (50%)	13/39 (33%)	49/141 (35%)	10/28 (36%)	
(Krygiel *et al.* 2005) RP & RT		241/1420 (15%)		98/519 (18%)	

(Harnden *et al.* 2007c)

Design: Systematic review of cohort studies (prognosis), evidence level: 2+

Inclusion criteria Studies that assessed the prognostic value of a tertiary Gleason pattern in prostate biopsies or radical prostatectomy specimens of men with prostate cancer.

Population men treated with radical prostatectomy for prostate cancer

Interventions All men had radical prostatectomy.

Outcomes Tertiary Gleason components in the radical prostatectomy specimen as a risk factor for biochemical recurrence

Results 7 relevant studies were identified (1598 evaluable patients). Four studies were included in the meta-analysis.

The pooled estimated of the risk ratio of biochemical recurrence for men with tertiary grade present to men with tertiary grade absent was 2.521 (95% C.I. 2.051 to 3.098). Thus, risk of biochemical recurrence was significantly increased in those with tertiary grade present.

General comments Limited applicability as none of the series considered tertiary grade in biopsy cores.

(Harnden *et al.* 2007b)

Design: Systematic review of cohort studies (prognosis), evidence level: 2+

Inclusion criteria Papers published between 1990 and 2005, about the prognostic importance of perineural invasion on prostate biopsies for recurrence in men treated with radical therapy for prostate cancer.

Population men treated with radical therapy for prostate cancer.

Interventions Prostate biopsy (with assessment of perineural invasion). Radical therapy: surgery (10 published case series) or radiotherapy (11 case series). No studies were found in men managed with watchful waiting. Only 2/21 of the studies were prospective.

Outcomes Biochemical or clinical recurrence

Results On univariate analysis, perineural invasion (PI) was a significant prognostic factor for recurrence in 6/10 surgical series and in 5/11 radiotherapy series.

On multivariate analysis, perineural invasion was a significant independent prognostic factor for recurrence in 4 surgical series but not in 2 others. Recurrence free survival was consistently lower in men with perineural invasion in 4 series that reported this outcome.

On multivariate analysis, in one radiotherapy series perineural invasion was an independent prognostic factor in the subgroup of men with PSA <10 ng/ml, similarly in another radiotherapy series PI was an independent prognostic factor in the subgroup of men with PSA <20 ng/ml (but not for the whole group). Recurrence free survival was consistently lower in men with perineural invasion in 13 comparisons from 11 radiotherapy series.

General comments Variation in study design and reporting prevented meta-analysis. Authors concluded that perineural invasion was a prognostic factor for recurrence, especially in subgroups of men defined by PSA and Gleason score.

(Harnden *et al.* 2007a)

Design: Systematic review of cohort studies (diagnosis, screening), evidence level: 2++

Inclusion criteria Papers published between 1990 and 2007, about the pathology and prostate cancer. Specifically papers reporting the correlation between small volume (microfocal) cancer on biopsy and pathological findings and clinical outcomes.

Interventions Prostate biopsy (number of cores was often not reported, usually sextant scheme). Following biopsy treatment was radical prostatectomy, EBRT or watchful waiting.

Outcomes Biochemical recurrence, clinical recurrence, surgical stage (extracapsular extension, lymph node involvement or seminal vesicle involvement) and death from prostate cancer.

Follow up Follow-up was poorly reported in the primary studies. Proportion of patients with missing data was as high as 29%.

Results 29 papers reporting retrospective case series were included. Rates of clinical recurrence or prostate cancer mortality were very low (2% or less), but follow-up in the studies was too limited to allow a reliable estimate of these outcomes.

	RADICAL PROSTATECTOMY	EBRT	ANDROGEN DEPRIVATION	WATCHFUL WAITING
Biochemical recurrence	Estimated risk 8.6% (range 6.1 to 12.1%) from 6 studies	Rate of BCR ranged from 0% to 20% in 3 studies	not applicable	Rising PSA reported in 60% of men, in one study
Clinical progression	Rate of clinical progression ranged from 0% to 2% in 3 trials	Overall rate of metastatic progression ranged was 2% in 3 trials	Rate was 0%, from 1 trial	30% of patients converted to definitive therapy
Extracapsular extension	Estimated risk 17.6% (range 7.9 to 34.8%) from 5 studies	not applicable	not applicable	not applicable
Positive surgical margins	Estimated risk 11.7% (range 8.3 to 16.3%) from 5 studies	not applicable	not applicable	not applicable
Death due to prostate cancer	One reported death, from 3 studies	2 reported deaths, from 3 studies	No reported deaths in one trial	not reported

General comments Adverse effects of treatment not considered.

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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3.2 Initial treatment options

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

Rationale

Many localised prostate cancers are slow-growing and are unlikely to spread during a person's lifetime. In the US in particular, many such men have received immediate treatment, usually with surgery or radiotherapy, which can be associated with significant short- and long-term complications. On the other hand, some localised tumours are lethal. The question is whether we can identify those men with tumours at low risk of progression and offer them a choice. Observational strategies may delay the initiation of curative therapy or avoid it completely and so, given the high prevalence of low-risk prostate cancer, there is a need to clarify the role of active surveillance and other observational strategies as alternatives to immediate treatment.

Currently the most accepted criteria for active surveillance are the presence of low-risk, clinically localised disease; this was defined in GD58 as tumour stage T1c or less, Gleason score of 3+3, a PSA density of <0.15, and low volume disease, defined as having cancer in less than 50% of cores with 10 mm of any cores. Other authorities have used slightly different criteria, including PSA less than 10, and these 'low-risk' characteristics have not always been used consistently. In addition, patient characteristics such as age and overall health status, which reflect life expectancy, may also determine eligibility. The role of tissue-based biomarkers and other pathological features such as peri-neural invasion have not yet been fully explored, nor whether patients with a strong family history are good candidates for active surveillance. There is also evidence that in countries with a low rate of PSA testing where stage migration has not taken place, such as the UK, 30% of tumours that are apparently 'low-risk' have adverse features.

The recent NIH consensus statement agreed that tumour characteristics derived from biopsy were the mainstays of determining eligibility of men with low-risk tumours, but suggested that the minimum number of biopsy cores required and the use of PSA values normalised to prostate volume required clarification, and suggested that alternatives to Gleason scoring which avoided sampling error and reduced misclassification, might be required to best identify candidates. They also suggested that patient characteristics (such as attitudes, preferences with regard to general and disease-specific quality of life, life expectancy, and anxiety about cancer diagnosis) should be measured with standardised instruments and integrated into eligibility decision-making.

PICO question

Population	Prognostic factors	Outcomes
Men with biopsy-confirmed localised prostate cancer (T1 or T2, Gleason ≤ 7, PSA ≤ 20)	• Multiparametric MRI • MRI • PSA velocity • PSA level • PSA density • Free-to-total PSA • Clinical stage • Family history • Ethnicity • Pathological features on biopsy (Gleason score, perineural invasion, volume) • Biomarkers • Age	• Overall survival • Progression-free survival • Rate of conversion from active surveillance to other treatment • Conversion-free survival

How the information will be searched

Sources to be searched	

Can we apply date limits to the search	This topic differs from the one in the original guide-line - no date limit should be used.
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	We will not use study design filters: evidence will most likely come from case series or cohort studies.
List useful search terms.	

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? List subgroups here and planned statistical analyses	We will use the evidence table for cohort studies (NICE guidelines manual appendix J). Some of the studies will include men on active surveillance: these would provide information about rates of conversion to active treatment. Other studies of men on watchful waiting might provide evidence of natural history / prognostic factors of localised prostate cancer. The prognostic study checklist will be used (NICE guidelines manual appendix I).

Methods

Search strategy

The full strategy will be available in the full guideline. The search was not restricted by study design or date.

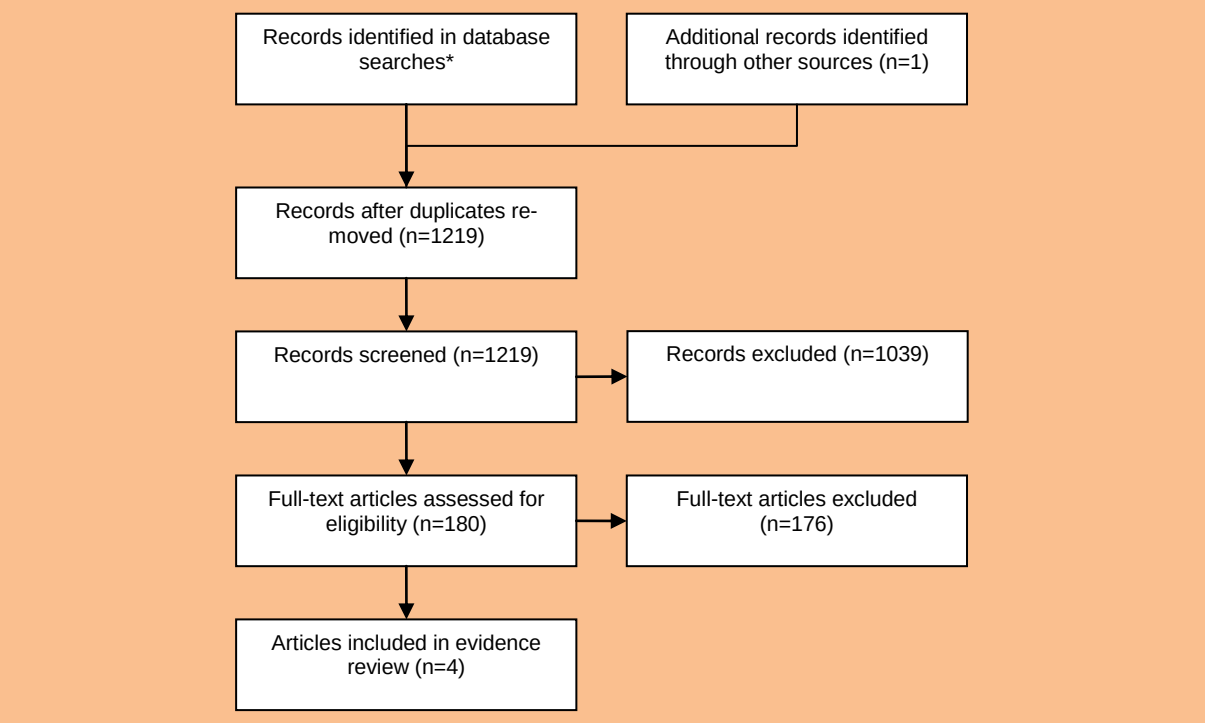
Selection of studies

The information specialist (EH) did the first screen of the literature search results. One reviewer (KC) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO question. The full articles were then obtained for possibly eligible studies and checked against the inclusion criteria. Studies with a median follow-up of less than 5 years were excluded. Only those studies that reported including patients with a Gleason score ≤ 7 were included.

Analysis

The variability in populations studied and multivariate models used precluded the undertaking of any meta-analysis. The results of any univariate or multivariate analyses, together with details of any confounding factors included in the models, were recorded and summarised narratively.

Results



*The database search incorporated both 5 and 6 topics.

The literature searches identified 1219 possibly relevant articles of which 180 were ordered in full text. Four publications referring to three different studies were included.

Quality assessment

The methodological quality of the included studies was assessed in a number of areas: study population, study attrition, prognostic factor and outcome measurement, confounding measurement and account, and analysis (see Table 74). The quality assessment tool designed for the systematic review of biomarkers as prognostic risk factors for localised prostate cancer by the NIHR HTA Programme was used as an aid (HTA 2009).

Included prognostic studies were required to have a median (or mean where median was not available) follow-up of 5 or more years and to only include low risk patients. All three included studies were prospective in nature. Median length of follow-up was 5.4 and 6.8 years for the studies by Selvadurai et al. (2013) and Klotz et al. (2010) respectively. Khatami et al. (2007 and 2009) only reported mean follow-up of patients which was 5.3 years.

Study population

The patients were not considered representative of the population in two of the studies as these assessed biochemical progression-free survival in active surveillance patients who had then undergone radical treatment. It was also unclear whether patients undergoing watchful waiting were included in one of the studies (Khatami 2007). Klotz et al. (2010) and Khatami et al. (2007) reported 1% and 0.4% of their included patients to have T-stage 3 disease respectively. However, all studies reported all included patients to have a Gleason score ≤ 7.

All studies provided information on the active surveillance protocol used. Klotz et al. (2010) undertook PSA investigation every 3 months for the first 2 years, then every 6 months in stable patients. Re-biopsy was undertaken 6-12 months after the initial biopsy, then every 3-4 years until the patient reached 80 years of age. Khatami et al. (2007; 2009) undertook PSA investigation every 6 months for the first 2 years, then annually in stable patients. Re-biopsy was recommended if there were signs of progression. While Selvadurai et al. (2013) undertook DRE and PSA every 3 months in first year,

every 4 months in second year, and every 6 months thereafter. TRUS biopsy was undertaken after 18-24 months, then every 2 years.

Over time the introduction of PSA testing has meant that many lower-stage cancers are now diagnosed, biopsy and surgical techniques have evolved, and the staging TNM classifications have undergone minor changes. Two of the studies began recruitment in 1995 but neither provided information on when recruitment was closed. This coincides with a period of rapid increase in the number of PSA tests undertaken.

Study attrition

It was not clear if any patient loss to follow-up was associated with key characteristics in two of the studies, i.e. whether there were any important differences between those who completed the study and those who did not, and information on missing data was only partly available. The total number of patients lost to follow-up was not reported by Klotz et al. (2010) but for 24 patients (5% of all active surveillance patients) who discontinued active surveillance the reported reason was loss to follow-up. Loss to follow-up was considered unlikely to be associated with key characteristics in the study by Khatami et al. (2007), though the exact number lost to follow-up was also not reported.

Prognostic factor and outcome measurement

A clear definition of the prognostic factors of interest was provided by the studies (where appropriate). Khatami et al. (2009) appeared to treat all variables as continuous in their model (though description of the approach was given), including PSA level at diagnosis. PSA level was treated as categorical Klotz et al. (2010), using a cut-off point of PSA > 10 versus ≤ 10, and PSA velocity was treated as categorical by both Selvadurai et al. (2013), using a cut-off point of > 1.0 versus ≤ 1.0 ng/ml/year.

Two of the studies assessed prognostic factors for the ability to predict biochemical disease recurrence after radical treatment. Klotz et al. (2010) used the internationally agreed definitions of PSA recurrence (PSA > 0.2 ng/mL after prostatectomy or PSA nadir + 2 ng/mL for patients who received radiation). Khatami et al. (2007; 2009) used two consecutive PSA values above 0.2 ng/ml to define biochemical disease recurrence.

Confounding measurement and account

The study by Klotz et al. (2010) only undertook univariate analyses while Khatami et al. (2007; 2009) only reported the results of multivariate analyses. It was not clearly stated by Khatami et al. (2007; 2009) which confounding factors were taken into account in the multivariate model. Therefore where a table of results from the multivariate analyses was presented, it was assumed that this contained all factors in the model (as both significant and non-significant factors were reported). The two analyses by Khatami et al. (2007; 2009) and the study by Selvadurai et al. (2013) adjusted for different potentially confounding variables which make the results less comparable.

Analysis

The multivariate models used were all considered appropriate for the design of the study. However, the number of events per variable used by both Khatami et al. (2007; 2009) and Klotz et al. (2010) was not appropriate, being less than ten in each case. Where the number of predictors is much larger than the number of outcome events there is a risk of overestimating the predictive performance of the model; for each candidate predictor, at least ten events are recommended.

Evidence statements

PSA velocity

Conversion-free survival

One study provided moderate quality evidence on the ability of a PSA velocity to predict treatment-free survival in patients undertaking active surveillance. Selvadurai et al. (2013) found a PSA velocity > 1.0 ng/mL/year was a significant predictor of conversion to active treatment in univariate and multivariate analyses (HR 1.4 95% CI 1.3-1.6 for the latter).

PSA level at diagnosis

Progression-free survival

Two analyses of one study assessed the ability of initial PSA level to predict biochemical progression; only one of which (Khatami 2009) provided very low quality evidence that PSA level was a significant predictor in multivariate analyses (HR 1.86 95% CI 1.19-2.92). This may be due to different confounding factors being taken into account in the first analyses (free-to-total PSA and total cancer length in biopsy).

Conversion-free survival

One study provided very low quality evidence on the ability of PSA level at diagnosis to predict treatment-free survival in patients undertaking active surveillance. Klotz et al. (2010) found that an initial PSA level > 10 ng/mL did not significantly predict conversion to active treatment in univariate analyses.

PSA density

Conversion-free survival

One study provided moderate quality evidence on the ability of a PSA density to predict treatment-free survival in patients undertaking active surveillance. Selvadurai et al. (2013) found a PSA density did not significantly predict conversion to active treatment in univariate or multivariate analyses.

Free-to-total PSA

Progression-free survival

One low quality study assessed the free-to-total PSA (ftPSA) as a prognostic factor for biochemical progression at radical prostatectomy in an active surveillance cohort (Khatami 2007). FtPSA was not found to significantly predict progression in multivariate analyses.

Conversion-free survival

One study provided moderate quality evidence on the ability of ftPSA to predict treatment-free survival in patients undertaking active surveillance. Selvadurai et al. (2013) found ftPSA was a significant predictor of conversion to active treatment in both univariate and multivariate analyses (HR 0.91 95% CI 0.89-0.95 for the latter).

PSA doubling time (PSAdt)

Progression-free survival

Three studies provided very low quality evidence of the ability of PSAdt to predict biochemical progression at radical treatment in an active surveillance cohort. Klotz et al. (2010) undertook univariate analyses and found patients with PSAdt < 3 years to have an 8.5-times greater risk of biochemical progression (compared with patients with PSAdt ≥ 3 years). However, among patients with a PSAdt < 3 years the absolute categorical value (i.e. PSAdt 0-1, 1-2 or 2-3 years) was not predictive of biochemical progression.

Khatami et al. (2007) found PSAdt to be a significant predictor in their multivariate analyses (accounting for initial PSA level, free-to-total PSA, and total cancer length at biopsy). However, Khatami et al. (2009) did not find PSAdt to be significant in a second analysis using a multivariate model which took into account initial PSA level, tumour volume, Gleason score at diagnosis, and percentage of cells with Ki-67 biomarker expression.

Total cancer length at biopsy

Progression-free survival

One low quality study assessed total cancer length at biopsy as a prognostic factor for biochemical progression at radical prostatectomy in an active surveillance cohort (Khatami 2007). Total cancer length was not found to significantly predict progression in multivariate analyses.

Tumour volume

Progression-free survival

One very low quality study assessed tumour volume as a prognostic factor for biochemical progression at radical prostatectomy in an active surveillance cohort (Khatami 2009). Tumour volume was not found to significantly predict progression in multivariate analyses.

Gleason score at diagnosis

Progression-free survival

One study provided very low quality evidence on the ability of Gleason score at diagnosis to predict biochemical disease progression (Khatami 2009) in an active surveillance cohort. Gleason score was not found to be a significant predictor in multivariate analyses.

Conversion-free survival

Two studies provided low quality evidence on the ability of Gleason score at diagnosis to predict treatment-free survival in patients undertaking active surveillance. Both Klotz et al. (2010) and Selvadurai et al. (2013) found Gleason score > 6 to be a significant predictor in univariate analyses, however, the latter did not find it to be significant in multivariate analyses.

Clinical stage at diagnosis

Conversion-free survival

Two studies provided low quality evidence on the ability of clinical stage at diagnosis to predict treatment-free survival in patients undertaking active surveillance. Both Klotz et al. (2010) and Selvadurai et al. (2013) found that an initial T stage of 2a or greater significantly predicted later conversion to active treatment in univariate analyses. However, Selvadurai et al. (2013) did not find it to be a significant predictor in multivariate analyses.

Biomarker Ki-67% expression

Progression-free survival

One very low quality study assessed the percentage of cells expressing biomarker Ki-67 as a prognostic factor for biochemical progression at radical prostatectomy in an active surveillance cohort (Khatami 2009). The multivariate analyses found Ki-67% to be a significant predictor (HR 2.49 95% CI 1.07-5.80) when initial PSA level, PSAdt, tumour volume, and Gleason score were taken into account.

Table 73 Summary of evidence on prognostic factors for an active surveillance cohort

Abbreviations: PSAdt = PSA doubling time; Ki-67% = percentage of tumour cells which are Ki-67 positive at prostatectomy; HR = hazard ratio; ftPSA = free-to-total PSA; PSAv = PSA velocity

Prognostic factor	Categorical analysis group (where applicable)	Univariate analysis			Multivariate analysis			
		HR	95% CI	p-value	HR	95% CI	p-value	Factors accounted for
PSA velocity (ng/ml/year) (median follow-up 5.4 years)								
Conversion-free survival[4]	> 10 vs. ≤ 10	1.5	1.4-1.6	**<0.001**	1.4	1.3-1.6	**<0.001**	T stage; Gleason score; ftPSA; max % cancer in any core; volume; PSA density
PSA level at diagnosis (ng/mL) (median/mean follow-up 5.1-8.1 years)								
Progression-free survival[1,2]	-	-	-	-	1.27	NR	p=0.18	Free:total PSA; total cancer length in biopsy; PSAdt
	-	-	-	-	1.86	1.19-2.92	**p=0.0068**	PSAdt; Ki-67%; tumour volume; Gleason score
Conversion-free survival[3,4]	> 10 vs. ≤ 10	1.53	0.89-2.63	0.1275	-	-	-	-
	-	1.0	1.0-1.1	0.354	-	-	-	-
PSA density (follow-up 5.4 years)								
Conversion-free survival[4]	-	2.1	1.0-4.5	0.044	-	-	0.895	T stage; Gleason score; ftPSA; max % cancer in any core; volume; PSAv
Free-to-total PSA (follow-up 5.3-5.4 years)								
Progression-free survival[1]	-	-	-	-	0.92	NR	0.29	PSA level; total cancer length in biopsy; PSAdt
Conversion-free survival[4]	-	0.90	0.88-0.93	**<0.001**	0.91	0.89-0.95	**<0.001**	T stage; Gleason score; PSA density; max % cancer in any core; volume; PSAv
PSA doubling time (PSAdt) (years) (median/mean follow-up 5.3-6.8 years)								
Progression-free survival[1,2,3]	-	-	-	-	0.38	NR	**p=0.03**	PSA level; free:total PSA; total cancer length at biopsy
	-	-	-	-	0.50	0.24-1.09	p=0.0816	PSA level; Ki-67%; tumour volume; Gleason score
	0-1 vs. 2-3	1.11	0.24-5.18	0.8902	-	-	-	-
	1-2 vs. 2-3	1.91	0.66-5.54	0.2356	-	-	-	-
	2-3 vs. ≥ 3	3.36	1.47-7.72	0.0042	-	-	-	-
	0-2 vs. 2-3	1.66	0.62-4.45	0.3190	-	-	-	-
	< 3 vs. ≥ 3	8.50	4.84-14.93	**<0.0001**	-	-	-	-
Total cancer length at biopsy (mean follow-up 5.3 years)								
Progression-free survival[1]	-	-	-	-	1.15	NR	0.26	PSA level at diagnosis; free:total PSA; PSAdt
Tumour volume (ml) (mean follow-up 5.3 years)								
Progression-free survival[2]	-	-	-	-	1.85	0.69-5.02	0.2221	PSA level; PSAdt; Ki-67%; Gleason score
Gleason score at diagnosis (median/mean follow-up 5.1-8.1 years)								

Progression-free survival[2]	-	-	-	-	1.23	0.29-5.22	0.7717	PSA level; PSAdt; Ki-67%; tumour volume
Conversion-free survival[3,4]	> 6 vs. ≤ 6	1.83	1.09-3.10	**0.0233**	-	-	-	-
	-	2.1	1.3-3.5	**0.004**	-	-	0.139	T stage; PSA density; ftPSA; maxi % cancer in any core; volume; PSAv
Clinical stage at diagnosis (median follow-up 6.8-7.8 years)								
Conversion-free survival[3,4]	T ≥ 2a vs. T < 2a	2.02	1.31-3.13	**0.0016**	-	-	-	-
		1.7	1.1-2.5	**0.01**	-	-	0.201	Gleason score; PSA density; ftPSA; max % cancer in any core; volume; PSAv
Ki-67% expression (mean follow-up 5.3 years)								
Progression-free survival[2]	-	-	-	-	2.49	1.07-5.80	**0.0346**	PSA level; PSAdt; tumour volume; Gleason score

[1]Khatami et al. (2007); [2]Khatami et al. (2009); [3]Klotz et al. (2010); Selvadurai et al. (2013)

Table 74 Quality assessment of included studies using tool developed by NIHR HTA Programme (2009)

Potential bias	Items to be considered for assessment of potential opportunity for bias	Khatami (2007)	Khatami (2009)	Klotz (2010)	Selvadurai (2013)
Study population	Inclusion and exclusion criteria are adequately described (including AS protocol, start/finish date of recruitment)	✓	Partly	✓	✓
	Baseline study sample is adequately described for key characteristics: age, PSA, clinical &/or pathological stage, biopsy &/or Gleason grade	✓	Partly	✓	✓
	Study sample represent population of interest on key characteristics, sufficient to limit potential bias to results (note inherent bias from treatment selection)	✗	✗	✓	✓
Study attrition	Statement as to exclusions due to missing data: baseline variables	✓	NA	Partly	NA
	Statement as to exclusions due to missing data: loss to follow-up	NA	NA	✗	✓
	Statement as to possible effect on the results from missing data	NA	NA	✗	✗
	Loss to follow-up is not associated with key characteristics i.e. there are no important differences between key characteristics and outcomes in participants who completed the study and those who did not, sufficient to limit potential bias	✓	NA	Unsure	Unsure
Prognostic factor measurement	Clear definitions of the prognostic factors measured are provided e.g. extraction method, measurement described	✓	✓	NA	NA
	Material storage is described	NA	✓	NA	NA
	Continuous variables are reported or appropriate (i.e. not data dependent) cut-points are used	✓	✓	Partly	✓
	The prognostic factor(s) of interest is(are) adequately measured in study participants to sufficiently limit potential bias	✓	✓	Partly	✓
Outcome measurement	Is the outcome clearly defined?	Partly	✓	✓	✓
	If the study has an outcome of PSA recurrence have the internationally agreed definitions of PSA recurrence been used: PSA > 0.2 ng/mL after prostatectomy	✓	✓	✓	✓
	If there is a biochemical outcome (PSA), is a consistent definition of failure used?	✓	✓	✓	✓
	The outcome of interest is adequately measured in study participants to sufficiently limit potential bias	✓	✓	Partly	✓
Confounding measurement & account	Does the model include all appropriate confounders (PSA, age, stage and grade)?*	Partly	Partly	Unsure	Partly
Analysis	There is sufficient presentation of data to assess the adequacy of the analysis	Partly	Partly	✓	✓
	The strategy for model building (i.e. inclusion of variables) is appropriate and is based on a conceptual framework or model	Unsure	✗	NA	✓
	The selected model is adequate for the design of the study	✓	✓	Partly	✓
	The number of events or events per variable is reported	✓	✓	✓	✓
	Events per variable appropriate (minimum 10, 20 more robust)**	✗	✗	✗	✓
	The statistical analysis is appropriate for the study design, limiting the potential for the presentation of invalid results	Partly	Partly	Partly	✓
	Overall quality	Moderate	Low	Low	Moderate
	*Marked down for failure to include appropriate confounders	-	-	-	-

**Marked down for failure to reach ≥ 10 events per variable	)			-
Final quality assessment	**Low**	**Very low**	**Very low**	**Moderate**

Table 75 Summary of study characteristics

Abbreviations: AS = active surveillance; PCa = prostate cancer; RCT = randomised controlled trial; PSA = prostate-specific antigen; EBRT = external beam radiotherapy; PSAv = PSA velocity; RP = radical prostatectomy

Study	Study type	Country /ies	Study period	No. of patients on AS	Median follow-up (range)	Inclusion criteria (in AS group)	Follow-up whilst on AS	Criteria for definitive treatment	Definition of biochemical progression after curative treatment
Khatami et al. (2007)	Nested cohort in RCT	Sweden	1995 –	270	5.3 years*	Born 1930-1944, screened positive, primarily managed with surveillance, then received radical RP.	PSA & clinical investigation every 6 months. If no signs of progression after 2 years evaluated annually. Re-biopsy if signs of T-stage and/or PSA progression. Bone scans not recommended if PSA < 20ng/mL and Gleason score < 8.	PSA, stage or grade progression, or patient's desire	Two consecutive PSA values above 0.2 ng/ml
Khatami et al. (2009)				50					
Klotz et al. (2010)	Prospective cohort	Canada	1995 –	450	6.8 years	Favourable risk or > 70 years with PSA ≤ 15 ng/mL or Gleason score < 7 (until January 2000).	PSA investigation every 3 months for first 2 years, then every 6 months in stable patients. Re-biopsy 6-12 months after initial biopsy, then every 3-4 years until 80 years of age.	PSAdt < 3 years, Gleason score ≥ 7 or clinical progression	PSA > 0.2 ng/ml after RP or PSA ≥ nadir +2 ng/ml after radiation
Selvadurai et al. (2013)	Prospective cohort	UK	2002 – 2012	471	5.7 years	Age 50-80 years, PCa T1-T2, PSA < 15 ng/ml, Gleason ≤ 6 (or ≤ 7 if age > 65 years), positive cores ≤ 50%	DRE & PSA every 3 months in first year, every 4 months in second year, every 6 months thereafter. TRUS biopsy after 18-24 months, then every 2 years.	PSAv > 1 ng/ml/year or at biopsy: Gleason ≥ 7 or > 50% positive cores	PSA > 0.2 ng/ml after RP or PSA ≥ nadir + 2 ng/ml (Phoenix criteria) after EBRT

*Mean reported where median not available

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Klotz, L et al. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. Journal of Clinical Oncology 2010; 28(1): 126-131.

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Excluded studies

Length of follow-up < 5 years

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

Rationale

At present this remains an uncertain question. There are various ways of following up men with low risk prostate cancer. These range from so called active monitoring which is where the patient is examined regularly, a digital rectal examination is performed and the PSA is measured to look at PSA velocity, PSA doubling times or indeed PSA density. Other forms of protocol include immediate re-biopsy using 20 or 22 cores, immediate re-biopsy using a template where may be up to 70 cores or more may be taken through to repeat biopsy at a year using standard Transrectal ultrasound scan biopsies and so on and so forth. The previous guideline GD58, recommended use of the follow-up protocol from the PROSTART study (examination and PSA q 3monthly for 2 years, and 6 monthly thereafter, with repeat TRUS-guided biopsies at 1,4,7 and 10 years), although no evidence was given to support this approach.

These approaches are part of a 'curative' strategy, as opposed to 'watchful waiting', which is used for patients whose combination of stage, performance status and overall life expectancy, make them unsuitable for radical treatment but who may, at some stage, need some intervention for disease control.

There is an important question here which is yet to be answered by biologists and clinicians. This is the question of whether repeated biopsy of a cancer through initiation of peptide growth factor signalling cascades could initiate tumour progression of itself. Whilst this may be a theoretical question it is now becoming a potentially important clinical issue as many thousands of men may be subjected to repeat biopsy.

In determining the most effective follow up protocol for active surveillance one needs to decide what the main outcome of active surveillance should be. Clearly the most important outcome is cancer free survival rates. The presence of local progression causing severe symptoms or bony metastasis should also be looked at a failure of this approach. If there are repeated biopsies carried out these will carry significant risks of surveillance related morbidity including infection, haematuria and progressive periprostatic fibrosis leading to erectile impotence and ejaculatory problems. Clearly what is required is further research here where different protocols for active surveillance and randomly compared with one another and outcomes would include surveillance related morbidity and conversion free survival rates. Eventually these trials will produce cancer free survival rates and progression free survival rates. A number of trials are in progress including ones in Scandinavia and in Europe and the UK.

The ProtecT Trial is using a method of active monitoring which does not include repeated biopsies and will provide further data in around 2016/2017.

PICO question

Population	Intervention	Comparison	Outcomes
Men undergoing active surveillance	Follow up protocols	Each other	• Overall survival • Progression-free survival • Biochemical disease-free survival • Surveillance-related morbidity (tumour seeding) • Surveillance-related mortality • Treatment-related morbidity • Treatment-related mortality • Adverse events

			• Health-related quality of life (anxiety, psychosocial issues) • Conversion free survival

How the information will be searched

Sources to be searched	
Can we apply date limits to the search	This is an update of a topic in the 2008 guideline so we can limit the search to studies published since.
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	We will not use study design filters: evidence will most likely come from case series or cohort studies.
List useful search terms.	

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results?	We will use the evidence table for randomised trials or cohort studies (NICE guidelines manual appendix J).
Which quality checklist will we use for appraisal?	The RCT or cohort study checklists will be used (NICE guidelines manual appendix C,D).
List subgroups here and planned statistical analyses	

Evidence Summary

Evidence statements

Relative effectiveness of active surveillance protocols

Our literature searches identified no studies comparing the effectiveness of active surveillance protocols in use against one another.

Active surveillance protocols in use

A systematic review (Dahabreh et al, 2012) summarised the protocols from 16 cohorts of active surveillance in men with low risk or clinically localised (T1 or T2) prostate (see Table 76). Eligibility was typically based on Gleason score (12/16 studies), PSA level (10/16) and number of positive biopsy cores (8/16). Most studies used PSA kinetics, DRE and re-biopsy in the follow up of men on active surveillance.

UK active surveillance protocols

Results of our active surveillance protocol survey of 31 cancer networks in England, Wales and Northern Ireland are summarised in Table 77 and Table 78. We received 24 protocols from 19 networks.

Table 76 Eligibility Criteria and Follow-up Protocols in Studies of Active Surveillance in men with low risk or clinically localised (T1-T2) prostate cancer (Dahabreh et al 2012)

				Eligibility Criteria			Follow up Protocol		
AS Cohort or Centre	**Country**	**Year Enrolment Began**	**Term Used in Original Article**	**Age (years)**	**Gleason score**	**PSA Level, □g/L**	**PSA Level or kinetics**	**DRE**	**Rebiopsy**
Baylor College of Medicine and Memorial Sloan-Kettering Cancer Center	USA	1984	EM, deferred therapy	NR	<7	NR	PSAV>0.75 µg/L/y	Used	Used
McGill University	Canada	1987	WW, AS	NR	NR	NR	Used but not specified	Used	Used
University of Connecticut Health Center	USA	1990	AS	NR	NR	NR	Used but not specified	Used	Used
Four tertiary care academic medical centres	USA	1991	AS	≤75	≤6	≤10	Used but not specified	Used	Used
University of Miami	USA	1991	WW, AS	≤80	≤6	≤15 , ≤10*	PSA increase of 25%-50% per year	Used	Used
University of California, San Francisco	USA	After 1991	AS	NR	≤6	<10	PSAV > 0.75 µg/L/y PSADT < 1 y	Used	Used
Royal Marsden Hospital	UK	1993	AS	NR	<3+ 4	≤20 , ≤15*	PSAV > 1.0 µg/L/y PSADT < 4 y	Used	Not routine
Johns Hopkins University	USA	1994	AS, EM with curative intent	NR	≤6	PSAD ≤ 0.15 µg/L/y	PSA kinetics were not used as triggers for intervention	Used	Used
Toronto – Sunnybrook Regional Cancer Center	Canada	1995	WW, AS	NR	≤6 ≤3 + 4 (if age ≥70 y)	≤10 ≤15 (if age ≥70 y)	PSADT < 2 y Protocol changes in PSADT assessment or calculation in 1999 and after 2002. In 2005 the group developed a general linear mixed model to aid clinical decision making	Used	Used
Memorial Sloan-Kettering Cancer Center	USA	1997	AS	NR	No Gleason score 4 or 5	< 10	>10 µg/L	Used	Used
ProtecT	UK	2000	Active monitoring	NR	NR	NR	Used but not specified	Used	Not routine
Dana-Farber Cancer Institute	USA	2000	AS	NR	≤6 with no pattern 4	NR	Used but not specified	Used	Used
Kagawa Medical University	Japan	2002	AS	50-80	≤6	≤20	PSADT < 2y	NR	Used
Cleveland Clinic	USA	2004	Surveillance	NR	No Gleason score 4 or 5	≤10	Used but not specified	NR	Used
PRIAS	Multinational	2006	AS	NR	≤3 + 3	≤10	PSADT 0 - 3y	Used	Used

AS Cohort or Centre	Country	Year Enrolment Began	Term Used in Original Article	Eligibility Criteria			Follow up Protocol		
				Age (years)	Gleason score	PSA Level, □g/L	PSA Level or kinetics	DRE	Rebiopsy
						PSAD ≤ 0.2 µg/L/y			
PASS	USA	2008	AS	NR	NR	NR	PSADT < 3y	Used	Used

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

Table 77 Eligibility Criteria in Active Surveillance Protocols from UK Cancer Networks

Cancer Network	T Stage	Gleason	PSA (ng/mL)	Other	Notes
Anglia	T1/T2a & T2b	6 or 7(3+4)	NR	Older frail patients Those with serious medical conditions Asymptomatic Patients with preference for AS	
Anglia (Norfolk & Norwich)	≤ T2b	≤ 7	≤ 15	> 10 year predicted survival ≤ 78 years of age	
Anglia (Peterborough)	T1c or T2	≤ 6	≤ 10	≤ 2 cores positive with no core > 50% involved	
Anglia (James Paget University Hospital)	≤ T2	≤ 7	< 10		
Avon, Somerset & Wiltshire	≤ T2a	6	< 10	Small volume	Most appropriate for this population but suitable for any patient with localised prostate cancer considered suitable for radical treatment by the Network MDT
Dorset	T1c	6	< 0.15 (ng/ml^2)	No core > 50% involved, < 10 mm of any core involved & ≥ 10 cores involved ≥ 1 re-biopsy during follow-up	
Essex	T1-T2c	≤ 7	< 20		Preferred treatment for low risk patients (PSA < 10, Gleason ≤ 6, and T1-T2a) but also an option for intermediate risk (NICE)
Greater Manchester & Cheshire					Currently being updated
Greater Midlands					
Lancashire & South Cumbria	T1a-T2b	well & moderately differentiated tumours		> 10 year predicted survival	
Merseyside & Cheshire	T1-T2c	≤ 7	< 20		Preferred treatment for low risk patients (PSA < 10, Gleason ≤ 6, and T1-T2a) but also an option for intermediate risk (NICE)
Mount Vernon	T1-T2			> 10 year predicted survival	Option for stage T3 if limited extracapsular extension, Gleason < 8, and PSA < 20 ng/mL
North of England	T1c or T2	≤ 6	< 10	> 10 year predicted survival Fit for active treatment If < 60 years of age, < 50% core involvement & < 3 cores involved	
North Trent	T1-T2a	≤ 7 (3+4)	< 10	< 3 cores positive and < 50% or 5 mm length of any involved core	
Pan Birmingham	T1a	≤ 6	< 10	If Gleason = 7 with PSA < 15 and aged > 70 years also recommended (< 2% chance of prostate cancer death within 8 years of therapy)	May be an option for all localised tumours
South Wales					
South East Wales					
South West Wales	T1-T2a	< 6	< 10	Patient understands active surveillance	Based on NICE low risk stratification
South West London	T1c	6	< 0.15 (ng/ml^2)	> 10 year predicted survival < 50% all biopsy cores involved and < 10 mm any core involved	An option for men with low risk disease who would benefit from radical treatment if disease progression. Should be discussed as an option with men who intermediate risk disease.
Surrey, West Sussex & Hampshire	T1c	6	< 15	< 50% of all biopsy cores involved and < 10 mm of any core involved	An option for men with low-intermediate risk disease but particularly recommended for indications listed
Sussex	T1c or T2	6 – 7(3+4)	< 10	≤ 15 year predicted survival PSA density < 0.2	
Thames Valley	T1c or T2	6	< 10	≤ 2 biopsies with < 50% core length Patient preference	
UCLH					
Yorkshire	T1-T2c	≤ 7	< 20		Preferred treatment for low risk patients (PSA < 10, Gleason ≤ 6, and T1-T2a) but also an option for intermediate risk (NICE)

Abbreviations: NICE, National Institute of Health and Clinical Excellence; PSA, prostate-specific antigen

Table 78 Guidance for undertaking Active Surveillance in Protocols from UK Cancer Networks

Cancer Network	Initial frequency of PSA testing	Until	Later frequency of PSA testing	Frequency of DRE testing	Consider re-biopsy at:	Other	Notes
Anglia	3-monthly	stable	6-monthly	Annually		Measure PSAdt 6-monthly	May involve repeat biopsies. AS should not be considered standard practice due to lack of RCT evidence
Anglia (Norfolk & Norwich)	3-monthly	18 months	6-monthly		12 months		Discuss TRUSB at 12 months (not compulsory)
Anglia (Peterborough)	3-monthly	12 months	6-monthly	Same as PSA (3- or 6-monthly)	Every 12 months		Assess PSAdt only after 1 year of follow-up & using 5 PSA measurements
Anglia (James Paget University Hospital)	4-monthly	-	4-monthly		9 months & 2 years		No imaging undertaken
Avon, Somerset & Wiltshire	≤ 3-monthly	2 years	6-monthly if PSAdt low	Annually	≤ 6 months		Consider re-biopsy if sharp rise in PSA, change in clinical stage, or patient develops symptoms suggestive of progression
Dorset	3-monthly	2 years	6-monthly	Same as PSA (3- or 6-monthly)	2 & 5 years		
Essex							
Greater Manchester & Cheshire	4-monthly	2 years	6-monthly	Same as PSA (3- or 6-monthly)	Annually		Currently being updated
Greater Midlands					1 year		Follow up could be in primary care, agreed by local protocol
Lancashire & South Cumbria	3-monthly				2 years		Indication guidelines should be modified with patient age and comorbidity
Merseyside & Cheshire	3-monthly	2 years	6-monthly		1-2 years		At least 10 biopsy cores should be taken using the standard template
Mount Vernon							
North of England	3-monthly	2 years	6-monthly	Annually	1 & 5 years, then every 5 years until aged 75 years		
North Trent	3-monthly	2 years	6-monthly	Same as PSA (3- or 6-monthly)	≤ 1 year, then every 2 years		

Pan Birmingham	3-6 monthly			Same as PSA (3-6 monthly)	1 & 2 years if evidence of disease progression		
South Wales	4-monthly	2 years	6-monthly if stable	Annually	1-2 years		
South East Wales	4-monthly	2 years	6-monthly if stable	Annually	1-2 years		
South West Wales	3-monthly	2 years	6-monthly if stable	6-monthly	1 year (10 cores), then every 2 years		
South West London	3-monthly	2 years	6-monthly		1, 4 & 7 years		Should include at least one re-biopsy and may follow the ProSTART trial protocol
Surrey, West Sussex & Hampshire					18 months, 3 & years		
Sussex	3-monthly	18 months	-		18 months		After 18 months of 3-monthly PSA, decision regarding definitive treatment
	3-monthly	2 years	6-monthly		18 months, then following clinical discretion		Follow-up should be supervised in secondary care.
Thames Valley	4-monthly	1 year	6-monthly		12-18 months		
UCLH	4-6 monthly					MRI annually	
Yorkshire	3-monthly	-	3-monthly		1 year		

Abbreviations: DRE, digital rectal examination; PSA, prostate-specific antigen ;PSAV, PSA velocity; PSADT, PSA doubling time; TRUSB, trans-rectal ultrasound guided biopsy.

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In men with prostate cancer receiving active surveillance, what are the indicators for intervention with radical treatment?

Short summary

The systematic review of Martin and co-workers (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.

PICO

POPULATION	INTERVENTION and COMPARISON	OUTCOME
Men whose prostate cancer is being followed by active surveillance	Compare criteria for intervention based on: • PSA measures (density, velocity) • Biopsy • MRS (in those not undergoing 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

The systematic review of Martin and co-workers (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 (see table 4.11.1). There was no evidence about the effect of definition of disease progression on outcomes.

Table 79. Definitions of biochemical and histological progression, the proportion of men experiencing disease progression and the reasons for abandoning active surveillance (Martin *et al.* 2006)

Study	Definition of biochemical progression	Definition of histological progression	Percent progression*	Reasons for initiation of treatment or abandoning surveillance.
(Chen *et al.* 2003)	Progressive increased PSA	Not specified	8%	3 men (6%) progressed to stage T2a, and 1 (2%) developed bone metastases
(Patel *et al.* 2004)	PSAV > 0.75 ng/ml/year	Increase in Gleason score, or any new Gleason pattern 4 or 5	25%	17 men (19%) developed objective progression, 7 men (8%) had anxiety and 7 a combination of anxiety and signs of progression
(Choo *et al.* 2002)	PSADT <2 years and PSA > 8 ng/ml	Gleason pattern predominant 4 or higher, Gleason score 7 or more	17%	15 men (7%) had clinical progression, 16 (8%) PSA progression, 5 (2%) had histological progression, 23 (11%) asked for treatment and 10 (5%) stopped surveillance for other reasons
(Mohler *et al.* 1997)	3 consecutive PSA increase, with total increase > 5 ng/ml	Not specified	33%	4 men (15%) developed PSA progression.
(Khan *et al.* 2003)	Not specified	Gleason score upgraded to 7or more, any Gleason pattern 4 or 5	29%	Reasons not reported in detail.

*Using the individual studies criteria for disease progression

The short follow-up and small sample sizes in these series means that there were relatively few disease progression events, and attempts to identify predictive factors for progression are unreliable The overall rate of disease progression was between 8% and 33%, depending on the definition used. The actuarial estimates of probabilities of disease progression at 4 to 5 years of follow-up were 28% to 33% (Patel *et al.* 2004; Chen *et al.* 2003; Choo *et al.* 2002). Between 8% and 11% of men stopped active surveillance without meeting the full criteria for disease progression, usually to due anxiety or biochemical progression.

Martin and co-workers (Martin *et al.* 2006) noted that a rapidly rising PSA was accepted as an indication for treatment, so there was no chance to see whether patients with biochemical failure would progress clinically. There was no consensus, however, on the definition of biochemical progression that should trigger radical treatment. One of the series (Khan *et al.* 2003) observed a correlation between PSA volume (PSAV) and histological progression, but there was no clear PSAV cut-off discriminating men with and without histological progression. Khan and co-workers (Khan *et al.* 2003) reported that using a combination of free PSA (fPSA), PSAV and prostate volume predicted unfavourable histological features on repeat biopsy with 65% sensitivity and 90% specificity.

Choo and co-workers (Choo *et al.* 2002) found PSA doubling time (PSADT) was significantly shorter in men experiencing clinical or histological progression (5.4 and 3.4 years respectively) compared with those experiencing no clinical or no histological progression (7.4 and 7.5 years respectively). This series (Choo *et al.* 2002) used a PSADT of less than 2 years as a trigger for radical treatment. Patel and co-workers (Patel *et al.* 2004) did not find a significant correlation between PSADT and other measures of disease progression.

Histological progression was defined as predominant Gleason pattern 4 or 5 with Gleason score 7 or more in two studies (Choo *et al.* 2002; Khan *et al.* 2003). One study (Patel *et al.* 2004) defined it as any new Gleason pattern 4 or 5 or increase in Gleason score. An increased proportion of biopsy cores with cancer was also considered evidence of disease progression in two of the studies (Patel *et al.* 2004; Khan *et al.* 2003). Studies using prostate re-biopsy in the surveillance protocol (Patel *et al.* 2004; Choo *et al.* 2002; Khan *et al.* 2003) reported relatively high rates of progression in the initial two to three years. Martin and co-workers (Martin *et al.* 2006) suggested this could be an artifact of biopsy sampling error, where high grade disease was missed on the initial biopsy.

The other measures used to define disease progression requiring radical treatment were: increased tumour stage on digital rectal examination (Patel *et al.* 2004; Chen *et al.* 2003; Choo *et al.* 2002; Mohler *et al.* 1997) and urinary symptoms (Choo *et al.* 2002; Mohler *et al.* 1997).

Health Economic Summary

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.

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3.3 Surgery versus radiotherapy

Prostatectomy versus watchful waiting or other radical therapies.

Short summary

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

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

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOMES
Men with localised or locally advanced prostate cancer, of any age, with no prior treatment.	Radical prostatectomy	• Watchful waiting • Brachytherapy • EBRT • Cryosurgery • HIFU • Conformal Radiotherapy • Conventional radiotherapy	• overall survival • disease-specific survival • biochemical disease-free survival • time until next intervention • 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)

Evidence summary

<u>Outcomes of watchful waiting</u>

Overall survival, disease-specific survival

Albertsen and co-workers (Albertsen *et al.* 1998; Albertsen *et al.* 2005) followed a cohort of 767 men with clinically localised prostate cancer for 20 years. Men were either not treated or treated with hormonal therapy only.

Table 80 Fifteen year outcome data (percentages) from Albertsen et al (1998), reported in (Parker *et al.* 2006). The bracketed figures are adjusted for the effects of screening and a contemporary population.

Gleason score < 7	Age at diagnosis (years)			
	55–59	60–64	65–70	70–74
Alive	62 (71)	48 (57)	31 (39)	14 (20)
Death due to other causes	26 (28)	38 (42)	52 (60)	64 (79)
Death due to prostate cancer	12 (1)	13 (1)	17 (1)	22 (1)

Gleason score = 7	Age at diagnosis (years)			
	55–59	60–64	65–70	70–74
Alive	15 (42)	14 (37)	11 (27)	7 (15)
Death due to other causes	15 (31)	24 (45)	36 (63)	51 (79)
Death due to prostate cancer	70 (27)	62 (18)	53 (10)	42 (6)

Gleason score > 7	Age at diagnosis (years)			
	55–59	60–64	65–70	70–74
Alive	3 (11)	3 (11)	3 (12)	2 (7)
Death due to other causes	10 (25)	16 (38)	25 (57)	38 (75)
Death due to prostate cancer	87 (64)	81 (51)	72 (31)	60 (18)

Survival outcomes in the Albertsen cohort were summarised by Gleason score and age. Parker and co-workers (Parker *et al.* 2006) revised the Albertsen data, using a competing risks model to account for lead time bias due to screening and better survival in contemporary populations. They also reduced Albertsen's Gleason stratification from five to three groups, using weighted means. The original and adjusted estimates of 15 year outcome are summarised in Table 80 above.

Radical prostatectomy versus watchful waiting

Two randomised trials comparing radical prostatectomy and watchful waiting were identified. The earlier of the trials (Graversen *et al.* 1990) was conducted in the USA by the Veterans Administration Cooperative Urological Research Group (VACURG). Small sample size, high loss to follow-up and outdated staging procedures mean the results of this trial are unlikely to be applicable. The other trial was a Scandinavian Prostatic Cancer Group study (Bill-Axelson *et al.* 2005); Steineck, 2002), which involved men with localised, well to moderately well differentiated prostate cancer.

Other evidence comes from population based cohort studies (Wong *et al.* 2006; Aus *et al.* 2005).

Overall survival

Bill-Axelson and co-workers (Bill-Axelson *et al.* 2005) reported significantly lower 10 year overall mortality in the group treated with prostatectomy than in the watchful waiting group (27.0% vs. 32.0%; RR = 0.74 [95% CI 0.56 to 0.99]; p=0.04).

Wong and co-workers (Wong *et al.* 2006) reported overall survival in a large population based cohort of 44630 elderly American men with clinically localised prostate cancer. They adjusted for prognostic risk factors and attempted to adjust statistically for treatment selection bias. The hazard ratio for mortality in the 13292 men treated with prostatectomy compared to the 12608 men managed with observation only was 0.50 [95% CI 0.47 – 0.53], suggesting significantly less mortality in the prostatectomy group.

The Bill-Axelson and co-workers (Bill-Axelson *et al.* 2005) trial contained mostly men with symptomatic disease and palpable tumours. In contemporary populations prostate cancer is often non palpable and detected through increased PSA level. Parker and co-workers (Parker *et al.* 2006) modelled the effect of radical treatment on survival using data from the cohort reported by Albertsen et al (Albertsen *et al.* 1998; Albertsen *et al.* 2005) and the Scandinavian trial (Bill-Axelson *et al.* 2005). Adjustments were made to account for lead time bias due to screening as well as the improved survival seen in contemporary populations. See Table 81 below.

Table 81 The effect of radical therapy on fifteen year outcomes, by age and Gleason score (Parker *et al.* 2006). Figures represent the predicted change in the percentage of men experiencing each outcome, in each age–Gleason score group.

Gleason score < 7	Age at diagnosis (years)			
	55–59	60–64	65–70	70–74
Alive	0	1	0	1
Death due to other causes	0	0	0	0
Death due to prostate cancer	0	-1	0	-1

Gleason score = 7	Age at diagnosis (years)			
	55–59	60–64	65–70	70–74
Alive	12	9	6	3
Death due to other causes	1	1	1	1
Death due to prostate cancer	-13	-10	-7	-4

Gleason score > 7	Age at diagnosis (years)

	55–59	60–64	65–70	70–74
Alive	26	20	12	6
Death due to other causes	6	7	7	6
Death due to prostate cancer	-32	-27	-19	-12

According to this analysis, the benefit of radical therapy depends on age and Gleason score, with less benefit for older men and those with lower Gleason score. For example, at least a hundred men with screen detected prostate cancer and Gleason score < 7 would need to have radical prostatectomy to save a single man from prostate cancer death within 15 years of therapy.

disease-specific survival

Bill-Axelson and co-workers (Bill-Axelson *et al.* 2005) reported significantly lower 10 year prostate cancer mortality in the group treated with prostatectomy than in the watchful waiting group (9.6% vs. 14.9%; RR = 0.56 [95% CI 0.36 to 0.88]; p=0.01).

Aus and co-workers (Aus *et al.* 2005) reported disease specific mortality in a Swedish population based cohort of men without metastases and younger than 75 at diagnosis of prostate cancer. They used Cox proportional hazards regression, with tumour grade, PSA level and TNM stage as covariates, to examine the effects of treatment. The 546 men treated with radical prostatectomy had significantly lower prostate cancer mortality than the watchful waiting group (HR 0.40, 95% CI 0.27 to 0.59; p<0.0001).

time until next treatment

In the Bill-Axelson trial (Bill-Axelson *et al.* 2005) hormonal therapy was administered less often in the prostatectomy group than in the watchful waiting group (110/347 patients vs. 117/348 patients respectively, p<0.01). The mean time until hormonal therapy was 4.5 years for the radical prostatectomy group and 4.8 years in the watchful waiting group. Palliative radiotherapy was administered less often in the prostatectomy group than in the watchful waiting group (29/347 patients vs. 38/348 patients respectively, p=0.30) as was laminectomy (4/347 patients vs. 11/348 patients, p=0.04).

side effects

Steineck and co-workers (Steineck *et al.* 2002) reported side effects and quality of life in Swedish men enrolled in the Scandinavian Prostatic Cancer Group study. Men completed a symptom questionnaire at a median of 4 years after enrolment in the study.

Table 82 The treatment side effects in the Scandinavian Prostatic Cancer Group study.

Outcome	Radical prostatectomy	Watchful waiting	Relative risk
Erectile dysfunction	129/161	71/158	RR 1.8 (95% CI 1.5 to 2.2)
Urinary leakage	80/164	33/155	RR 2.3 (95% CI 1.6 to 3.2)

Weak urinary stream	46/164	68/153	RR 2.3 (95% CI 1.6 to 3.2)
Faecal leakage	11/164	16/156	RR 0.7 (95% CI 0.3 to 1.4)

Erectile dysfunction and urinary leakage were significantly more likely in the prostatectomy group. Symptoms of urinary obstruction tended to be less likely after prostatectomy.

Quality of life

Table 83 Quality of life and psychological measures in the Scandinavian Prostatic Cancer Group study.

Outcome	Radical prostatectomy	Watchful waiting	Relative risk
Decreased general physical capacity	89/164	89/157	RR 1.0 (95% CI 0.8 to 1.2)
Anxiety (moderate or high)	37/164	48/157	RR 0.7 (95% CI 0.5 to 1.1)
Depression (moderate or high)	57/164	60/157	RR 0.9 (95% CI 0.7 to 1.2)
Psychological well being (low or moderate)	57/164	57/158	RR 1.0 (95% CI 0.7 to 1.3)
Subjective quality of life (low or moderate)	64/159	68/151	RR 0.9 (95% CI 0.7 to 1.2)

There was no significant difference in psychological measures or in subjective quality of life between the treatment groups in the Scandinavian trial (Steineck *et al.* 2002).

Radical prostatectomy versus radiotherapy

Two small randomised trials were identified. Akakura and co-workers ((Akakura *et al.* 2006) compared radiotherapy with prostatectomy (both with neoadjuvant and adjuvant hormonal therapy) in group of men with locally advanced prostate cancer. Paulson (Paulson *et al.* 1982) compared radiotherapy with prostatectomy in men with clinically localised prostate cancer.

Table 84 Characteristics of randomised trials comparing radiotherapy with prostatectomy.

Trial	Disease stage	Treatment arms	Number of patients
(Akakura *et al.* 2006)	Mostly locally advanced	EBRT (60 – 70 Gy) + HT	49 EBRT

		RP + HT	46 RP
(Paulson *et al.* 1982)	Clinically localised	EBRT (65 – 70 Gy)	59 EBRT
		RP	47 RP

Paulson and co-workers (Paulson *et al.* 1982) reported time to treatment failure, but no other outcomes. The applicability of the trial is limited by its small sample size and other methodological problems. The interpretation of the other trial (Akakura *et al.* 2006) is also difficult due to its small sample size and the use of adjuvant and neoadjuvant hormonal therapy in all patients.

Systematic reviews of case series ((Nilsson *et al.* 2004; Hummel *et al.* 2003) and other observational evidence (Aus *et al.* 2005; Wong *et al.* 2006) are also included.

Overall survival

Wong and co-workers (Wong *et al.* 2006) reported overall survival in a large population based cohort of 44630 older men with clinically localised prostate cancer. They adjusted for prognostic risk factors and used propensity scores to adjust for treatment selection bias. The hazard ratio of mortality in men treated with radiotherapy compared to those managed with watchful waiting was 0.81 [95% CI 0.78 – 0.85]. The corresponding hazard ratio in men treated with prostatectomy was 0.50 [95% CI 0.47 – 0.53]. Calculating the hazard ratio of mortality in prostatectomy compared to radiotherapy groups gives HR = 0.62 [95% CI 0.60 to 0.62] suggesting lower mortality with prostatectomy.

Nilsson and co-workers (Nilsson *et al.* 2004) reviewed evidence from retrospective case series comparing overall survival in men with prostate cancer treated with radiotherapy or prostatectomy. Useful comparisons could not be made in the one series that reported overall survival, due to large baseline differences in prognosis between the treatment groups.

In the Akakura and co-workers trial (Akakura *et al.* 2006) 10 year overall survival was 67.9% after prostatectomy and 60.9% after radiotherapy, this difference was not statistically significant.

Disease-specific survival

Akakura and co-workers (Akakura *et al.* 2006) reported ten year disease specific survival rates as 85.7% after prostatectomy and 77.1% after radiotherapy, the difference approached significance (log-rank test, p=0.06).

Nilsson et al (Nilsson *et al.* 2004) reported a retrospective case series comparing disease specific survival in men with low risk prostate cancer treated with radiotherapy or prostatectomy. At 7 years, there was no significant difference in disease specific survival, 99% for the prostatectomy group and 97% for the radiotherapy group.

Aus and co-workers (Aus *et al.* 2005) reported disease specific mortality in a Swedish population based cohort of men without metastases and younger than 75 at diagnosis of prostate cancer. The 289 men treated with radiotherapy did not have significantly lower prostate cancer mortality than the 1252 men managed with watchful waiting (HR 1.01, 95% CI 0.72 to 1.41; p=0.98). The 546 men treated with radical prostatectomy had significantly lower prostate cancer mortality than the watchful waiting group (HR 0.40, 95% CI 0.27 to 0.59; p<0.0001).

Biochemical disease-free survival

Nilsson (Nilsson *et al.* 2004) reviewed five retrospective case series comparing biochemical recurrence rates at 5 to 8 years after radiotherapy or prostatectomy. The literature suggests equivalent biochemical recurrence free survival after radiotherapy and prostatectomy, if patients are grouped by risk.

Side effects

Nilsson and co-workers (Nilsson *et al.* 2004) reported case series and a meta-analysis of erectile dysfunction in men after curative treatment for prostate cancer. In all but one of eleven case series, erectile dysfunction was more likely after prostatectomy than after radiotherapy. The meta-analysis (Robinson *et al.* 2002) predicted the probabilities of maintaining erectile function after curative therapy for prostate cancer as follows: after brachytherapy 76%, after combined brachytherapy and EBRT 60%, after EBRT 55%, after nerve sparing prostatectomy 34%, after standard prostatectomy 25% and after cryotherapy 13%.

Hummel and co-workers (Hummel *et al.* 2003) estimated the incidence of late adverse treatment effects occurring a year or more after radical therapy. The estimates for late effects are mean values (weighted by patient numbers) and ranges, taken from existing trials, meta-analyses and case series.

Table 85 Incidence of late adverse treatment effects due to radical therapy (Hummel *et al.* 2003)).

Treatment	Impotence			Urinary symptoms			Bowel symptoms		
	Central	Low	High	Central	Low	High	Central	Low	High
Watchful waiting	0	0	0	0	0	0	0	0	0
Radical prostatectomy	0.58	0.44	0.6	0.15	0.05	0.25	0	0	0
Conventional radiotherapy	0.31	0.29	0.36	0.2	0.09	0.23	0.15	0.08	0.26
3D-CRT	0.36	0.32	0.39	0.2	0.09	0.23	0.05	0.02	0.12
Brachytherapy	0.18	0.04	0.51	0.14	0.14	0.3	0.03	0.01	0.05
Cryotherapy	0.86	0.67	0.93	0.18	0.14	0.46	0.004	0.004	0.005

Steineck and co-workers (Steineck *et al.* 2002) reported the rates of late adverse effects in the Scandinavian trial of prostatectomy vs. watchful waiting (see prostatectomy vs. watchful waiting section).

Quality of life

Hummel and co-workers (Hummel *et al.* 2003) estimated the quality adjusted life years (QALYs) after radical therapy for prostate cancer. Utility values, taken from eight published studies, were assigned to each of the adverse events in Table 85. An important central assumption was that (with the exception of watchful waiting) all treatments were equally as effective in terms of metastatic disease progression and overall survival. Thus, any differences in QALYs are entirely due to the estimated adverse event rates.

Table 86 Variation in QALYs by treatment, age and tumour differentiation (Hummel et al, 2003).

Treatment	Age (years)*			Tumour differentiation†		
	55	65	75	Well	Moderate	Poor
Watchful waiting	9.17	7.52	5.49	8.88	7.52	3.99
RP	9.91	7.78	5.48	8.93	7.78	6.83
Radical radiotherapy	9.52	7.47	5.26	8.56	7.47	6.57
3D-CRT	9.87	7.75	5.46	8.89	7.75	6.51
Brachytherapy	10.28	8.07	5.69	9.28	8.07	7.07
Cryotherapy	9.63	7.56	5.32	8.66	7.56	6.65

*For a man with moderately differentiated tumour. †For a man aged 65

The Hummel review (Hummel *et al.* 2003) concluded that although brachytherapy appears to offer the most QALYs in their analysis, this finding is not robust due to uncertainty about the estimates of adverse events and clinical effectiveness of brachytherapy.

Evidence Tables

Randomized controlled trials

(Steineck *et al.* 2002)

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

Country: United States, setting: Tertiary care

Inclusion criteria Men enrolled in the Scandinavian PCG-4 trial between 1989 and 1996. Men had newly diagnosed, histologically confirmed, T1 or T2 prostate cancer. Well to moderately well differentiated tumour. Life expectancy of more than 10 years. PSA < 50 ng/ml. Negative bone scan.

Population number of patients = 376.

Interventions Men were randomised to either prostatectomy or watchful waiting. Hormonal treatment was recommended for symptomatic progression in the radical prostatectomy group and for metastatic progression in both groups.

Outcomes Symptoms (sexual, urinary and bowel) were assessed using questionnaires. Two psychometric measures were used to assess mental state: The State-Trait Anxiety Inventory and the Centre for Epidemiological Studies Measure of Depression.

Follow up Median time from randomisation to completion of questionnaires was 4 years (range 1 to 7.5 years). Response rate to the questionnaire was 88% for prostatectomy group and 86% for the watchful waiting group.

Results -

COMPARISON IN MEN WITH CLINICALLY LOCALISED PCA	RADICAL PROSTATECTOMY	WATCHFUL WAITING	OVERALL RESULT
Erectile dysfunction	129/161	71/158	RR 1.8 (95% CI 1.5 to 2.2)
Urinary leakage	80/164	33/155	RR 2.3 (95% CI 1.6 to 3.2)
Weak urinary stream	46/164	68/153	RR 2.3 (95% CI 1.6 to 3.2)
Faecal leakage	11/164	16/156	RR 0.7 (95% CI 0.3 to 1.4)
Decreased general physical capacity	89/164	89/157	RR 1.0 (95% CI 0.8 to 1.2)
Anxiety (moderate or high)	37/164	48/157	RR 0.7 (95% CI 0.5 to 1.1)
Depression (moderate or high)	57/164	60/157	RR 0.9 (95% CI 0.7 to 1.2)
Psychological well be-	57/164	57/158	RR 1.0 (95% CI 0.7 to

ing (low or moderate)			1.3)
Subjective quality of life (low or moderate)	64/159	68/151	RR 0.9 (95% CI 0.7 to 1.2)

General comments The characteristics of those who did not respond to the questionnaire are not reported. This group is a potential source of bias.

(Bill-Axelson *et al.* 2005)

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

Country: International, setting: Tertiary care

Inclusion criteria Men with early prostate cancer were enrolled between 1989 and 1999. 14 centres in Sweden, Finland and Iceland participated. Men with new diagnosed, histologically confirmed, T1 or T2 prostate cancer were included. Well to moderately well differentiated tumour. Life expectancy of more than 10 years. PSA < 50 ng/ml. Negative bone scan.

Population number of patients = 695, mean age = 65 years.

Interventions Men were randomly assigned to radical prostatectomy (347 men) or watchful waiting (348 men). Hormonal treatment was recommended for symptomatic progression in the radical prostatectomy group and for metastatic progression in both groups.

Outcomes Disease specific and overall survival (determined by panel blinded to treatment information). Distant metastases and local progression.

Follow up Median follow up was 8.2 years. Men were seen every 6 months for the first 2 years and then annually for clinical examination and PSA tests. 9 patients did not continue follow-up due to old age and comorbidity.

Results -

COMPARISON IN MEN WITH CLINICALLY LOCALISED PCA	RADICAL PROSTATECTOMY	WATCHFUL WAITING	OVERALL RESULT
Overall mortality at 10 years	27% (95% CI 21.9 to 33.1%)	32% (95% CI 26.9 to 33.1%)	Favours RP RR 0.74 (95% CI 0.56 to 0.99; p=0.04)
Disease specific mortality at 10 years	9.6% (95% CI 6.5 to 14.2%)	14.9% (95% CI 11.2 to 19.8%)	Favours RP, RR 0.56 (95% CI 0.36 to 0.88; p=0.01)
Distant metastases at 10 years	15.2% (95% CI 11.4 to 20.3%)	25.4% (95% CI 20.4 to 31.5%)	Favours RP, RR 0.60 (95% CI 0.42 to 0.86; p<0.01)
Local progression at 10	19.2% (95% CI 15.0 to	44.3% (95% CI 38.8 to	Favours RP, RR 0.33 (95% CI 0.25 to 0.44;

years	24.6%)	50.5%)	p<0.001)
Initiation of hormone therapy	110/347 had HT, at a mean time of 4.5 years after randomisation	177/348 had HT, at a mean time of 4.8 years after randomisation	Favours RP (p<0.01)
Palliative radiotherapy	4/347	11/348	Favours RP (p=0.04)

(Akakura *et al.* 2006)

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

Country: Japan, setting: Tertiary care

Inclusion criteria Men with T2b to T3 N0, M0 prostate cancer. Aged 75 or less. Men were enrolled between 1989 and 1993.

Exclusion criteria -

Population number of patients = 100.

Interventions Men were randomised to receive either radical radiotherapy (60 to 70Gy) or radical prostatectomy. All men received neoadjuvant and adjuvant hormone therapy until disease progression.

Outcomes Overall survival, disease specific survival, biochemical recurrence free survival (3 consecutive increase in PSA were defined as recurrence) and clinical recurrence free survival. Treatment related morbidity is reported but it is not clear how it was classified.

Follow up Median follow-up was 8.5 years. 5% of patients were lost to follow-up.

Results -

COMPARISON IN MEN WITH LOCALISED OR LOCALLY ADVANCED PROSTATE CANCER, WITH NO METASTASES	RADICAL PROSTATECTOMY	RADICAL RADIOTHERAPY	OVERALL RESULT
Overall survival	At ten years 67.9%	At ten years 60.9%	No significant difference (log rank test, p not reported)
Disease specific survival	At ten years 85.7%	At ten years 77.1%	No significant difference (log rank test, p=0.06)
Biochemical progression free survival	At ten years 76.2%	At ten years 71.1%	No significant difference (log rank test, p not reported)
Clinical progression free survival	At ten years 83.5%	At ten years 66.1%	No significant difference (log rank test, p not reported)
Incontinence	At ten years 40% (more than 1 pad per day)	At ten years 15% (more than 1 pad per day)	Favours radiotherapy (p<0.001)
Erectile dysfunction	At ten years 90%	At ten years 90%	No significant difference

(Graversen *et al.* 1990)
Design: Randomized controlled trial (), evidence level: 1- Country: United States, setting: Tertiary care **Inclusion criteria** Men with newly diagnosed and untreated prostate cancer (stage I or II), were enrolled from 15 participating hospitals. **Exclusion criteria** - **Population** number of patients = 142. **Interventions** Clinical staging: DRE, serum acid phosphatase and skeletal and chest X-rays. Men were randomised to either radical prostatectomy or watchful waiting. It was not possible to establish whether hormone therapy or any other treatment had been given to the patients. **Outcomes** Overall survival. **Follow up** 31/142 (22%) were excluded from analysis for various reasons. 16 of the remaining 111 were lost to follow-up at 15 years. **Results** No significant differences were seen between the prostatectomy and watchful waiting group. **General comments** High loss to follow-up, incomplete outcome data. Authors note that the findings should be treated with caution.

(Paulson *et al.* 1982)
Design: Randomized controlled trial (therapy), evidence level: 1- Country: United States, setting: Tertiary care **Inclusion criteria** Patients with T1 to T2, N0, M0 prostate cancer. **Population** number of patients = 106. **Interventions** Men received either radiotherapy (45 to 50 Gy pelvic field, with 20 Gy boost to the prostate) or prostatectomy **Outcomes** Treatment failure, defined as either consecutive elevations in acid phosphatase, **Follow up** 16/106 patients did not receive the treatment they were randomised to receive The duration of follow-up is not reported, but it is clear from the survival graphs that some patients were followed up for less than a year. The maximum follow up was five years.

Results Treatment failure was more likely in the radiotherapy group (p=0.037).

COMPARISON IN MEN WITH CLINICALLY LOCALISED PCA	RADICAL PROSTATECTOMY	RADICAL RADIOTHERAPY	OVERALL RESULT
Treatment failure	From graph: at 2.5 years 13%, at five years 4	From graph: at 2.5 years 30%, at five years 40%	Favours prostatectomy (p=0.037)

General comments No intention to treat analysis. Definition of treatment failure is outdated. Some patients chose their treatment.

Systematic review of cohort studies

(Nilsson *et al.* 2004)

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

Country: International, setting: Tertiary care

Inclusion criteria Papers reporting radiotherapy for prostate cancer published up to January 2003 and included in Medline.

Exclusion criteria -

Population -

Interventions 26 non randomised studies (17018 patients) reported outcomes after conventional external beam radiotherapy.

Outcomes Prostate cancer specific survival, biochemical recurrence free survival, safety of radiotherapy.

Follow up Length of follow up varied between studies.

Results There was no statistical meta-analysis, but a narrative summary of outcomes as follows:

Disease-specific survival:

Evidence from retrospective case series suggests that ten year prostate cancer specific survival after conventional RT is of the order of 90%, 75% and 50% for men with well differentiated, moderately differentiated and poorly differentiated disease respectively.

Biochemical disease-free survival

The rate of biochemical control after conventional radiotherapy was related to pre-treatment PSA level. At five years, disease free survival for men with pre-treatment PSA of <4ng/ml, 4-10 ng/ml, 10-20 ng/ml and more than 20 ng/ml was of the order of 85%, 55%m 45% and 15%

respectively.

Adverse effects

The review concluded that conventional EBRT with curative intent can be administered safely; however, there was no detailed analysis of side effects.

General comments -

Prospective cohort study

(Albertsen *et al.* 1998)
Design: Prospective cohort study (prognosis), evidence level: 2+ Country: United States, setting: Registry **Inclusion criteria** Men were identified from a regional tumour registry, as having clinically localised prostate cancer between 1971 and 1984. To be included they were: either not treated or treated with immediate or delayed hormonal therapy. **Exclusion criteria** Men with metastases. **Population** number of patients = 767, age range 55 to 74 years. **Interventions** Patients were treated with either observation or androgen withdrawal therapy alone. **Outcomes** Estimates of the probability of dying from prostate cancer or other competing hazards. **Follow up** Cause of death was not determined in 57/610 cases, but was imputed from the existing data. Follow-up was at least 10 years. Some men were lost to follow up **Results** Death from prostate cancer Men with tumours that have Gleason scores of 2 to 4, 5, 6, 7, and 8 to 10 face a 4% to 7%, 6% to 11%, 18% to 30%, 42% to 70%, and 60% to 87% chance, respectively, of dying from prostate cancer within 15 years of diagnosis depending on their age at diagnosis. Overall survival Men with tumours that have Gleason scores of 2 to 4, 5, 6, 7, and 8 to 10 had a 20% to 69%, 18% to 67%, 11% to 57%, 7% to 15%, and 2% to 3% chance, respectively, of surviving within 15 years of diagnosis depending on their age at diagnosis. **General comments** Pre PSA era study. Gleason scores may not be comparable with current scoring criteria. Sparse data for the younger age group.

(Albertsen *et al.* 2005)
Design: Prospective cohort study (prognosis), evidence level: 2+ Country: United States, setting: Registry **Inclusion criteria** Men were identified from a regional tumour registry, as having clinically localised prostate cancer between 1971 and 1984. To be included they were: either not

treated or treated with immediate or delayed hormonal therapy.

Exclusion criteria Metastatic disease

Population number of patients = 767, age range 55 to 74 years, median age = 69 years.

Interventions Patients were treated with either observation or androgen withdrawal therapy alone.

Outcomes Probability of mortality from prostate cancer or other competing medical conditions, given a patient's age at diagnosis and tumour grade.

Follow up Cause of death was not determined in 25/717 cases, but was imputed from the existing data. The median observation period was 24 years (range 16 to 33 years).

Results Prostate cancer death

Men with tumours with Gleason scores of 2 to 4, 5, 6, 7, and 8 to 10 had a 7%, 14%, 27%, 45%, and 66% chance, respectively, of dying from prostate cancer within 20 years of diagnosis. Risk varied with age at diagnosis. For Gleason grade 7 and above younger men tended to have a greater risk of death from prostate cancer within 20 years of diagnosis.

Overall survival

Men with tumours with Gleason scores of 2 to 4, 5, 6, 7, and 8 to 10 had a 12%, 10%, 6%, 2%, and 1% chance, respectively, of surviving within 20 years of diagnosis. Risk also depended on age at diagnosis, younger men were much more likely to survive

General comments Update of Albertsen 1998. Sparse data for the younger age group.

(Aus *et al.* 2005)

Design: Prospective cohort study (therapy), evidence level: 2+

Country: Sweden, setting: Community

Inclusion criteria Men recorded in a Swedish regional population-based registry of 8887 patients with newly diagnosed prostate carcinoma from 1987 to 1999. Separate analysis was done for men with or without metastases at diagnosis.

Exclusion criteria -

Population number of patients = 8887, age range 40 to 96 years, median age = 75 years.

Interventions Diagnostic and staging investigations (not specified in detail). Primary treatment was either watchful waiting, radical prostatectomy or radiotherapy (64 - 70 Gy). After watchful waiting secondary treatment was: radical therapy for 2.5%, palliative hormones for 33.5% and no further treatment for 64% of men. In men treated with curative intent secondary treatment was hormones in 18.1% of cases, 81.9% received no further treatment.

Outcomes Overall survival, prostate cancer specific survival

Follow up The median follow-up was 80 months for surviving patients.

Results Analysis was done for the subgroup of 4121 men without metastases at diagnosis of prostate cancer. The authors used Cox proportional hazards regression, with tumour grade, PSA level and TNM stage as covariates, to examine the effects of treatment.

COMPARISON IN MEN WITH LOCALISED OR LOCALLY ADVANCED PROSTATE CANCER, WITH NO METASTASES	WATCHFUL WAITING	RADICAL PROSTATECTOMY	RADICAL RADIOTHERAPY	OVERALL RESULT
Disease specific survival	HR = 1	for RP vs. WW, HR = 0.40 [95% CI 0.27-0.59] (p<0.00001)	for RT vs. WW, HR = 1.01 [95% CI 0.27-0.59] (p=0.98)	Suggests disease specific survival benefit for radical prostatectomy

General comments -

Retrospective cohort study

(Wong *et al.* 2006)

Design: Retrospective cohort study (), evidence level: 2++

Country: United States, setting: Community

Inclusion criteria Men aged between 65 and 80 who had an incident prostate cancer diagnosis between 1991 and 1999 in the Medicare database. Only those with Gleason score of 7 or less, T1 or T2 tumours were included.

Exclusion criteria Men diagnosed at death. T3 or T4 disease, men with Gleason score of 8 or more, men with unknown T stage or grade, men with metastases. Men who had enrolled in a managed care plan from 3 months before to 6 months after diagnosis. Men who received hormone therapy only. Men who died within a year of diagnosis.

Population number of patients = 44630.

Interventions The study compared observation alone, with radical prostatectomy and radiotherapy (external beam or brachytherapy).

A model was developed to predict the odds of receiving treatment based on comorbidity, disease, patient and sociodemographic variables (the propensity score).

Comparison of overall survival for each treatment group was done using Cox proportional haz-

ards methods, adjusting for propensity scores.

Outcomes Overall survival (the interval from the date of diagnosis to the date of death recorded in Medicare).

Results

COMPARISON IN MEN WITH CLINICALLY LOCALISED PCA	OBSERVATION ONLY	RADICAL PROSTATECTOMY	RADICAL RADIOTHERAPY	OVERALL RESULT
Mortality (hazard ratio compared with observation)	HR 1	HR = 0.50 (95% CI 0.47 to 0.53)	HR = 0.81 (95% CI 0.78 to 0.85)	Favours radical treatment over observation only

Other studies

(Parker *et al.* 2006)

Population –Men with screen detected prostate cancer

Interventions The authors developed a competing-risks hazard model to estimate the natural history of screen-detected prostate cancer, and the impact of radical treatment on overall survival.

Hazard due to other-cause mortality was assumed to Weibull survival distribution, and prostate cancer survival was assumed to follow an exponential survival distribution. The parameters of the two distributions were fitted using prostate cancer survival data from Albertsen's cohort (1998, 2005), and other cause mortality data from US life tables. Adjustment was then made for lead time bias due to screening and reductions in other cause mortality.

Outcomes Overall survival, prostate cancer specific survival

Results Estimates of 15-year prostate cancer mortality for conservative management of screen-detected prostate cancer ranged from 0 to 2% for Gleason scores <7, 9 to 31% for Gleason score 7 and 28-72% for Gleason scores >7.

Benefit of radical treatment was dependent upon Gleason score and age, with younger men and those with higher grade disease standing to benefit the most.

For men aged 55-59 years at diagnosis, the predicted absolute 15-year survival benefit from curative treatment was 0, 12 and 26% for men with Gleason scores <7, 7 and >7, respectively.

Health Economics

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

Introduction

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

Existing Economic Evidence

The systematic literature review identified five relevant studies. One of these studies (Horwitz et al. 1999) compared 3D conformal radiation therapy with conventional techniques, in a US setting, but was only available as an abstract. The most recent study, by Konski et al. 2006, was also performed in a US setting, and compared 3D conformal radiotherapy with intensity modulated radiotherapy (IMRT). The main limitation with this study was that differences in treatment effect were estimated using non-randomised studies, and few details of the literature search used to identify the non-randomised studies were provided. That is, people receiving IMRT were assumed to have a 2% lower probability of biochemical failure each year compared to people receiving 3D conformal radiotherapy, but the evidence base to support this notion is weak. The remaining two studies were both performed in the UK (Hummel et al. 2003; Calvert et al. 2003). Hummel et al. (2003) assessed the costs and effects of a number of different treatment options, including active surveillance and radical prostatectomy, from an NHS cost perspective. However, a core assumption within the analysis was that the treatment options did not differ in terms of slowing the progression of the underlying prostate cancer. Differences in treatment effect were therefore only estimated in terms of expected side-effect profiles, although none of the evidence was derived from randomised trials. While the baseline estimates suggested brachytherapy was cost-effective compared to active surveillance and radical prostatectomy, the authors concluded that this finding was not robust given the significant uncertainty surrounding the relative side-effects of brachytherapy (and other treatments).

The economic evaluation by Calvert et al. (2003) compared policies of watchful waiting with radical prostatectomy in 60-year-old men with Gleason scores of 5-7[1]. Costs were considered from a National Health Services (NHS) perspective and survival was adjusted for changes in health-related quality-of-life in terms of the underlying prostate cancer and adverse effects of treatment such as incontinence and impotence. The results of the analysis suggested that watchful waiting was less costly and more effective than radical prostatectomy (that is, it produced more Quality-Adjusted Life-years [QALYs]). However, it should be noted the number of QALYs gained per patient was almost equivalent suggesting that gains in survival attributable to radical prostatectomy were more than offset by increases in the incidence of post-operative complications.

The evaluation by Buron et al. (2007) compared the costs and benefits of (interstitial) brachytherapy with radical prostatectomy for men with a mean Gleason score of approximately 6. The evaluation was performed from a (French) societal perspective using data for almost 550 patients treated in French hospitals collected between 2001 and 2002. The results suggested that the mean societal costs of the two treatment options were similar (Euros 8,000-8,700) but that side-effect profiles, and hence health-related quality-of-life scores, differed. More specifically, impotence and urinary incontinence were more pronounced after radical prostatectomy, whereas urinary frequency, urgency and urination pain were more prevalent following brachytherapy. However, there were a number of significant limitations with the analysis: 1) changes in health-related quality-of-life were not measured using a utility-based instrument (meaning it is unclear which, if either treatment, was to be preferred on quality-of-life grounds); 2) patients in the study

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

were not randomised to the treatment options and 3) the treatment options were assumed to be clinically equivalent in terms of the progression of the underlying prostate cancer.

In terms of developing the understanding of the cost-effectiveness of the treatment options for men with localised prostate cancer, there are arguably two main limitations with the existing literature. Firstly, only the evaluation by Hummel et al. (2003) attempted to assess the cost-effectiveness of more than two treatment options. Secondly, none of the studies incorporates information from the more recently published RCT that compares radical prostatectomy versus watchful waiting (Bill-Axelson et al. 2005).

Aims

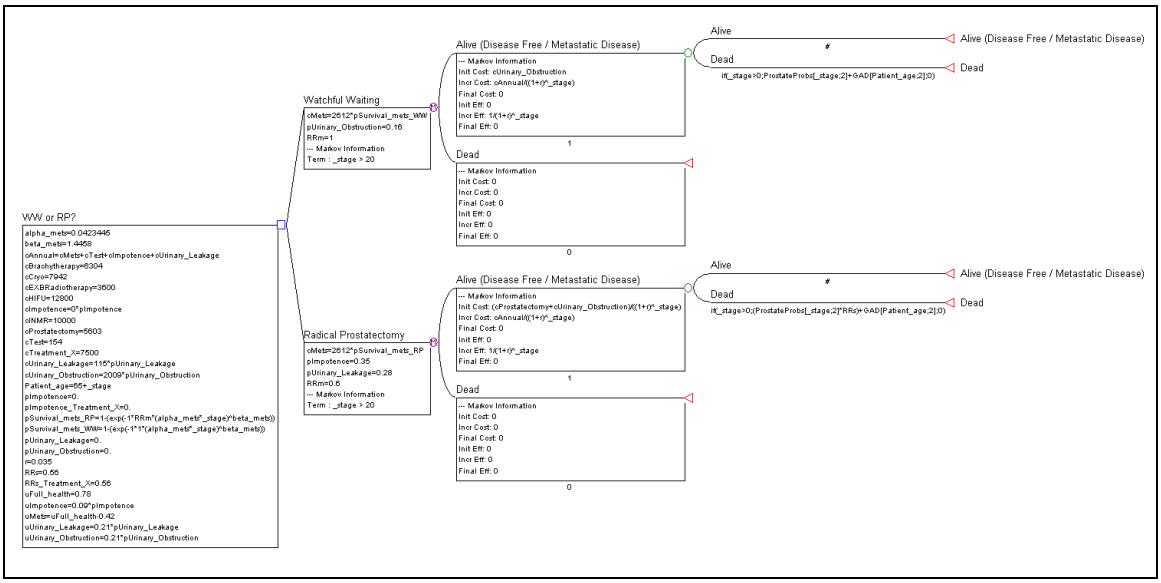
The primary aim of this study was to perform an economic evaluation of watchful waiting versus radical prostatectomy using the 10 year RCT published by Bill-Axelson et al. (2005). In the absence of suitable RCT data, a secondary objective was to estimate how effective other therapies (brachytherapy, standard external beam radiotherapy, intensity modulated radiotherapy, HIFU and cryotherapy) would need to be in order to be considered cost-effective compared by conducting a threshold analysis on the number of additional QALYs that were required to achieve certain willingness to pay thresholds for a gain value of one additional QALY.

Method

The economic evaluation was based on a Markov model and performed from a NHS cost perspective. Markov models divide a patients' possible prognosis into a series of discrete health states. Costs and benefits are assigned to each health state and transition probabilities define the movement (as a consequence of disease progression and treatment) of an individual between these health states over a particular time frame (cycle length). The costs and benefits of comparative treatments are then estimated on the basis of the length of time individuals spend in each health state.

The original and preferred model structure was to base the economic evaluation on a three-state Markov model (clinically localised disease, metastatic disease and dead), in line with Calvert et al. (2003) However, the RCT evidence published in Bill-Axelson et al. (2005) did not allow an estimate to be made of the probability of death given metastatic disease. Therefore, a Markov model with only two health states was constructed; alive and dead. The possibility of patients' progressing from clinically localised disease to metastatic disease was contained within the health state 'alive' (Figure 17). This approach represents a mathematical means of staying true to the observed trial (Bill-Axelson et al. 2005) while at the same time allowing for disease progression in terms of developing more advanced prostate cancer. An alternative approach would have been to use the three-state Markov model as described above, using estimates of the probability of death given metastatic disease from alternative published sources. However, as the RCT was considered to represent the highest quality data source, this approach was considered to be less appropriate.

Figure 17 Schematic / Programming of Markov Model Showing Life-Years Gained As the Outcome Measure



The model's cycle length was yearly (as the progression of prostate cancer in the model cohort of patients was considered to be relatively slow), and the time horizon for the analysis was 20-years, by which time, the overwhelming majority of hypothetical patients had died. In the base case (the scenario which was considered to be the most likely given all the available evidence and necessary assumptions), hypothetical patients were assumed to have a mean age of 65 years and a modal Gleason score of 5-6, in line with Bill-Axelson et al. (2005).

Each cycle, patients allocated to receive watchful waiting or radical prostatectomy had an annual probability of 1) continuing to have localised disease / be cured 2) developing metastatic disease, 3) dying from natural causes or 4) dying from prostate cancer. All patients who developed metastatic disease were assumed to receive hormonal therapy until death. Patients who were allocated to receive radical prostatectomy were assumed to receive surgery on entry to the model. All patients were assumed to receive two PSA tests per year on an outpatient basis until death.

Three baseline results were generated:

- Cost per additional life-year gained
- Cost per QALY gained (side-effects excluded)
- Cost per QALY gained (side-effects included)[2]

Transition Probabilities and Treatment Effects

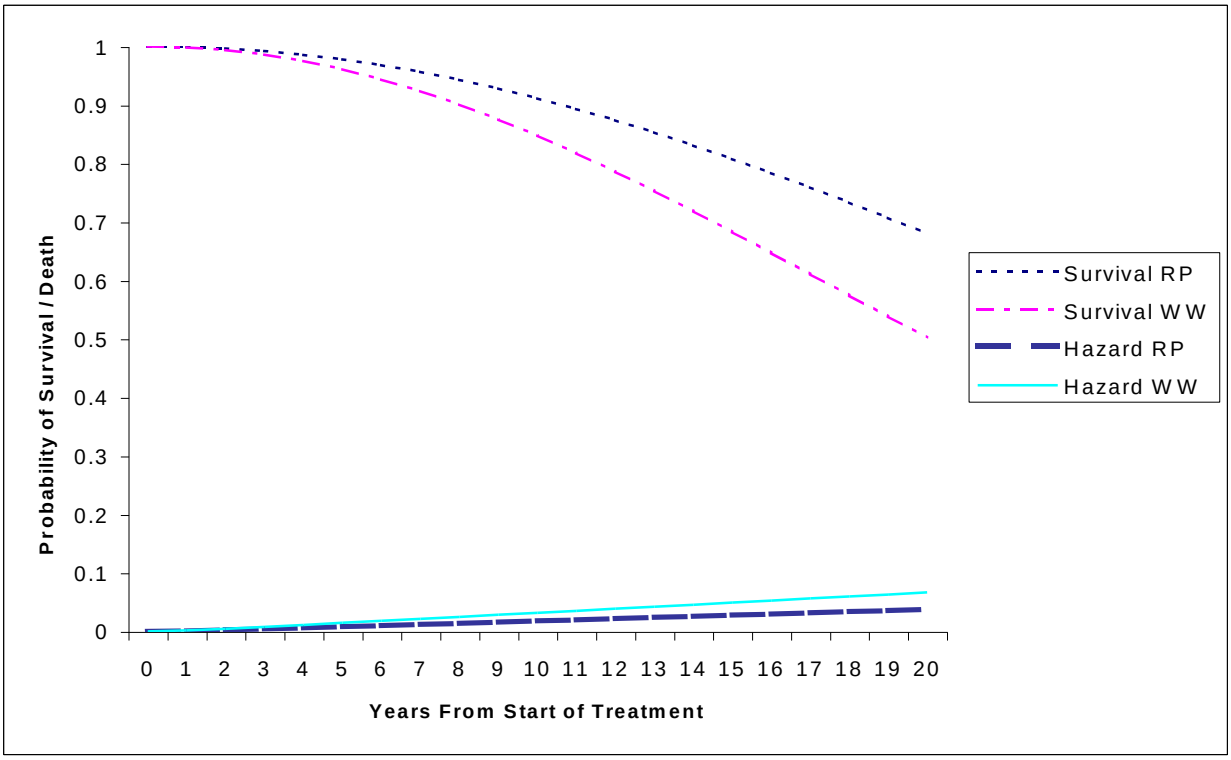
The baseline annual probability of death from prostate cancer for the watchful waiting strategy was taken from Bill-Axelson et al. (2005). Standard regression techniques were used to estimate a Weibull function[3]

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

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

from the published 10-year Kaplan-Meier disease-specific survival curve (Figure 18). To this was added the annual probability of death from other causes, taken directly from the UK Government's Actuarial Department (http://www.gad.gov.uk/Life_Tables/eoltable.htm). The annual probability of developing metastatic disease was also estimated from Bill-Axelson et al. (2005) by again fitting a Weibull function. However, as a consequence of using a two rather than three-state model, the probability of developing metastatic disease was assumed to be cumulative, and as such, represented at any single point in time, the proportion of patients who were in the health state 'alive' but living with metastatic disease.

Figure 18 Reported and extrapolated disease-specific survival curves and hazard functions derived from Bill-Axelson et al. (2005)



RP, Radical Prostatectomy; WW, Watchful Waiting

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

The effectiveness of radical prostatectomy was modelled by adjusting the baseline probabilities of death from prostate cancer and metastatic disease by the associated relative risks, as published in Bill-Axelson et al. (2005) 0.56 (95%CI 0.36-0.88) (Figure 18) and 0.6 (95%CI 0.42-0.86) respectively.

A number of side effects are possible as a result of treatment for prostate cancer. Indeed, the choice of treatment is often based on the anticipated side-effect profiles given the presenting patient, and is therefore an important concern.

In an ideal scenario, the disutility (reduction in health-related quality-of-life) associated with side effects would be derived from randomised studies comparing the relevant treatment options using an appropriate utility-based instrument. A next best solution would be to calculate the proportion of patients in each arm of a RCT that experienced each side effect and to estimate the overall level of disutility by linking this information to relevant published utility weights.

In the context of this modelling exercise, Bill-Axelson et al. (2005) did report a selection of side-effects for both the watchful waiting and radical prostatectomy arms. However, utilities were not measured within the trial and specific utility weights were not available for the majority of the reported outcomes (e.g. pain during intercourse).

The main quality of life conclusions from the RCT were published by Steineck et al. (over 4 rather than the full 10 years). The authors concluded that erectile dysfunction (80% versus 45%) and urinary leakage (49% versus 21%) were more common in the radical prostatectomy treatment arm whereas urinary obstruction was more common in the watchful waiting arm (44% versus 28%). Levels of bowel function, anxiety, depression and well being were all reported as being similar across the trial arms. Therefore the following and only assumptions were included in the model with respect to reductions in health related quality-of-life as a result of side-effects: 35% more people receiving radical prostatectomy experienced erectile dysfunction and 28% more people experienced urinary leakage compared to watchful waiting. It was also assumed that 16% more people in the watchful waiting arm experienced urinary obstruction compared to those receiving radical prostatectomy. In the main baseline scenario, the side effects were assumed to occur at the beginning of the model and to be permanent. Sensitivity analysis was used to test the robustness of the results to these and other assumptions.

Health-Related Quality-of-Life (HRQoL) / Utility weights

The systematic literature review revealed that there have been a reasonable number of HRQoL studies involving men with prostate cancer. However, relatively few have reported utilities, which are required to incorporate HRQoL into economic evaluations in order to estimate Quality-Adjusted Life-Years (QALYs). Therefore, it was assumed that men aged 65 years with localised disease had levels of health equivalent to the general population. Using the UK EQ-5D dataset, this is equivalent to a utility[4] value of 0.78[5]. The utility value associated with metastatic disease was taken from Cowen et al. (1999) as 0.42 [6]. Cowen et al. (1999) also reported a number of utility scores with respect to treatment-related side-effects for localised prostate cancer; a mean of 0.69 for impotence (taken herein to be equivalent to sexual dysfunction) and 0.57 for incontinence (taken herein to represent both urinary obstruction and leakage)[6].

Further simplifying assumptions were required to operationalise the model with respect to incorporating reductions in health-related quality-of-life as a consequence of side effects. Specifically, a disutility weight was calculated for the three possible side effects by subtracting the side-effect specific utility from the utility value for localised disease:

Disutility for impotence = 0.78 – 0.69 = 0.09

Disutility for urinary obstruction / leakage = 0.78 – 0.57 = 0.21

[4] Utility values of 0 and 1 are taken to equal death and perfect health respectively. States of health between death and perfect health are therefore taken to have utility values somewhere between these two points.

[5] A number of utility values representing clinically localised prostate cancer were available, however, they were not adjudged to differ significantly from 0.78 and were not always UK specific.

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

The disutility weights were also assumed to be additive, meaning for example, that a person with localised disease, with impotence and urinary obstruction experienced a utility of 0.48 (0.78 – 0.09 – 0.21). Whereas, for a person with metastatic disease with impotence but no urinary obstruction, the utility value was 0.33 (0.42 – 0.09).

Costs

Costs were only considered from a National Health Service's perspective. The costs of treatment and PSA testing were taken from published sources, mostly Hummel et al. (2003), Calvert et al. (2003) and the NHS Cost Index (Table 87). The costs of complications associated with treatments for localised prostate cancer have not been well documented, therefore the following assumptions were made. For urinary obstruction, all patients were assumed to receive a transurethral resection of the prostate (TURP). An annual cost of treating incontinence was also included, although it is noted that the study from which this value was taken relates to men with severe urinary storage problems and was not prostate-cancer specific; no published costs for urinary problems in men with prostate cancer could be identified.

Table 87 Unit cost estimates

Cost	Estimate	Source
Radical Prostatectomy	£5603	Calvert et al. (2003)
Hormonal Therapy (annual)	£2612	Hummel et al. (2003)
Transurethral Resection (elective)	£2009	NHS Unit Costs [a]
Urinary Incontinence	£115 (per annum)	Turner et al. [b]
Twice yearly PSA test	£154	Calvert et al.(2003)
External Beam Radiotherapy (30 fractions)	£3600	NHS Unit Costs (@ £120 per fraction)
Two Phase Intensity Modulated Radiotherapy	£10000	Assumption
Brachytherapy	£6304	Hummel et al. (2003)
Cryotherapy	£7942	Hummel et al. (2003)]
HIFU	£7500	EDAP-TMS – quoted in comments on consultation draft

[a]One-off cost

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

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

Discounting

In the base case analysis, costs and health outcomes were both discounted at 3.5% per annum in line with NICE recommendations (NICE 2004).

Sensitivity Analysis

A number of one-way sensitivity analyses (where one input variable is changed, the model re-run and a revised ICER calculated) were undertaken to highlight the variables that were the most important in terms of determining the cost-effectiveness of treatment.

Threshold analysis was also undertaken to determine how effective, in terms of additional QALYs, other therapies (brachytherapy, standard external beam radiotherapy, intensity modulated radiotherapy, HIFU and cryotherapy) would need to be, to be considered cost-effective compared to watchful waiting. Threshold analysis is undertaken by fixing the threshold willingness to pay for an extra unit of health outcome, and determining the size of health benefit survival required to produce an incremental cost-effectiveness ratio (ICER) equal to this willingness to pay value[7]. NICE does not have an absolute level indicating cost-effectiveness. However, NICE's method document suggests that technologies with ICERs above £30,000 per additional QALY are unlikely to be considered cost-effective in the absence of 'robust' evidence (NICE 2007). Therefore, £30,000 per additional QALY was taken to represent the threshold willingness to pay.

Results

The baseline results are shown in Table 88. The results show that radical prostatectomy costs approximately £4400 more than watchful waiting, but that radical prostatectomy produces an average discounted increase in life expectancy of 0.5 years. This is equivalent to an ICER of approximately £9000 per life-year gained. When no post-operative complications were assumed, radical prostatectomy was also associated with approximately 0.5 extra QALYs, with an associated ICER of £7918. However, when treatment related side effects were assumed to occur, as described in the methods section, radical prostatectomy was 'dominated' by watchful waiting (the main baseline result). That is, radical prostatectomy was more costly and less effective than watchful waiting.

Table 88 Baseline incremental cost-effectiveness ratios

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

RP, Radical Prostatectomy; WW, Watchful Waiting; ICER, incremental cost-effectiveness ratio

In QALYs[1], there is 0 probability of complications following treatment whereas in QALYs[2], the additional probabilities of urinary obstruction, urinary leakage and impotence are assumed.

[7] An incremental cost-effectiveness ratio (ICER) is calculated by dividing the difference in health benefits (in this instance, additional life-years or QALYs) between the different treatment options, into the difference in costs.

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

Sensitivity Analysis

Sensitivity analysis was performed with respect to the scenario that assumed the possibility of side effects (i.e. the main baseline result). Analysis showed that the baseline ICER was not sensitive to changes regarding, the costs of watchful waiting or the costs of metastatic disease. However, the ICER was found to be extremely sensitive to differing assumptions regarding the possible side effects associated with radical prostatectomy and watchful waiting. For example, when the additional proportion of people undergoing watchful waiting who experienced urinary obstruction was assumed to increase to 40% (from 16%), the ICER was found to be £20,155 per QALY if radical prostatectomy was used instead of watchful waiting. Thus, radical prostatectomy under this assumption appears to be a lot more cost-effective than under the baseline assumptions. The ICER was similarly sensitive to the probability of urinary leakage. For example, when the probability of urinary leakage following radical prostatectomy was assumed to be 9%, the ICER equalled £30,000 per additional QALY. However, because the disutility associated with impotence was relatively small (0.09) compared to the disutility associated with urinary problems (both 0.21), the baseline results were not so sensitive to the probability of people becoming impotent post-surgery.

The side effect data from the Bill-Axelson et al. (2005) are only published in detail after a mean follow-up period of 4-years. When it was assumed that all treatment related side effects resolved after 4 years, the main baseline ICER was £33,926 if radical prostatectomy was used instead of watchful waiting.

One-way sensitivity analysis also showed that the baseline ICERs were relatively sensitive to the cost of radical prostatectomy. However, only when the cost reduced to under £1000 per patient (equivalent to 18% of its original costs), was it judged to be cost-effective compared to watchful waiting at the £30,000 per QALY gained level.

The baseline model did not include the possibility of patients developing hormone-refractory prostate cancer. However, as a proxy, a threshold analysis was undertaken to demonstrate how costly treatment for hormone-refractory prostate cancer would need to be for radical prostatectomy to be cost-effective (at the £30,000 per QALY gained level) compared to watchful waiting. This value was found to be approximately £30,000 per year. Considering the costs quoted in a recent NICE Assessment Report for using docetaxel in combination with a steroid, a cost of £30,000 per year is highly unlikely (http://guidance.nice.org.uk/page.aspx?o=285230).

The baseline ICER was shown to be sensitive to the relative risk of survival. However, only when the relative risk was reduced to approximately 0.04 (from 0.56), was radical prostatectomy cost-effective at the £30,000 per QALY gained level. Given the lower 95% confidence interval reported by Bill-Axelson et al. (2005) of 0.36, this scenario is considered to be unlikely.

No sub-group specific relative risk of survival was reported by Bill-Axelson et al. (2005) for people with more advanced disease (higher Gleason scores), as it was not found to be a significant predictor of disease-specific mortality. However, disease-specific mortality was shown to differ by age. One-way sensitivity analysis showed that expected costs and QALYs for the two different treatment options differed markedly when different starting ages were assumed. However, in all instances, radical prostatectomy remained the dominated option.

In the absence of suitable RCT data, an estimate was made of the relative risk of disease-related survival that would be required for men with Gleason scores above 6. This was attempted by assuming men with Gleason scores above 6 had double the baseline risk of cancer related death compared with those enrolled in the Bill-Axelson RCT (Bill-Axelson et al. 2005). To achieve a threshold willingness-to-pay per QALY gained of £30,000, a relative risk of approximately 0.4 was required. When the baseline risk was quadrupled, this relative risk increased to approximately 0.59, which is above the original baseline relative risk as reported by Bill-Axelson et al. (2005).

Threshold analysis was also conducted in order to calculate how many QALYs the various other therapies (brachytherapy, standard external beam radiotherapy, intensity modulated radiotherapy, HIFU and cryotherapy) would need to produce in order to be cost-effective[8].

The original intention was to perform this analysis in relation to the expected costs and QALYs of treating men with radical prostatectomy. However, since in the main baseline result, radical prostatectomy was dominated by watchful waiting, this would have been nonsensical, as it is not considered to be an economically relevant option in the first instance. Therefore, threshold QALYs were calculated in relation to watchful waiting (using a threshold willingness-to-pay of £30,000 per additional QALY).

The results from the threshold analysis showed that relatively modest gains in QALYs are required over 20 years if any of the listed treatments are to be considered cost-effective (Table 89). For example, external beam radiotherapy cost an additional £2103 than watchful waiting (£8288 - £6185), meaning that 0.07 QALYs are required to make it cost-effective compared to watchful waiting, over a 20 year period. For IMRT, the most costly option at £14688, the equivalent value was 0.29 QALYs, or an additional 4.3 months of perfect health over 20 years.

Table 89 Results from the threshold analysis over a 20 year period compared to watchful waiting.

Treatment	Expected Cost of Treatment	Required QALY Increase[a]	Equivalent Health Gain In Months[b]
External beam	£8288	0.07	1
Brachytherapy	£10992	0.16	2
HIFU	£12188	0.20	2.4
Cryotherapy	£12630	0.21	2.6
IMRT	£14688	0.28	3.4

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

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

[8] The main assumption underpinning this analysis is that these treatments have been assumed to be equally effective as radical prostatectomy in terms of slowing the progression of the underlying cancer. Thus, any results are contingent on this assumption.

Discussion

The primary aim of this study was to perform an economic evaluation of watchful waiting versus radical prostatectomy using the 10 year RCT published by Bill-Axelson et al. (2005) (in men with Gleason scores of 5-6). The results suggest that the cost-effectiveness of radical prostatectomy is highly dependent on the choice of health outcomes included in the analysis. If only patient survival is considered, then radical prostatectomy is arguably cost-effective. However, when quality-of-life considerations with respect to both the underlying prostate cancer and treatment-related side effects are included, watchful waiting becomes the dominant option. These results are in line with conclusions drawn by Calvert et al. (2003) The sensitivity analysis, however, showed that the results were not robust to certain assumptions, specifically surrounding the health-related effects and treatment-related side-effects; a conclusion also drawn by Hummel et al. (2003). Importantly, the results suggest that the cost-effectiveness of radical prostatectomy (and all treatments for that matter) is more dependent on the side-effect profiles than the relative risk of disease progression. Therefore, in order to be able to draw firmer conclusions regarding the cost-effectiveness of radical prostatectomy, more needs to be known about the relative probabilities of the side-effects, their duration and impact on health-related quality-of-life (it is anticipated that the ongoing MAPS study will provide more information in these issues https://www.charttrials.abdn.ac.uk/maps/faq.php as will the ProtecT study http://www.hta.nhsweb.nhs.uk/project/1230.asp).

In the absence of RCT data, threshold analyses were undertaken to calculate how many additional QALYs other therapies (brachytherapy, standard external beam radiotherapy, intensity modulated radiotherapy, HIFU and cryotherapy) would need to produce in order to be cost-effective at a £30,000 per additional QALY level. Radical prostatectomy was ruled out as an option, therefore these QALY gains were calculated with respect to watchful waiting. The results suggest that relatively modest improvements are required for these treatments to be cost-effective. For example, external beam radiotherapy only needed to generate an extra 0.07 QALYs over a 20 year period compared to watchful waiting for it to be considered cost-effective. This is equivalent to approximately one extra month of perfect health. For IMRT, the most costly option, the equivalent figure was 3.4 months. Thus while the absence of randomised controlled trials prevents a robust economic evaluation of these 'newer' treatments, it is possible to conclude that the scope for them to cost-effectiveness is relatively large. Indeed, it is feasible that they could be cost-effective even if it is proved that their greatest impact is on improving the side effects more commonly associated with the 'older' treatments. In the mean time, decision-makers will need to judge how likely it is that these QALY gains will be realised.

There are a number of limitations with this economic evaluation. Firstly, the cost-effectiveness of active surveillance has not been estimated. This is partly because active surveillance has not been subject to a RCT but also because modelling its cost-effectiveness would require a much more complicated model. Assuming that PSA testing is the favoured method of monitoring for progressive disease, PSA levels would themselves need to be modelled, pre and post treatment, rather than cancer stages as has been performed herein. However, the relative effect of treatment on PSA would still be uncertain given the absence of RCT data. Therefore, even if it could be concluded that radical prostatectomy is cost-effective compared with watchful waiting, it is unclear whether it is cost-effective compared with a policy of active surveillance. Similarly, it is also unclear how cost-effective watchful waiting would be compared to active surveillance. Ultimately, however, the cost-effectiveness of active surveillance is likely to depend on a combination of the proportion of patients who develop progressive disease, the ability to accurately detect progressive disease and treatment efficacy in patients with progressive disease.

A second limitation was that a robust sub-group analysis was not performed for men with differing Gleason scores. This is typically performed using a sub-group specific relative risk of disease progression derived from RCTs and using a sub-group specific relative risk of death. However, this information was not available, and indeed was reported by Bill Axelson et al. (2005) not to be statistically significant at the 5% level in a pre-planned sub-group analysis. However, as an indicator to cost-effectiveness, the baseline

risks of death were doubled and quadrupled for men with Gleason scores of >6, in order to ascertain how effective treatment should be in terms of preventing deaths in order to be cost-effective. The results showed that when the baseline risk of prostate-specific death was quadrupled, and a relative risk akin to the value reported by Bill-Axelson et al. (2005) was assumed, radical prostatectomy was cost-effective at the £30,000 per QALY gained level. However, it is unclear how plausible a relative risk estimate this is in the absence of RCT data in this patient group.

The major conclusion that can be drawn from this evaluation is that the cost-effectiveness of all the modelled treatment options for men with clinically localised prostate cancer is highly dependent on the side effects (and therefore reductions in health-related quality-of-life) associated with each of the treatments. Indeed, the baseline assumptions suggest that radical prostatectomy should not be an option for people with Gleason scores of <6 because of its associated post-operative complications. However, different assumptions regarding side effect profiles dramatically altered the findings. Thus, future studies that attempt to quantify these relative side-effect profiles would help to produce more accurate estimates of cost-effectiveness.

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Conventional radiotherapy versus watchful waiting

Short summary

No randomised trials comparing conventional radiotherapy with watchful waiting were found. Evidence about outcomes after conventional radiotherapy comes from observational studies, or randomised trials comparing radiotherapy techniques. A systematic review (Nilsson *et al.* 2004) identified 26 retrospective observational studies (17018 patients) which reported outcomes after conventional external beam radiotherapy. A large cohort study (Wong *et al.* 2006) comparing unspecified radiotherapy (conventional, conformal external beam radiotherapy or brachytherapy) with watchful waiting, found an overall survival advantage with radiotherapy.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOMES
Men with localised or locally advanced prostate cancer, of any age, with no prior treatment.	Conventional radiotherapy	• Watchful waiting also • Brachytherapy • EBRT • Conformal Radiotherapy • Conventional radiotherapy • Cryosurgery • HIFU	• overall survival • disease-specific survival • biochemical disease-free survival • time until next intervention • 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)

Evidence summary

<u>Conventional radiotherapy versus watchful waiting</u>

No randomised trials comparing conventional radiotherapy with watchful waiting were found. Evidence about outcomes after conventional radiotherapy comes from observational studies, or randomised trials comparing radiotherapy techniques (see conformal versus conventional radiotherapy section). A systematic review (Nilsson *et al.* 2004) identified 26 retrospective observational studies (17018 patients) reporting outcomes after conventional external beam radiotherapy.

Overall survival

The Nilsson review did not analyse overall survival, but five of the included retrospective series (3152 patients) reported this outcome. In men treated with conventional radiotherapy, overall survival at five years, ten years and fifteen years after diagnosis was of the order of 86%, 66% and 50% respectively.

Disease-specific survival

Evidence from retrospective case series suggests that ten year prostate cancer specific survival in men treated with conventional radiotherapy is of the order of 90%, 75% and 50% for men with well differentiated, moderately differentiated and poorly differentiated disease respectively (Nilsson *et al.* 2004).

Biochemical disease-free survival

The Nilsson review reported that the rate of biochemical control after conventional radiotherapy correlates with pre-treatment PSA level. At five years, disease free survival for men with pre-treatment PSA of <4ng/ml, 4–10 ng/ml, 10–20 ng/ml and more than 20 ng/ml was of the order of 85%, 55%m 45% and 15% respectively.

Side effects

The Nilsson review concluded that conventional radiotherapy with curative intent can be administered safely; however, there was no detailed analysis of side effects. Randomised trials comparing conventional and conformal radiotherapy have reported acute and late toxicity after conventional radiotherapy (see section on radical prostatectomy).

Unspecified radiotherapy versus watchful waiting

Two cohort studies ((Wong *et al.* 2006; Aus *et al.* 2005) have compared outcomes in men treated with radiotherapy with those in men managed with watchful waiting, without specifying radiotherapy technique.

Overall survival

Wong and co-workers (Wong *et al.* 2006) reported overall survival in a population based cohort of 44630 elderly American men with clinically localised prostate cancer. They attempted to adjust statistically for prognostic risk factors and treatment selection bias. The hazard ratio of mortality in 18249 men treated with radiotherapy compared to 12608 managed with watchful waiting was 0.81 [95% CI 0.78 – 0.85], suggesting a survival advantage with radical radiotherapy.

Disease-specific survival

Aus and co-workers (Aus *et al.* 2005) reported disease specific mortality in a Swedish population based cohort of men without metastases and younger than 75 at diagnosis of prostate cancer. They used Cox proportional hazards regression, with tumour grade, PSA level and TNM stage as covariates, to examine the effects of treatment. The 289 men treated with radiotherapy did not have significantly lower disease specific mortality than the 1252 men managed with watchful waiting (HR 1.01, 95% CI 0.72 to 1.41; p=0.98).

Quality of life

Nilsson and co-workers (Nilsson *et al.* 2004) reviewed ten studies of quality of life after curative radiotherapy, with the conclusion that despite physical deterioration, satisfaction with treatment has generally been high and overall quality of life good.

Evidence Tables

(Nilsson *et al.* 2004)
Design: Systematic review of cohort studies (therapy), evidence level: 2- Country: International, setting: Tertiary care **Inclusion criteria** Papers reporting radiotherapy for prostate cancer published up to January 2003 and included in Medline. **Exclusion criteria** - **Population** - **Interventions** 26 non randomised studies (17018 patients) reported outcomes after conventional external beam radiotherapy. **Outcomes** Prostate cancer specific survival, biochemical recurrence free survival, safety of radiotherapy. **Follow up** Length of follow up varied between studies. **Results** There was no statistical meta-analysis, but a narrative summary of outcomes as follows: Disease-specific survival: Evidence from retrospective case series suggests that ten year prostate cancer specific survival after conventional RT is of the order of 90%, 75% and 50% for men with well differentiated, moderately differentiated and poorly differentiated disease respectively. Biochemical disease-free survival The rate of biochemical control after conventional radiotherapy was related to pre-treatment PSA level. At five years, disease free survival for men with pre-treatment PSA of <4ng/ml, 4-10 ng/ml, 10-20 ng/ml and more than 20 ng/ml was of the order of 85%, 55%m 45% and 15% respectively. Adverse effects The review concluded that conventional EBRT with curative intent can be administered safely; however, there was no detailed analysis of side effects. **General comments** -

(Aus *et al.* 2005)
Design: Prospective cohort study (therapy), evidence level: 2+ Country: Sweden, setting: Community **Inclusion criteria** Men recorded in a Swedish regional population-based registry of 8887 pa-

tients with newly diagnosed prostate carcinoma from 1987 to 1999. Separate analysis was done for men with or without metastases at diagnosis.

Exclusion criteria -

Population number of patients = 8887, age range 40 to 96 years, median age = 75 years.

Interventions Diagnostic and staging investigations (not specified in detail). Primary treatment was either watchful waiting, radical prostatectomy or radiotherapy (64 - 70 Gy). After watchful waiting secondary treatment was: radical therapy for 2.5%, palliative hormones for 33.5% and no further treatment for 64% of men. In men treated with curative intent secondary treatment was hormones in 18.1% of cases, 81.9% received no further treatment.

Outcomes Overall survival, prostate cancer specific survival

Follow up The median follow-up was 80 months for surviving patients.

Results Analysis was done for the subgroup of 4121 men without metastases at diagnosis of prostate cancer. The authors used Cox proportional hazards regression, with tumour grade, PSA level and TNM stage as covariates, to examine the effects of treatment.

COMPARISON IN MEN WITH LOCALISED OR LOCALLY ADVANCED PROSTATE CANCER, WITH NO METASTASES	WATCHFUL WAITING	RADICAL PROSTATECTOMY	RADICAL RADIOTHERAPY	OVERALL RESULT
Disease specific survival	HR = 1	for RP vs. WW, HR = 0.40 [95% CI 0.27-0.59] (p<0.00001)	for RT vs. WW, HR = 1.01 [95% CI 0.27-0.59] (p=0.98)	Suggests disease specific survival benefit for radical prostatectomy

General comments -

(Wong *et al.* 2006)

Design: Retrospective cohort study (), evidence level: 2++

Country: United States, setting: Community

Inclusion criteria Men aged between 65 and 80 who had an incident prostate cancer diagnosis between 1991 and 1999 in the Medicare database. Only those with Gleason score of 7 or less, T1 or T2 tumours were included.

Exclusion criteria Men diagnosed at death. T3 or T4 disease, men with Gleason score of 8 or more, men with unknown T stage or grade, men with metastases. Men who had enrolled in a managed care plan from 3 months before to 6 months after diagnosis. Men who received hormonal therapy only. Men who died within a year of diagnosis.

Population number of patients = 44630.

Interventions The study compared observation alone, with radical prostatectomy and radiotherapy (external beam or brachytherapy).

A model was developed to predict the odds of receiving treatment based on comorbidity, disease, patient and sociodemographic variables (the propensity score).

Comparison of overall survival for each treatment group was done using Cox proportional hazards methods, adjusting for propensity scores.

Outcomes Overall survival (the interval from the date of diagnosis to the date of death recorded in Medicare).

Results

COMPARISON IN MEN WITH CLINICALLY LOCALISED PCA	OBSERVATION ONLY	RADICAL PROSTATECTOMY	RADICAL RADIOTHERAPY	OVERALL RESULT
Mortality (hazard ratio compared with observation)	HR 1	HR = 0.50 (95% CI 0.47 to 0.53)	HR = 0.81 (95% CI 0.78 to 0.85)	Favours radical treatment over observation only

Health Economics

The health economics analysis relating to this topic can be found at the end of section 4.2.

Reference List

Aus, G., Robinson, D., Rosell, J., Sandblom, G. & Varenhorst, E. (2005) Survival in prostate carcinoma - Outcomes from a prospective, population-based cohort of 8887 men with up to 15 years of follow-up: Results from three counties in the population-based national prostate cancer registry of Sweden. *Cancer,* 103: 943-951.

Nilsson, S., Norlen, B. J. & Widmark, A. (2004) A systematic overview of radiation therapy effects in prostate cancer. [Review] [390 refs]. *Acta Oncol,* 43: 316-381.

Wong, Y. N., Mitra, N., Hudes, G., Localio, R., Schwartz, J. S., Wan, F., Montagnet, C. & Armstrong, K. (2006) Survival associated with treatment vs observation of localized prostate cancer in elderly men. *JAMA,* 296: 2683-2693.

3.4 Radical prostatectomy

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

PICO question

Population	Intervention	Comparator	Outcomes
Men undergoing radical prostatectomy for clinically localised (N0, Nx) prostate cancer (covariates – surgical volume)	• Open prostatectomy (including retropubic and transperineal approaches) • Laparoscopic prostatectomy • Robot-assisted laparoscopic radical prostatectomy	Each other	• Overall survival • Disease-free survival • Biochemical disease-free survival • Treatment-related morbidity (transfusion rate) • Treatment-related mortality • Adverse events (incontinence, erectile dysfunction) • Health-related quality of life • Operating time • In-patient hospital stay • Positive margins

How the information will be searched

Sources to be searched	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science and Biomed Central. Consideration will be given to subject-specific databases and used as appropriate.
Can we apply date limits to the search	We will update HTA vol 16 no. 41
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	See search strategy of HTA vol 16 no 41.
List useful search terms.	

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? List subgroups here and planned statistical analyses	We will use the evidence table for randomised trials (NICE guidelines manual appendix J). The RCT checklist will be used (NICE guidelines manual appendix C). Time to events meta-analysis will be done for survival outcomes. Dichotomous outcomes will be meta-analysed using risks ratios or odds ratios. Given the numerous interventions being compared a mixed treatment comparison may be appropriate.

Methods

Selection of studies

The information specialist (EH) did the first screen of the literature search results. Two reviewers (KC and SOC) selected eligible studies by comparing their title and abstract to the inclusion criteria in the PICO question. Due to the wide availability of studies published since 2006, only studies which were

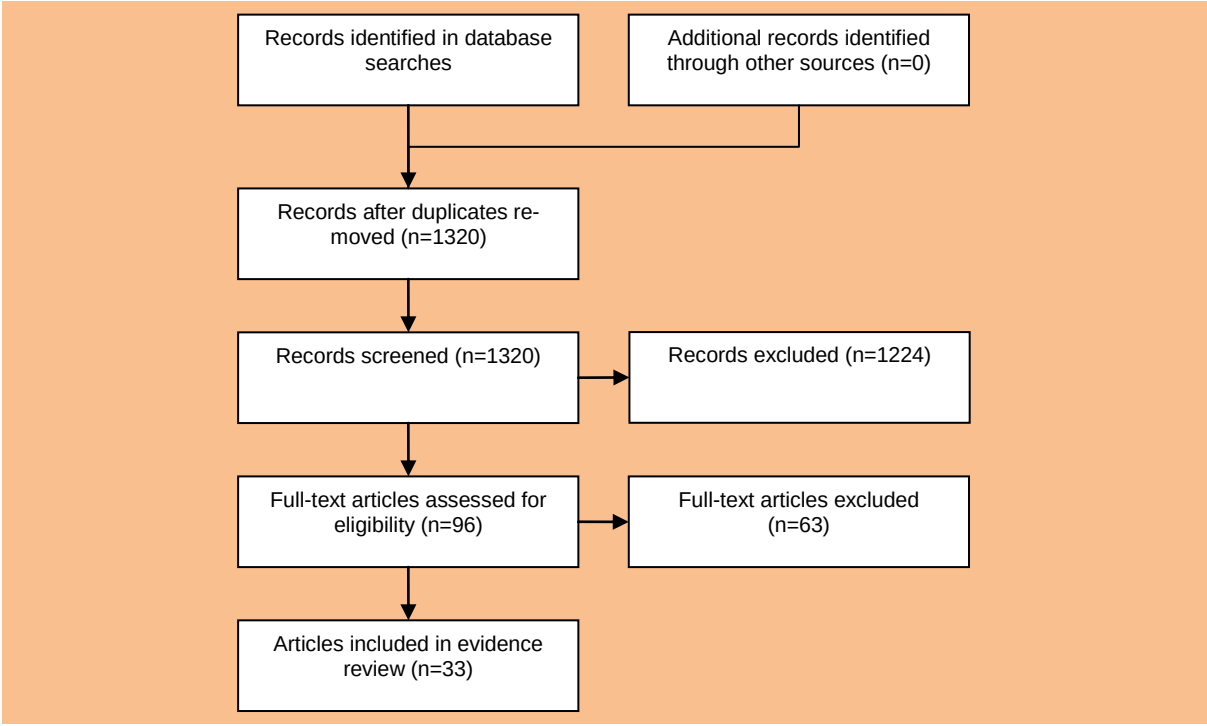
identified as clearly comparative in nature from the abstract were included. Studies were included if they stated that patients had clinically localized prostate cancer or if ≥ 90% of participants were stage T1-T2. Conference abstracts were excluded unless they reported the results of a randomised controlled trial. A third reviewer (NB) checked the included studies and a random selection of the excluded studies. The full articles were then obtained for possibly eligible studies and checked against the inclusion criteria.

Analysis

The HTA undertook a network meta-analysis comparing laparoscopic with robot-assisted prostatectomy. However, data for open, laparoscopic and robot-assisted laparoscopic prostatectomy were extracted and reported. This data was taken from the HTA and combined in a meta-analysis with studies identified by the new search. Where a study reported outcomes for both perineal open and retropubic open prostatectomy, the latter was used for a comparator with laparoscopic or robot-assisted laparoscopic prostatectomy. Information on the effect of surgical volume on the rate of positive surgical margins was extracted from the HTA and reported. For the meta-analysis, the median was used where the mean was not reported and where standard deviation was not reported it was calculated from a linear regression of log(SD) on log(mean/median) from studies where standard deviation was reported (except where there were not enough SDs reported to conduct a reliable linear regression).

Results

Results of the literature searches



The literature searches identified 1320 possibly relevant articles of which 96 were ordered in full text. Thirty-three articles referring to 31 studies were included; five of these had previously been included in the HTA and were excluded. Twenty-eight articles referring to 26 new studies were included alongside the HTA.

Characteristics of included studies

Of the included studies, two (Guazzoni 2006; Asimakopoulos 2011) were RCTs and the rest were observational studies. Four of the studies were only available as abstracts. None of the studies were set in the UK.

Intervention

Three (12%) studies compared OP versus LP versus RALP, six (24%) studies compared OP versus LP, seven (28%) compared OP versus RALP, and nine (36%) compared LP versus RALP. Of the included studies which reported outcomes for OP, seven (44%) did not specify whether they were retropubic or perineal, nine (56%) assessed retropubic OP, three (12%) (Salomon 2002; Namiki 2006; Mirza 2011) reported outcomes for both retropubic and perineal OP, and one (4%) included both retropubic and perineal but reported overall OP outcomes.

Outcomes

The definitions used to determine biochemical recurrence varied between studies; three (16%) used a PSA > 0.3 ng/ml, four (21%) used a PSA > 0.2 ng/ml, two (1%) used two consecutive PSAs > 0.2 ng/ml, three (16%) used a PSA > 0.1 ng/ml, two (1%) used any detectable post-operative PSA, and five (26%) gave no definition.

Where reported, definitions of urinary incontinence varied, the most common being use of pads. Definitions of erectile dysfunction and potency also varied were reported, the most common being the inability to have sexual intercourse. Seven different tools were used by 14 studies reporting quality of life outcomes, the most common being the UCLA-PCI followed by the VAS and EPIC (three studies used more than one tool).

Evidence statements

Overall survival

Studies varied considerably in length of follow-up and outcome reported; therefore meta-analysis was not possible. One study (Poulakis 2007) provided very low quality evidence of no deaths following either OP or LP (time of follow-up not reported).

Three very low quality studies compared overall survival following OP and RALP. Carlsson et al. (2010) found a 0.2% prevalence of death within 30 days following OP, but none following RALP. Krambeck et al. (2008) found no deaths due to prostate cancer to occur at 1.3 years following OP or RALP but overall mortality was 0.8% and 1.6% respectively. While Tewari et al. (2003) reported no deaths following either OP or RALP at a mean of 0.6 and 1.5 years after surgery.

Four very low quality studies (Hu 2006; Menon 2002; Rozet 2007; Asimakopoulos 2011) found no deaths following either LP or RALP (follow-up 3-12 months where reported).

Disease-free survival

No studies reporting disease-free survival were found.

Biochemical disease-free survival

Ten studies provided very low quality evidence of PSA recurrence following LP compared with OP with varying results over a wide range of follow-up durations. Three of these (Artibani 2003; Poulakis 2007; Lama 2009) were combined in a meta-analysis; they found no significant difference in risk of biochemical recurrence at 12 months following LP compared to OP (p=0.70).

Nine studies provided very low quality evidence of PSA recurrence following RALP compared with OP, these again varied in length of follow-up and findings. Three of the studies (Schroeck 2008; Krambeck 2008; Ou 2009) contributed to the meta-analysis and found a borderline significantly lower rate of biochemical recurrence at 12 months following RALP compared with OP. The RR of 0.70 (95% CI 0.50-0.99) suggests that for every 100 patients undergoing prostatectomy, three fewer would experience biochemical recurrence at 12 months if a robot-assisted laparoscopic technique was used.

One very low quality study found no significant difference in PSA recurrence between LP and RALP groups at 3 months (2.3% and 1.4% respectively) (Wolanski 2012). Another low quality study (Magheli 2011) found that 6% of patients in both the LP and RALP groups had experienced bio-

chemical progression at 5 years. Another very low quality study by Drouin et al. (2009) found that 10% and 12% of patients undergoing RALP and LP respectively experienced biochemical progression at a mean of 4.1 years. Six studies (Artibani 2003; Krambeck 2009; Lama 2009; Ou 2009; Poulakis 2007; Schroek 2008) of very low quality were included in a network meta-analysis in 2010 but not evidence of a difference between the two techniques was found. This is unlikely to have changed since 2010 as no new studies have been published reporting this information.

Treatment-related morbidity (transfusion rate)

Eighteen studies provided low quality evidence of blood transfusion rates in patients undergoing LP compared with OP; all but two found a higher rate in patients undergoing OP. Seventeen of the studies contributed to the meta-analysis and found a significantly lower rate of the blood transfusion during and following LP compared with OP. The OR of **0.29 (95% CI 0.19-0.45)** suggests that for every 100 patients undergoing prostatectomy, **41** fewer would need a blood transfusion if a laparoscopic technique was used.

Thirteen studies provided low quality evidence of blood transfusion rates in patients undergoing RALP compared with OP; all of which found a higher rate in patients undergoing OP. All of the studies contributed to the meta-analysis and found a significantly lower rate of the blood transfusion during and following RALP compared with OP. The OR of **0.29 (95% CI 0.19-0.43)** suggests that for every 100 patients undergoing prostatectomy, 11 fewer would need a blood transfusion if a robot-assisted laparoscopic technique was used.

Ten studies provided very low quality evidence of blood transfusion rates in patients undergoing RALP compared with LP; findings varied across the studies. Nine of the studies contributed to the standard meta-analysis which reported no significant difference in blood transfusion rates between RALP and LP (p=0.52). Thirty studies of very low quality were included in a network meta-analysis in 2010 but no evidence of a difference between the two techniques was found. The predicted transfusion rates were 3.5% and 5.0% for RALP and LP respectively. Following restriction of the network meta-analysis to studies at low risk of bias there remained no significant difference. This result is unlikely to have changed since 2010 as none of the four studies (Stolzenburg 2010; Asimakopoulos 2011; Wolanski 2012; Stolzenburg 2013) published since then found a significant difference in blood transfusion rates.

Treatment-related mortality

No studies reporting data on treatment-related mortality were found.

Adverse events (incontinence, erectile dysfunction)

Incontinence

Eleven studies compared incontinence following LP to OP (see Table 90). A variety of different definitions and timescales were used to measure incontinence and results were inconsistent. Five studies of very low quality reported incontinence at 6 months following prostatectomy, four of which were included in a meta-analysis and found no significant difference in incontinence rates between LP and OP (p = 0.27). Eight studies of very low quality reported incontinence at 12 months following prostatectomy, five of which were included in a meta-analysis which found no significant difference in incontinence rates between LP and OP (p = 0.32).

Seven studies compared incontinence following RALP to OP (see Table 90). A variety of different definitions and timescales were used to measure incontinence and results were inconsistent. Two studies of low quality reported incontinence at 6 months following prostatectomy; one of which found a significantly lower rate following RALP compared to OP. The OR of 0.37 (95% CI 0.17-0.82) suggests that for every 100 patients undergoing OP 10 less would be incontinent if they had undergone RALP. Six studies of very low quality reported incontinence at 12 months following prostatectomy, five of which were included in a meta-analysis which found no significant difference in incontinence rates between RALP and OP (p = 0.08).

Eight studies of very low quality compared incontinence following RALP to LP. Two studies (Asimakopoulos 2011; Willis 2011) reporting incontinence at 12 months following prostatectomy were in-

cluded in a meta-analysis which found no significant difference in incontinence rates following RALP compared to LP (p=0.31). Ten studies of very low quality were included in a network meta-analysis in 2010 but no evidence of a difference between the two techniques at 12 months was found. This result is unlikely to have changed since 2010 as neither of the two studies (Willis 2011; Asimakopoulos 2011) published since then found a significant difference in incontinence at 12 months. The probability of urinary incontinence at 12 months predicted by the network meta-analysis was 4.5% and 7.9% for RALP and LP respectively.

Erectile dysfunction

Eight studies compared erectile dysfunction following LP to OP (see Table 90). A variety of different definitions and timescales were used to measure erectile dysfunction and potency and results were inconsistent. Two studies (Ghavamian 2006; Crisan 2010) of very low quality reported erectile dysfunction at 6 months following prostatectomy, when included in a meta-analysis which found a significantly lower rate following LP compared to OP. The RR of 0.74 (95% CI 0.58-0.94) suggests that for every 100 patients undergoing OP, 17 less would experience erectile dysfunction if they had undergone LP. Seven studies (Wagner 2007; Anastadiasis 2003; Dahl 2006; Ficara 2009; Ghavamian 2006; Greco 2010; Lama 2009) of very low quality reported incontinence at 12 months following prostatectomy, five of which were included in a meta-analysis which found no significant difference in incontinence rates between LP and OP (p = 0.63).

Seven studies compared erectile dysfunction following RALP to OP (see Table 90). A variety of different definitions were used to measure erectile dysfunction and potency and results were inconsistent. Four studies (Krambeck 2008; Ficarra 2009; Ou 2009; Nadler 2010) of very low quality reported erectile dysfunction or potency at 12 months following prostatectomy, when included in a meta-analysis they found a significantly lower rate following RALP compared to OP. The RR of 0.61 (95% CI 0.41-0.91) suggests that for every 100 patients undergoing OP, 15 fewer would experience erectile dysfunction if they had undergone RALP.

Five studies of very low quality compared erectile dysfunction following RALP to LP. Joseph et al. (2005) reported that 46% and 36% of patients interviewed at 3 months following RALP and LP respectively required drug aid for erectile function. Fiori et al. (2012) reported rates of 37% and 57% respectively for impotence at 3 months compared to rates of 51.9% and 50.0% respectively by Wolanski et al. (2012) and 86.4% and 91.2% by Stolzenburg et al. (2013). Asimakopoulos et al. (2011) reported rates of 58% and 77% respectively for erectile dysfunction at 12 months following RALP and LP. It was not possible to conduct a network meta-analysis on erectile dysfunction due to the diversity of definitions and types of data reported by the studies.

Health-related quality of life

Nine studies compared quality of life between patients undergoing LP and OP. A variety of different tools and timescales were used to measure quality of life and results were inconsistent (see Table 90). Four studies (Ball 2006; Namiki 2005; Namiki 2006; Soderdahl 2005) of very low quality used the UCLA-PCI, two of these were included in a meta-analysis and found no significant difference in urinary function, urinary bother, sexual function, or sexual bother at 6 or 12 months. Two studies (Namiki 2005; Namiki 2006) of very low quality used the SF-36, when included in a meta-analysis they found no significant difference in physical function, role limitation, bodily pain, mental health, or general health perception at 6 or 12 months.

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

Four studies provided low quality evidence of a difference in quality of life between patients undergoing RALP and LP. Miller et al. (2007) found a significant difference in the physical component of the SF-12 between the two groups at 6 weeks (MD 3.6 95% CI 2.6-4.6) but not the mental component.

Willis et al. (2011) found no significant difference in the urinary function summary score or urinary function, urinary bother, sexual function, or sexual bother subscales of the EPIC between RALP and LP at 12 months. However, there was a borderline significant difference in the urinary irritative/obstructive subscale at 12 months (MD -3.1 95% CI -5.9 to -0.3) in favour of LP. It was not possible to undertake meta-analyses due to differences in the outcomes reported. Ball et al. (2006) found a significant difference in the proportion of patients reaching their baseline score of sexual function at 6 months in favour of RALP using the UCLA-PCI, but not in those reaching the baseline score of sexual bother, urinary function, or urinary bother. While Berge et al. (2013) also used to UCLA-PCI and found no significant difference in urinary function change from baseline between RALP and LP at 12 or 36 months, or in sexual function at 12 months.

Operating time

Twenty-one studies provided very low quality evidence of a difference in operating time between LP and OP; all but one reported a longer operating time for LP surgery than for OP. Nineteen of the studies were included in a meta-analysis which reported a significant mean difference of 73 minutes (95% CI 55-91) between the two techniques in favour of LP ($p < 0.001$).

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

In-patient hospital stay

Eighteen studies provided very low quality evidence of a difference in length of in-patient stay following LP and OP; all were included in a meta-analysis and found a significant reduction in hospital stay for LP compared to OP, with a mean difference of 1.4 days less (95% CI -1.7 - -1.0).

Eleven studies provided very low quality evidence of a difference in length of in-patient stay following RALP and OP; all but one reported a longer operating time for OP surgery than for RALP. Two of the studies were included in a meta-analysis which reported no significant difference in hospital stay between the two techniques ($p = 0.07$).

Seven studies provided very low quality evidence of a difference in length of in-patient stay following RALP and LP; results were inconsistent. Three of the studies were included in a standard meta-analysis which reported no significant difference in length of in-patient stay between the two techniques ($p = 0.32$). No network meta-analysis was possible due to the diversity of summary outcome measures reported.

Positive margins

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

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

Seventeen studies provided very low quality evidence of a difference in the proportion of patients with positive surgical margins following RALP and LP; results were inconsistent. All of the studies were included in a standard meta-analysis which reported no significant difference in the rate of positive margins between the two techniques ($p = 0.96$). Thirty-seven very low quality studies were included in a network meta-analysis in 2010 and found a significant difference in the rate of positive margins. The OR of 0.69 (95% CI 0.51-0.96) suggests that for every 100 patients six fewer will have positive surgical margins following RALP compared to LP.

This conclusion is likely to remain valid as of the eleven studies published since 2010, ten (91%) found no significant difference in positive margin rates between RALP and LP. The remaining study (Magheli 2010) found a significantly higher rate in patients undergoing RALP than in those undergoing LP. The network meta-analysis predicted a probability of positive surgical margins of 18% following RALP compared to 24% following LP. However, these results should be treated with caution as none of the studies reported the same methodology for ascertainment of positive margin status.

Impact of surgical volume

Thirty-four very low quality studies provided information on the number of procedures carried out by participating surgeons. No evidence was found of a trend in the proportion of positive surgical margins with increasing surgeon experience for either LP or RALP (regression modeling; R^2<0.02%).

Inclusion criteria were extended to include 10 case series involving more than 200 patients and reporting the rate of positive margins for a set number of cases performed for either LP or RALP. There was no evidence that learning contributed differently to positive margin rates between the two procedures (p=0.76). The quality of these new studies was not reported.

Table 90 Health-related quality of life and adverse event outcomes reported by included studies

Abbreviations: RALP = robot-assisted laparoscopic prostatectomy; LP = laparoscopic prostatectomy; OP = open prostatectomy; OPP = open perineal prostatectomy; ORP = open retropubic prostatectomy; SD = standard deviation

Study	Tool/definition	Follow-up	Outcome	RALP	LP	OP	
						(OPP)	(ORP)
Health-related quality of life							
Ball (2006)	UCLA-PCI	6 months	Urinary function: % of baseline score	69%	69%	75%	
			Urinary bother: % of baseline score	78%	75%	74%	
			Sexual function: % of baseline score (mean (SD))	43 (43)	25 (21)	33 (33)	
			Sexual bother: % of baseline score (mean (SD))	32 (41)	38 (45)	27 (41)	
	AUA SI	6 months	% of baseline score (mean (SD))	123 (52)	106 (34)	104 (42)	
Berge (2013)	UCLA-PCI	12 months	Urinary function (mean (SD))	77 (22)	79 (23)	-	
			Sexual function (mean (SD))	39 (25)	35 (23)	-	
		36 months	Urinary function (mean (SD))	77 (23)	80 (23)	-	
Guazzoni (2006)	VAS	1 day	Post-operative pain (mean (SD))	-	1.7 (1.45)	2.65 (1.44)	
		3 days	Post-operative pain (mean (SD))	-	1.03 (0.82)	1.53 (1.13)	
Jacobson (2007)	I-PSS	12 months	Mean (SD)	-	5.9 (2.9)	5.8 (5.0)	
Malcolm (2010)	UCLA-PCI	6 months	Urinary function (mean)	69	-	80	
			Urinary bother (mean)	77	-	77	
			Sexual function (mean)	33	-	37	
			Sexual bother (mean)	42	-	28	
		12 months	Urinary function (mean)	74	-	79	
			Urinary bother (mean)	81	-	84	
			Sexual function (mean)	40	-	43	
			Sexual bother (mean)	47	-	40	
		36 months	Urinary function (mean)	78	-	83	
			Urinary bother (mean)	86	-	88	
			Sexual function (mean)	46	-	48	
			Sexual bother (mean)	45	-	58	
Miller (2007)	SF-12 v.2	6 weeks	Mental component (mean (SD))	57.4 (4.3)	58.0 (4.7)	-	
			Physical component (mean (SD))	56.4 (1.7)	52.8 (4.7)	-	
Mirza (2011)	EPIC	12-18 months	Urinary summary (mean)	83	-	86	88
			Bowel summary (mean)	94	-	94	91
			Hormonal summary (mean)	89	-	88	88
			Sexual summary (mean)	44	-	43	39
			Sexual function (mean)	38	-	35	34
Namiki (2005)	SF-36	6 months	Physical function (mean (SD))	-	89.2 (11.1)	87.4 (12.8)	
			Role limitation (mean (SD))	-	85.0 (18.7)	83.2 (23.4)	

			Bodily pain (mean (SD))	-	82.7 (21.9)	86.0 (16.8)	
			General health perception (mean (SD))	-	59.8 (13.3)	64.0 (15.2)	
			Mental health (mean (SD))	-	74.6 (16.1)	75.9 (21.8)	
			Role limitation (mean (SD))	-	82.3 (21.6)	84.3 (20.4)	
			Social function (mean (SD))	-	79.2 (25.2)	85.6 (19.6)	
			Vitality (mean (SD))	-	72.3 (13.8)	71.5 (17.4)	
		12 months	Physical function (mean (SD))	-	87.8 (12.9)	89.5 (11.0)	
			Role limitation (mean (SD))	-	82.4 (25.0)	86.2 (22.0)	
			Bodily pain (mean (SD))	-	84.2 (17.9)	85.9 (17.1)	
			General health perception (mean (SD))	-	61.0 (19.0)	64.5 (16.4)	
			Mental health (mean (SD))	-	75.1 (18.6)	77.8 (18.6)	
			Role limitation (mean (SD))	-	83.1 (22.3)	86.6 (22.3)	
			Social function (mean (SD))	-	84.3 (19.6)	88.3 (19.9)	
			Vitality (mean (SD))	-	70.7 (14.6)	72.4 (19.0)	
	UCLA-PCI	6 months	Urinary function (mean (SD))	-	69.0 (27.5)	80.2 (21.8)	
			Urinary bother (mean (SD))	-	75.0 (28.9)	85.1 (24.4)	
			Sexual function (mean (SD))	-	7.5 (8.5)	13.0 (13.9)	
			Sexual bother (mean (SD))	-	48.8 (33.6)	51.5 (36.4)	
		12 months	Urinary function (mean (SD))	-	75.8 (19.2)	83.3 (20.4)	
			Urinary bother (mean (SD))	-	75.6 (24.2)	89.7 (20.5)	
			Sexual function (mean (SD))	-	8.4 (12.6)	11.7 (15.2)	
			Sexual bother (mean (SD))	-	60.6 (34.8)	59.0 (33.2)	
Namiki (2006)	SF-36	6 months	Physical function (mean (SD))	-	90.5 (9.3)	88.2 (16.7)	82.6 (12.9)
			Role limitation (mean (SD))	-	83.9 (19.6)	80.6 (21.8)	80.1 (26.2)
			Bodily pain (mean (SD))	-	88.8 (16.6)	84.1 (19.1)	82.3 (24.9)
			General health perception (mean (SD))	-	63.6 (14.6)	61.4 (16.3)	60.4 (18.2)
			Mental health (mean (SD))	-	75.7 (15.2)	75.7 (15.2)	74.8 (18.1)
		12 months	Physical function (mean (SD))	-	89.1 (9.0)	87.0 (13.4)	86.0 (14.0)
			Role limitation (mean (SD))	-	82.3 (24.4)	83.2 (20.3)	75.4 (27.1)
			Bodily pain (mean (SD))	-	88.9 (21.8)	86.6 (18.1)	75.8 (25.2)
			General health perception (mean (SD))	-	56.3 (14.5)	61.1 (17.0)	57.3 (20.2)
			Mental health (mean (SD))	-	71.7 (17.2)	71.7 (17.2)	72.5 (20.0)
	UCLA-PCI	6 months	Urinary function (mean (SD))	-	75.1 (27.5)	74.4 (21.8)	71.6 (27.5)
			Urinary bother (mean (SD))	-	78.8 (28.9)	81.3 (24.4)	75.0 (28.9)
			Sexual function (mean (SD))	-	9.7 (8.5)	7.2 (13.9)	7.5 (8.5)
			Sexual bother (mean (SD))	-	54.4 (33.6)	59.3 (36.4)	55.1 (33.6)
		12 months	Urinary function (mean (SD))	-	75.2 (19.2)	77.9 (20.4)	74.9 (19.2)

			Urinary bother (mean (SD))	-	77.8 (24.2)	84.4 (20.5)	80.9 (24.2)
			Sexual function (mean (SD))	-	10.2 (12.6)	10.4 (15.2)	8.8 (12.6)
			Sexual bother (mean (SD))	-	62.2 (34.8)	58.2 (33.2)	53.0 (34.8)
Poulakis (2007)	VAS	6 months	Overall bodily pain: % reaching baseline	-	78%	62%	
			Interference with work or daily activities: % reaching baseline	-	76%	59%	
			Overall disturbance by pain: % reaching baseline	-	76%	63%	
	EORTC QLQ-C30	6 months	Physical functioning: % reaching baseline	-	78%	65%	
			Social functioning: % reaching baseline	-	71%	59%	
			Emotional functioning: % reaching baseline	-	78%	75%	
			Cognitive functioning: % reaching baseline	-	80%	79%	
			Role functioning: % reaching baseline	-	71%	59%	
			Symptoms: % reaching baseline	-	78%	63%	
			Financial impact: % reaching baseline	-	78%	77%	
			Global quality of life: % reaching baseline	-	75%	63%	
Remzi (2005)	VAS	5 days	Post-operative pain (mean (SD))	-	1.6 (0.9) 2.3 (1.2)	2.3 (0.9)	
Soderdahl (2005)	UCLA-PCI	12 months	Urinary function: % of baseline score	-	70.7%	71.0%	
			Urinary bother: % of baseline score	-	83.8%	86.4%	
			Sexual function: % of baseline score	-	35.9	46.0	
			Sexual bother: % of baseline score	-	42.9	39.0	
Tewari (2003)	VAS	1 day	Post-operative pain (mean)	3	-	7	
Wagner (2007)	EPIC-UISS	12 months	% of baseline score	-	64%	73%	
	EPIC-SFSS	12 months	% of baseline score	-	45%	37%	
Willis (2012)	EPIC	6 months	Urinary function summary score (mean (SD))	82.7 (14.9)	83.4 (13.3)	-	
			Urinary function subscale (mean (SD))	81.7 (16.0)	82.7 (16.1)	-	
			Urinary bother subscale (mean (SD))	83.4 (15.5)	84.0 (13.6)	-	
			Urinary irritative/obstructive subscale (mean (SD))	90.5 (11.0)	90.5 (9.1)	-	
			Sexual function (mean (SD))	52.0 (21.6)	37.0 (23.3)	-	
			Sexual bother (mean (SD))	61.3 (25.8)	42.4 (29.3)	-	
		12 months	Urinary function summary score (mean (SD))	83.5 (16.1)	85.6 (13.4)	-	
			Urinary function subscale (mean (SD))	84.6 (16.5)	85.9 (15.4)	-	
			Urinary bother subscale (mean (SD))	82.7 (17.5)	85.5 (14.1)	-	
			Urinary irritative/obstructive subscale (mean (SD))	88.5 (13.6)	91.6 (9.3)	-	
			Sexual function (mean (SD))	51.8 (16.4)	48.0 (22.5)	-	

			Sexual bother (mean (SD))	60.4 (25.6)	56.1 (28.7)	-
Erectile dysfunction						
Anastasiadis (2003)	Unable to achieve and maintain an erection suitable for sexual intercourse	12 months	Impotence rate	-	59%	70%
Artibani (2003)	Unable to have intercourse spontaneously or sildenafil assisted	> 6 months	Sexual function not recovered	-	52/57	36/40
Asimakopoulos (2011)	Incapable of intercourse	12 months	Post-operative impotence	41/60	12/52	-
	IIEF-6 < 26		Erectile dysfunction	30/52	46/60	-
Choo (2013)	IIEF-5 < 12	24 months	Impotence	44%	-	49%
Crisan (2010)	Not able to have sexual intercourse	6 months	Erectile dysfunction	-	27/58	35/50
Dahl (2009)	-	12 months	Not returned to baseline state of erectile function	-	44/77	50/73
			Erections firm enough for intercourse	-	25/77	17/73
Ficarra (2009)	IIEF-5 > 17	12 months	Erectile function not recovered	12/64	-	21/41
Fiori (2012)	No recovery of erections	3 months	Impotence	36.8%	57.2%	-
Ghavamian (2006)	IIEF-5 < 3 questions 2 & 3	6 months	Erectile dysfunction	-	26/50	26/42
		12 months		-	18/50	19/40
Greco (2010)	Unable to achieve sexual intercourse	12 months	Erectile dysfunction	-	99/150	77/150
Joseph (2005)	-	12 months	Patients reporting spontaneous erections	40%	22%	-
		3 months	Require drug aid	46%	36%	-
Krambeck (2008)	Unable to achieve sexual intercourse	12 months	Impotence	61/203	-	155/417
Lama (2009)	-	12 months	Erectile dysfunction	-	41/56	33/59
Nadler (2010)	SHIM ≤ 17	12 months	Impotence	14/22	-	4/4
Ou (2009)	-	12 months	Impotence	2/16	-	½
			Unable to have sexual intercourse	6/16	-	½
Rocco (2009)	-	6 months	Unable to have sexual intercourse	61/107	-	158/229
		12 months		31/79	-	127/215
Stolzenburg (2013)	Unable to achieve intercourse	3 months	Impotence	86.4%	91.2%	-
Tewari (2003)	-	-	Time to return to erections (days, mean)	180	-	440
Wagner (2007)	No sexual intercourse during last 4 weeks	12 months	Impotence	-	22/37	14/25
Wolanski (2012)	Unable to achieve sexual intercourse	3 months	Impotence	51.9%	50.0%	-
Urinary incontinence						
Anastasiadis (2003)	No pad use	6 months	Diurnal continence	-	59.2%	43.3%
		12 months		-	76.1%	66.7%
Artibani (2003)	Any amount of urinary leakage	> 12 months	Incontinence	-	12/20	5/14
Asimakopoulos (2011)	-	12 months	Incontinence	3/52	10/60	-
Choo (2013)	Any leakage or use of > 1 pad	6 months	Incontinence	16%	-	8%
		12 months		6%	-	4%

		24 months		5%		2%
Crisan (2010)	Using > 1 absorbent tampon per day	6 months	Incontinence	-	36/58	9/50
Dahl (2009)	-	12 months	Not returned to baseline continence	-	37/78	37/72
			Use of pads during last 4 weeks	-	13/78	9/73
Ficarra (2009)	ICIQ-UI	12 months	Urinary incontinence	3/103	-	12/105
	-	-	Time to urinary continence (days, mean)	25	-	75
Fiori (2012)	Use of > 1 pay per day	3 months	Incontinence rate	20.0%	38.4%	-
Ghavamian (2006)	Leakage or pad use	6 months	Diurnal incontinence	-	21/70	20/70
		12 months		-	7/70	8/65
Greco (2010)	-	12 months	Absence of urinary continence	-	4/150	13/150
Jacobsen (2007)	Total pad weight gain > 8 mg	12 months	Incontinence	-	10/57	19/148
Joseph (2005)	Leakage on Valsalva	3 months	Incontinence	5/50	10/50	-
Krambeck (2008)	-	12 months	Use of pads	20/244	-	30/476
Lama (2009)	-	6 months	Incontinence	-	1/56	2/59
		12 months		-	0/56	2/59
Nadler (2010)	> 1 pad per day	12 months	Incontinence	6/44	-	5/46
Ou (2009)	Need to wear a pad	12 months	Incontinence	0/30	-	1/30
Poulakis (2007)	Use of a pad	6 months	Incontinence	-	38/72	33/70
Remzi (2005)	Use of pads	12 months	Incontinence	-	6/39	8/41
Rocco (2009)	Use of pads	6 months	Incontinence	8/110	-	40/229
		12 months		2/79	-	26/217
Stolzenburg (2013)	Use of > 1 pad per day	3 months	Incontinence	35/100	44/100	-
Sundaram (2004)	-	3 months	Use of pads	3/10	2/10	-
Suzuki (2012)	Use of pads	24 months	Incontinence	0/8	8/12	-
Tewari (2003)	Use of pads	NR	Incontinence	40/200	-	56/100
Wagner (2007)	-	12 months	Use of pads	-	24/67	35/66
Willis (2012)	EPIC	6 months	Urinary incontinence subscale (mean (SD))	71.2 (24.1)	72.6 (24.7)	-
		12 months		77.0 (22.4)	76.6 (24.5)	-
	Use of pads	6 months	Urinary incontinence	26/76	53/117	-
		12 months		11/44	32/116	-
Wolanski (2012)	Use of pads	3 months	Incontinence	40.3%	60.2%	-

Note: percentages reported where number of events not available.

Figure 19 Risk of biochemical recurrence at 12 months following laparoscopic (LP) versus open (OP) prostatectomy

Study or Subgroup	LP Events	LP Total	OP Events	OP Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Artibani 2003	12	63	5	44	30.2%	1.68 [0.64, 4.42]	2003
Poulakis 2007	17	204	11	70	41.7%	0.53 [0.26, 1.08]	2007
Lama 2009	6	56	7	59	28.1%	0.90 [0.32, 2.52]	2009
Total (95% CI)		**323**		**173**	**100.0%**	**0.87 [0.44, 1.74]**	
Total events	35		23				

Heterogeneity: Tau² = 0.17; Chi² = 3.60, df = 2 (P = 0.17); I² = 44%
Test for overall effect: Z = 0.39 (P = 0.70)

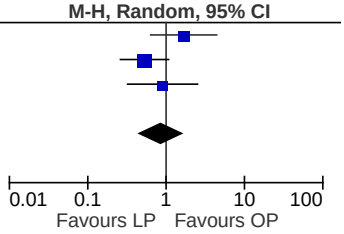


Figure 20 Risk of biochemical recurrence at 12 months following laparoscopic (RALP) versus open (OP) prostatectomy

Study or Subgroup	RALP Events	RALP Total	OP Events	OP Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Krambeck 2008	14	248	32	492	31.0%	0.87 [0.47, 1.60]	2008
Schroeck 2008	29	362	54	435	62.5%	0.65 [0.42, 0.99]	2008
Ou 2009	3	30	5	30	6.4%	0.60 [0.16, 2.29]	2009
Total (95% CI)		**640**		**957**	**100.0%**	**0.70 [0.50, 0.99]**	
Total events	46		91				

Heterogeneity: Tau² = 0.00; Chi² = 0.67, df = 2 (P = 0.72); I² = 0%
Test for overall effect: Z = 2.03 (P = 0.04)

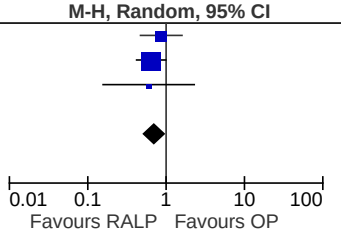


Figure 21 Blood transfusion rate during laparoscopic (LP) versus open (OP) prostatectomy

Study or Subgroup	Laparoscopic Events	Laparoscopic Total	Open Events	Open Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Salomon 2002	3	155	31	151	5.5%	0.09 [0.03, 0.30]	2002
Anastasiadis 2003	6	230	6	70	5.7%	0.30 [0.10, 0.91]	2003
Artibani 2003	45	71	17	50	8.0%	1.86 [1.22, 2.85]	2003
Martorana 2004	1	50	5	50	3.0%	0.20 [0.02, 1.65]	2004
Fornara 2004	2	32	6	32	4.3%	0.33 [0.07, 1.53]	2004
Brown 2004	1	60	31	60	3.2%	0.03 [0.00, 0.23]	2004
Guazonni 2006	8	60	32	60	7.2%	0.25 [0.13, 0.50]	2006
Ghavamian 2006	5	70	22	70	6.4%	0.23 [0.09, 0.57]	2006
Poulakis 2007	5	204	13	70	6.1%	0.13 [0.05, 0.36]	2007
Jurczok 2007	5	163	22	240	6.2%	0.33 [0.13, 0.87]	2007
Kim 2007	7	30	10	45	6.6%	1.05 [0.45, 2.45]	2007
Drouin 2009	5	85	8	83	5.8%	0.61 [0.21, 1.79]	2009
Lama 2009	7	56	23	59	6.9%	0.32 [0.15, 0.69]	2009
Bolenz 2010	4	211	32	156	6.0%	0.09 [0.03, 0.26]	2010
Al-Shaiji 2010	3	70	42	70	5.6%	0.07 [0.02, 0.22]	2010
Greco 2010	3	150	9	150	5.0%	0.33 [0.09, 1.21]	2010
Sugihara 2013	784	1627	1439	1627	8.6%	0.54 [0.52, 0.57]	2013
Total (95% CI)		**3324**		**3043**	**100.0%**	**0.29 [0.19, 0.45]**	
Total events	894		1748				

Heterogeneity: Tau² = 0.60; Chi² = 104.51, df = 16 (P < 0.00001); I² = 85%
Test for overall effect: Z = 5.44 (P < 0.00001)

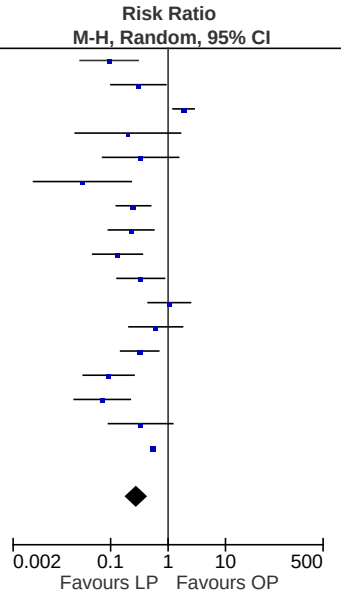


Figure 22 Blood transfusion rate during robot-assisted laparoscopic (RALP) versus open (OP) prostatectomy

Study or Subgroup	RALP Events	RALP Total	OP Events	OP Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Tewari 2003	0	200	67	100	1.8%	0.00 [0.00, 0.06]	2003
Chan 2008	5	660	11	340	6.8%	0.23 [0.08, 0.67]	2008
Fracalanza 2008	7	35	12	26	8.6%	0.43 [0.20, 0.95]	2008
Krambeck 2008	15	294	77	588	10.4%	0.39 [0.23, 0.67]	2008
Ou 2009	4	30	18	30	7.3%	0.22 [0.09, 0.58]	2009
Ficarra 2009	2	103	15	105	4.7%	0.14 [0.03, 0.58]	2009
Drouin 2009	4	71	8	83	6.1%	0.58 [0.18, 1.86]	2009
Doumerc 2010	2	212	10	502	4.5%	0.47 [0.10, 2.14]	2010
Carlsson 2010	58	1253	112	485	12.0%	0.20 [0.15, 0.27]	2010
Kordan 2010	7	830	14	414	7.7%	0.25 [0.10, 0.61]	2010
Nadler 2010	10	50	45	50	10.2%	0.22 [0.13, 0.39]	2010
Bolenz 2010	12	262	32	156	9.7%	0.22 [0.12, 0.42]	2010
Choo 2013	13	77	31	176	10.0%	0.96 [0.53, 1.73]	2013
Total (95% CI)		**4077**		**3055**	**100.0%**	**0.29 [0.19, 0.43]**	
Total events	139		452				

Heterogeneity: Tau² = 0.32; Chi² = 41.32, df = 12 (P < 0.0001); I² = 71%
Test for overall effect: Z = 6.16 (P < 0.00001)

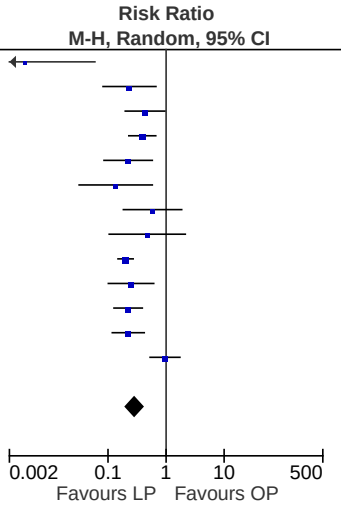


Figure 23 Blood transfusion rate during robot-assisted laparoscopic (RALP) versus laparoscopic (LP) prostatectomy

Study or Subgroup	RALP Events	RALP Total	LP Events	LP Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Menon 2002	0	40	1	40	4.1%	0.33 [0.01, 7.95]	2002
Hu 2006	5	322	8	358	14.3%	0.69 [0.23, 2.10]	2006
Joseph 2007	10	754	35	800	18.0%	0.30 [0.15, 0.61]	2007
Rozet 2007	13	133	4	133	14.4%	3.25 [1.09, 9.71]	2007
Drouin 2009	4	71	5	85	12.8%	0.96 [0.27, 3.43]	2009
Gosseine 2009	4	122	8	125	13.7%	0.51 [0.16, 1.66]	2009
Bolenz 2010	12	262	4	211	14.2%	2.42 [0.79, 7.38]	2010
Asimakopoulis 2011	0	52	3	60	4.6%	0.16 [0.01, 3.11]	2011
Wolanski 2012	0	73	1	87	4.0%	0.40 [0.02, 9.59]	2012
Total (95% CI)		**1829**		**1899**	**100.0%**	**0.79 [0.39, 1.61]**	
Total events	48		69				

Heterogeneity: Tau² = 0.60; Chi² = 19.58, df = 8 (P = 0.01); I² = 59%
Test for overall effect: Z = 0.65 (P = 0.52)

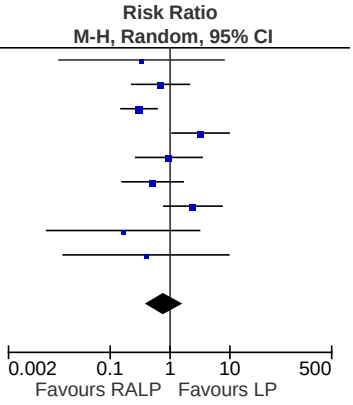


Figure 24 Incontinence rates at 6 months following laparoscopic (LP) versus open (OP) prostatectomy

Study or Subgroup	Laparoscopic Events	Laparoscopic Total	Open Events	Open Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Ghavamian 2006	21	70	20	70	30.9%	1.05 [0.63, 1.76]	2006
Poulakis 2007	38	72	33	70	35.3%	1.12 [0.80, 1.56]	2007
Lama 2009	1	56	2	59	5.8%	0.53 [0.05, 5.65]	2009
Crisan 2010	36	58	9	50	28.0%	3.45 [1.85, 6.44]	2010
Total (95% CI)		**256**		**249**	**100.0%**	**1.44 [0.78, 2.67]**	
Total events	96		64				

Heterogeneity: Tau² = 0.25; Chi² = 11.76, df = 3 (P = 0.008); I² = 75%
Test for overall effect: Z = 1.16 (P = 0.25)

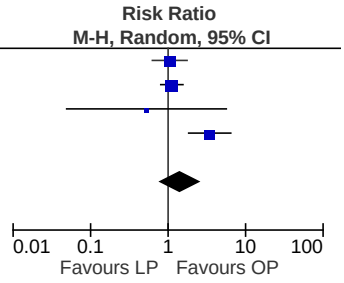


Figure 25 Incontinence rates at 12 months following laparoscopic (LP) versus open (OP) prostatectomy

Study or Subgroup	LP Events	LP Total	OP Events	OP Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Remzi 2005	6	39	8	41	22.6%	0.79 [0.30, 2.07]	2005
Ghavamian 2006	7	70	8	65	22.8%	0.81 [0.31, 2.11]	2006
Jacobsen 2007	10	57	19	148	32.1%	1.37 [0.68, 2.76]	2007
Lama 2009	0	56	2	59	3.4%	0.21 [0.01, 4.29]	2009
Greco 2010	4	150	13	150	19.0%	0.31 [0.10, 0.92]	2010
Total (95% CI)		**372**		**463**	**100.0%**	**0.76 [0.43, 1.35]**	
Total events	27		50				

Heterogeneity: Tau² = 0.14; Chi² = 6.03, df = 4 (P = 0.20); I² = 34%
Test for overall effect: Z = 0.95 (P = 0.34)

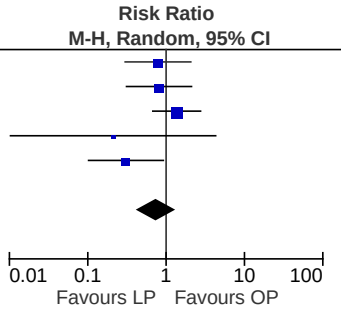


Figure 26 Incontinence rates at 12 months following robot-assisted laparoscopic (RALP) versus open (OP) prostatectomy

Study or Subgroup	RALP Events	RALP Total	OP Events	OP Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Rocco 2009	2	79	26	217	26.9%	0.21 [0.05, 0.87]	2009
Ou 2009	0	30	1	30	8.5%	0.33 [0.01, 7.87]	2009
Ficarra 2009	3	103	12	105	30.8%	0.25 [0.07, 0.88]	2009
Nadler 2010	6	44	5	46	33.8%	1.25 [0.41, 3.82]	2010
Total (95% CI)		**256**		**398**	**100.0%**	**0.43 [0.16, 1.15]**	
Total events	11		44				

Heterogeneity: Tau² = 0.44; Chi² = 5.41, df = 3 (P = 0.14); I² = 45%
Test for overall effect: Z = 1.68 (P = 0.09)

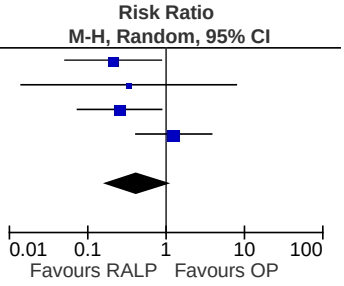


Figure 27 Incontinence rates at 12 months following robot-assisted laparoscopic (RALP) versus laparoscopic (LP) prostatectomy

Study or Subgroup	RALP Events	RALP Total	LP Events	LP Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Willis 2011	11	44	32	116	66.1%	0.91 [0.50, 1.64]	2011
Asimakopoulis 2011	3	52	10	60	33.9%	0.35 [0.10, 1.19]	2011
Total (95% CI)		**96**		**176**	**100.0%**	**0.65 [0.26, 1.62]**	
Total events	14		42				

Heterogeneity: Tau² = 0.23; Chi² = 1.95, df = 1 (P = 0.16); I² = 49%
Test for overall effect: Z = 0.92 (P = 0.36)

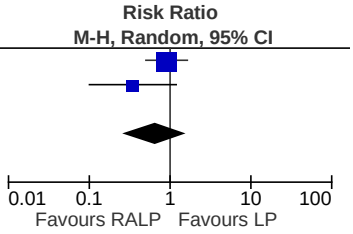


Figure 28 Erectile dysfunction rates at 6 months following laparoscopic (LP) versus open (OP) prostatectomy

Study or Subgroup	LP Events	LP Total	OP Events	OP Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Ghavamian 2006	26	50	26	42	46.1%	0.84 [0.59, 1.20]	2006
Crisan 2010	27	58	35	50	53.9%	0.67 [0.48, 0.93]	2010
Total (95% CI)		**108**		**92**	**100.0%**	**0.74 [0.58, 0.94]**	
Total events	53		61				

Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 2.43 (P = 0.02)

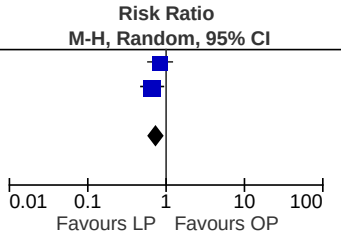


Figure 29 Erectile dysfunction rates at 12 months following laparoscopic (LP) versus open (OP) prostatectomy

Study or Subgroup	Laparoscopic Events	Laparoscopic Total	Open Events	Open Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Ghavamian 2006	18	50	19	40	12.7%	0.76 [0.46, 1.24]	2006
Wagner 2007	22	37	14	25	14.7%	1.06 [0.69, 1.64]	2007
Lama 2009	41	56	33	59	22.1%	1.31 [0.99, 1.73]	2009
Dahl 2009	44	77	50	73	23.7%	0.83 [0.65, 1.07]	2009
Greco 2010	99	150	77	150	26.8%	1.29 [1.06, 1.56]	2010
Total (95% CI)		**370**		**347**	**100.0%**	**1.06 [0.85, 1.32]**	
Total events	224		193				

Heterogeneity: Tau² = 0.04; Chi² = 11.01, df = 4 (P = 0.03); I² = 64%
Test for overall effect: Z = 0.50 (P = 0.61)

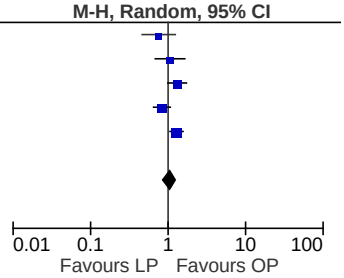


Figure 30 Erectile dysfunction rates at 12 months following robot-assisted laparoscopic (RALP) versus open (OP) prostatectomy

Study or Subgroup	RALP Events	RALP Total	OP Events	OP Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Krambeck 2008	61	203	155	417	41.4%	0.81 [0.63, 1.03]	2008
Ficarra 2009	12	64	21	41	23.4%	0.37 [0.20, 0.66]	2009
Ou 2009	2	16	1	2	4.0%	0.25 [0.04, 1.67]	2009
Nadler 2010	14	22	4	4	31.2%	0.70 [0.46, 1.07]	2010
Total (95% CI)		**305**		**464**	**100.0%**	**0.61 [0.41, 0.91]**	
Total events	89		181				

Heterogeneity: Tau² = 0.08; Chi² = 7.08, df = 3 (P = 0.07); I² = 58%
Test for overall effect: Z = 2.43 (P = 0.02)

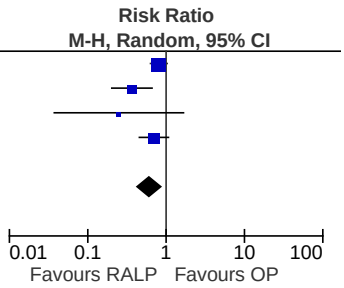


Figure 31 Mean operating time during laparoscopic (LP) versus open (OP) prostatectomy

Study or Subgroup	Laparoscopic Mean	SD	Total	Open Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Salomon 2002	266	73	155	181	46	151	5.5%	85.00 [71.37, 98.63]	2002
Bhayani 2003	348	72	33	168	33	24	5.0%	180.00 [152.11, 207.89]	2003
Fornara 2004	220	53.4	32	140	24.4	32	5.3%	80.00 [59.66, 100.34]	2004
Martorana 2004	358	83.2	50	159	32.6	50	5.1%	199.00 [174.23, 223.77]	2004
Soric 2004	302	71.3	26	272	112	26	3.9%	30.00 [-21.03, 81.03]	2004
Remzi 2005	279	70	39	195	72	41	4.9%	84.00 [52.88, 115.12]	2005
Ghavamian 2006	246.4	46.1	70	181.8	18.7	70	5.6%	64.60 [52.95, 76.25]	2006
Guazonni 2006	235	49.9	60	170	34.2	60	5.5%	65.00 [49.69, 80.31]	2006
Kim 2007	335.9	93.7	30	201.9	62.8	45	4.5%	134.00 [95.78, 172.22]	2007
Wagner 2007	282	53.4	75	162	39	75	5.5%	120.00 [105.03, 134.97]	2007
Poulakis 2007	144	36	72	150	30	70	5.6%	-6.00 [-16.89, 4.89]	2007
Raventos Busquets 2007	172.3	43.7	105	145.1	32.9	75	5.6%	27.20 [16.01, 38.39]	2007
Jurczok 2007	180	44.4	163	120	17.1	240	5.7%	60.00 [52.85, 67.15]	2007
Lama 2009	203	52	56	151	30	59	5.5%	52.00 [36.38, 67.62]	2009
Drouin 2009	257.3	94.3	85	208.5	76	83	5.1%	48.80 [22.93, 74.67]	2009
Crisan 2010	269	64.1	58	207	59.8	50	5.2%	62.00 [38.61, 85.39]	2010
Bolenz 2010	235	56.7	220	225	72.4	162	5.5%	10.00 [-3.43, 23.43]	2010
Al-Shaiji 2010	232	56	70	170	38.1	70	5.5%	62.00 [46.13, 77.87]	2010
Greco 2010	165	41	150	120	17.1	150	5.7%	45.00 [37.89, 52.11]	2010
Total (95% CI)			**1549**			**1533**	**100.0%**	**72.85 [54.95, 90.74]**	

Heterogeneity: Tau² = 1461.67; Chi² = 527.10, df = 18 (P < 0.00001); I² = 97%
Test for overall effect: Z = 7.98 (P < 0.00001)

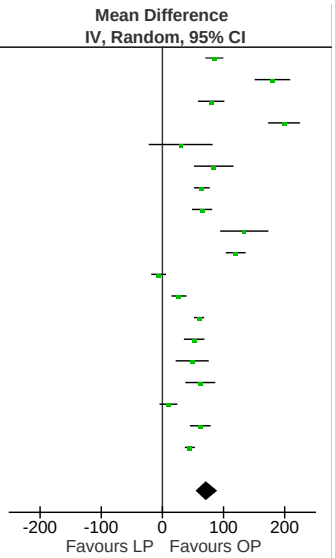


Figure 32 Mean operating time during robot-assisted laparoscopic (RALP) versus open (OP) prostatectomy

Study or Subgroup	RALP Mean	SD	Total	OP Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bolenz 2010	198	60.7	264	225	40.3	162	8.7%	-27.00 [-36.60, -17.40]
Choo 2013	220	62.12	77	151	44.02	176	8.5%	69.00 [53.68, 84.32]
Doumerc 2010	192	59.4	212	148	37.5	502	8.7%	44.00 [35.36, 52.64]
Drouin 2009	199.6	36.6	71	208.5	76	83	8.4%	-8.90 [-27.33, 9.53]
Ficarra 2009	185	58	103	135	36.9	105	8.6%	50.00 [36.76, 63.24]
Fracalanza 2008	195.6	45	35	127.2	31.7	26	8.4%	68.40 [49.15, 87.65]
Krambeck 2008	236	68.3	294	204	39.6	588	8.7%	32.00 [23.56, 40.44]
Martinschek 2012	217	51.9	19	174	57.7	19	7.5%	43.00 [8.10, 77.90]
Nadler 2010	341	87.6	50	235	40.6	50	8.0%	106.00 [79.24, 132.76]
Ou 2009	205	103	30	213	37	30	7.3%	-8.00 [-47.16, 31.16]
Rocco 2009	215	87.6	120	235	40.6	240	8.5%	-20.00 [-36.49, -3.51]
Truesdale 2010	153.4	51.3	99	204	32.9	217	8.7%	-50.60 [-61.61, -39.59]
Total (95% CI)			**1374**			**2198**	**100.0%**	**24.52 [-0.83, 49.86]**

Heterogeneity: Tau² = 1899.90; Chi² = 443.68, df = 11 (P < 0.00001); I² = 98%
Test for overall effect: Z = 1.90 (P = 0.06)

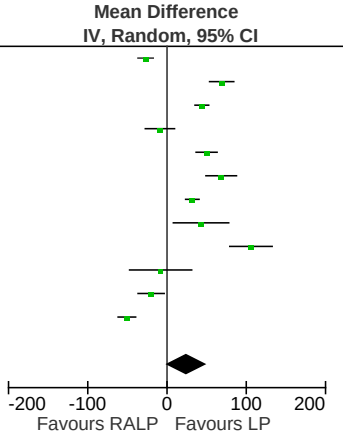


Figure 33 Mean operating time during robot-assisted laparoscopic (RALP) versus laparoscopic (LP) prostatectomy

Study or Subgroup	RALP Mean	RALP SD	RALP Total	LP Mean	LP SD	LP Total	Weight	Mean Difference IV, Random, 95% CI
Suzuki 2012	272	67	8	255	117	12	2.8%	17.00 [-63.86, 97.86]
Sundaram 2004	290	78.7	10	394	99.7	10	2.9%	-104.00 [-182.73, -25.27]
Menon 2002	274	94.3	40	258	80.3	40	5.8%	16.00 [-22.38, 54.38]
Drouin 2009	199.6	36.6	71	257.3	94.3	85	7.4%	-57.70 [-79.48, -35.92]
Stolzenburg 2010	84.55	30.8	25	83.38	34.3	25	7.7%	1.17 [-16.90, 19.24]
Gosseine 2009	237	67.4	122	241	68.3	125	7.8%	-4.00 [-20.92, 12.92]
Rozet 2007	166	51.2	133	160	49.8	133	8.1%	6.00 [-6.14, 18.14]
Bolenz 2010	198	58.7	264	235	66.9	220	8.1%	-37.00 [-48.33, -25.67]
Stolzenburg 2013	153.95	38.5	100	128.4	35.4	100	8.2%	25.55 [15.30, 35.80]
Fiori 2012	147.6	27.1	60	138.1	29.7	60	8.2%	9.50 [-0.67, 19.67]
Willis 2011	280.8	44.4	121	283.2	39.6	161	8.2%	-2.40 [-12.40, 7.60]
Hu 2006	186	55.9	322	246	69.3	358	8.2%	-60.00 [-69.42, -50.58]
Kasraeian 2011	120	38.9	200	150	49.3	200	8.3%	-30.00 [-38.70, -21.30]
Joseph 2007	194	57.8	754	179	54.3	800	8.4%	15.00 [9.42, 20.58]
Total (95% CI)			**2230**			**2329**	**100.0%**	**-12.10 [-28.65, 4.45]**

Heterogeneity: Tau² = 843.66; Chi² = 317.84, df = 13 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.43 (P = 0.15)

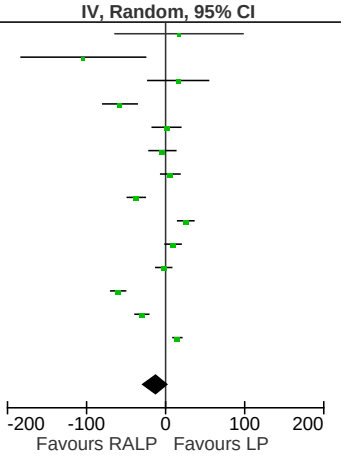


Figure 34 Mean in-patient stay following laparoscopic (LP) versus open (OP) prostatectomy

Study or Subgroup	Laparoscopic Mean	Laparoscopic SD	Laparoscopic Total	Open Mean	Open SD	Open Total	Weight	Mean Difference IV, Random, 95% CI	Year
Salomon 2002	6.8	3	155	12.1	7.6	151	4.0%	-5.30 [-6.60, -4.00]	2002
Bhayani 2003	2.97	0.55	33	3.04	0.21	24	8.9%	-0.07 [-0.28, 0.14]	2003
Artibani 2003	7.2	3.4	71	10.2	2	50	5.4%	-3.00 [-3.97, -2.03]	2003
Fornara 2004	12.4	5.5	32	11.2	5.1	32	1.5%	1.20 [-1.40, 3.80]	2004
Brown 2004	2.8	0.8	60	3	0.3	60	8.9%	-0.20 [-0.42, 0.02]	2004
Martorana 2004	5	1.7	50	6.9	1.8	50	6.8%	-1.90 [-2.59, -1.21]	2004
Soric 2004	12	5.2	26	12	5.9	26	1.2%	0.00 [-3.02, 3.02]	2004
Remzi 2005	7	2	39	10	4	41	3.8%	-3.00 [-4.38, -1.62]	2005
Ghavamian 2006	2	0.6	70	3	0.3	70	9.0%	-1.00 [-1.16, -0.84]	2006
Poulakis 2007	9	2	72	11	3	70	6.0%	-2.00 [-2.84, -1.16]	2007
Kim 2007	6.7	3.7	30	6.9	2.6	45	3.3%	-0.20 [-1.73, 1.33]	2007
Raventos Busquets 2007	4.8	1.3	105	5.79	1.67	75	7.9%	-0.99 [-1.44, -0.54]	2007
Jurczok 2007	9.4	3.9	163	11.2	5.1	240	5.8%	-1.80 [-2.68, -0.92]	2007
Lama 2009	7.3	4.7	56	10.7	9.2	59	1.5%	-3.40 [-6.05, -0.75]	2009
Greco 2010	7	2.7	150	9	3.2	150	6.8%	-2.00 [-2.67, -1.33]	2010
Crisan 2010	13	5.8	58	9	3.2	50	2.8%	4.00 [2.26, 5.74]	2010
Bolenz 2010	1	0.2	220	2	0.1	162	9.2%	-1.00 [-1.03, -0.97]	2010
Al-Shaiji 2010	3.4	1.84	70	5.6	1.49	70	7.4%	-2.20 [-2.75, -1.65]	2010
Total (95% CI)			**1460**			**1425**	**100.0%**	**-1.35 [-1.70, -1.00]**	

Heterogeneity: Tau² = 0.34; Chi² = 276.69, df = 17 (P < 0.00001); I² = 94%
Test for overall effect: Z = 7.60 (P < 0.00001)

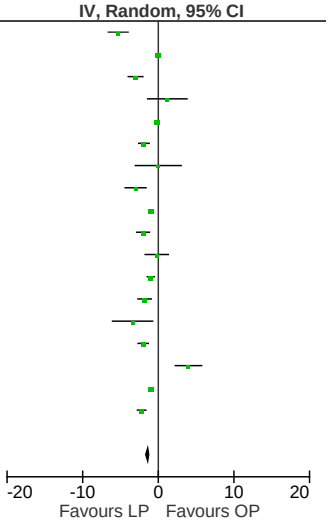


Figure 35 Mean in-patient stay following robot-assisted laparoscopic (RALP) versus open (OP) prostatectomy

Study or Subgroup	RALP Mean	RALP SD	RALP Total	OP Mean	OP SD	OP Total	Weight	Mean Difference IV, Random, 95% CI	Year
Ou 2009	7.3	2.3	30	8.37	2.2	30	63.4%	-1.07 [-2.21, 0.07]	2009
Martinschek 2012	8.58	1.17	19	11.74	5.22	19	36.6%	-3.16 [-5.57, -0.75]	2012
Total (95% CI)			**49**			**49**	**100.0%**	**-1.84 [-3.81, 0.14]**	

Heterogeneity: Tau² = 1.26; Chi² = 2.37, df = 1 (P = 0.12); I² = 58%
Test for overall effect: Z = 1.82 (P = 0.07)

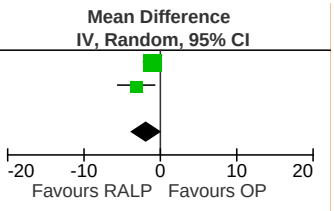


Figure 36 Mean in-patient stay following robot-assisted laparoscopic (RALP) versus laparoscopic (LP) prostatectomy

Study or Subgroup	RALP Mean	RALP SD	RALP Total	LP Mean	LP SD	LP Total	Weight	Mean Difference IV, Random, 95% CI	Year
Gosseine 2009	9	2.1	122	10.2	3.2	125	31.3%	-1.20 [-1.87, -0.53]	2009
Willis 2011	2.2	1.6	121	2.1	0.5	161	38.4%	0.10 [-0.20, 0.40]	2011
Fiori 2012	4.6	2.1	60	4.8	1.9	60	30.3%	-0.20 [-0.92, 0.52]	2012
Total (95% CI)			**303**			**346**	**100.0%**	**-0.40 [-1.18, 0.39]**	

Heterogeneity: Tau² = 0.39; Chi² = 12.06, df = 2 (P = 0.002); I² = 83%
Test for overall effect: Z = 0.99 (P = 0.32)

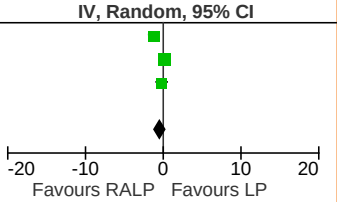


Figure 37 Risk of positive surgical margins following laparoscopic (LP) versus open (OP) prostatectomy

Study or Subgroup	Laparoscopic Events	Laparoscopic Total	Open Events	Open Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Salomon 2002	32	155	30	151	4.7%	1.04 [0.67, 1.62]	2002
Artibani 2003	21	71	12	50	2.9%	1.23 [0.67, 2.27]	2003
Anastasiadis 2003	61	230	20	70	5.0%	0.93 [0.60, 1.42]	2003
Soric 2004	6	26	3	26	0.8%	2.00 [0.56, 7.16]	2004
Brown 2004	10	59	12	60	2.0%	0.85 [0.40, 1.81]	2004
Fornara 2004	5	32	7	32	1.1%	0.71 [0.25, 2.02]	2004
Martorana 2004	12	50	13	50	2.4%	0.92 [0.47, 1.82]	2004
Remzi 2005	10	39	8	41	1.7%	1.31 [0.58, 2.98]	2005
Guazonni 2006	16	60	13	60	2.7%	1.23 [0.65, 2.33]	2006
Silva 2007	22	90	37	89	4.8%	0.59 [0.38, 0.91]	2007
Poulakis 2007	15	72	16	70	2.8%	0.91 [0.49, 1.70]	2007
Kim 2007	11	30	11	45	2.3%	1.50 [0.75, 3.01]	2007
Jurczok 2007	63	163	104	240	9.5%	0.89 [0.70, 1.14]	2007
Jacobsen 2007	22	67	60	148	5.6%	0.81 [0.55, 1.20]	2007
Wagner 2007	7	75	14	75	1.6%	0.50 [0.21, 1.17]	2007
Terakawa 2008	54	137	52	220	7.3%	1.67 [1.22, 2.29]	2008
Lama 2009	16	56	21	59	3.6%	0.80 [0.47, 1.37]	2009
Dahl 2009	43	286	124	714	7.3%	0.87 [0.63, 1.19]	2009
Drouin 2009	16	85	15	83	2.7%	1.04 [0.55, 1.97]	2009
Crisan 2010	10	58	9	50	1.8%	0.96 [0.42, 2.17]	2010
Greco 2010	12	150	17	150	2.3%	0.71 [0.35, 1.43]	2010
Magheli 2010	68	522	75	522	7.6%	0.91 [0.67, 1.23]	2010
Silberstein 2011	9	78	24	126	2.2%	0.61 [0.30, 1.23]	2011
Vickers 2011	512	2298	1704	6091	15.1%	0.80 [0.73, 0.87]	2011
Total (95% CI)		**4889**		**9222**	**100.0%**	**0.92 [0.82, 1.03]**	
Total events	1053		2401				

Heterogeneity: Tau² = 0.02; Chi² = 35.18, df = 23 (P = 0.05); I² = 35%
Test for overall effect: Z = 1.43 (P = 0.15)

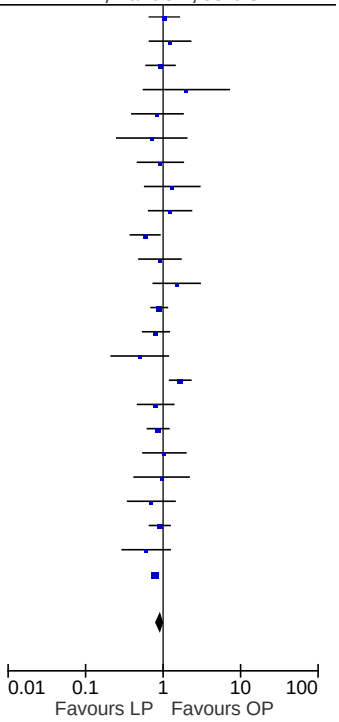


Figure 38 Risk of positive surgical margins following robot-assisted laparoscopic (RALP) versus open (OP) prostatectomy

Study or Subgroup	RALP Events	RALP Total	OP Events	OP Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Tewari 2003	18	200	23	100	3.8%	0.39 [0.22, 0.69]	2003
Fracalanza 2008	10	35	6	26	2.3%	1.24 [0.52, 2.97]	2008
Schroeck 2008	106	362	122	435	6.5%	1.04 [0.84, 1.30]	2008
Krambeck 2008	46	294	100	588	5.7%	0.92 [0.67, 1.27]	2008
Drouin 2009	12	71	15	83	3.1%	0.94 [0.47, 1.86]	2009
Ou 2009	15	30	6	30	2.6%	2.50 [1.12, 5.56]	2009
Rocco 2009	26	120	60	240	5.0%	0.87 [0.58, 1.30]	2009
Ficarra 2009	35	103	21	105	4.5%	1.70 [1.06, 2.71]	2009
White 2009	11	50	18	50	3.4%	0.61 [0.32, 1.16]	2009
Nadler 2010	5	50	12	50	2.0%	0.42 [0.16, 1.10]	2010
Barocas 2010	281	1413	148	491	6.8%	0.66 [0.56, 0.78]	2010
Kordan 2010	171	830	132	414	6.7%	0.65 [0.53, 0.78]	2010
Doumerc 2010	45	212	84	502	5.7%	1.27 [0.92, 1.75]	2010
Magheli 2010	102	522	75	522	6.1%	1.36 [1.04, 1.79]	2010
Loeb 2010	22	152	25	137	4.1%	0.79 [0.47, 1.34]	2010
Williams 2010	80	524	30	346	5.1%	1.76 [1.18, 2.62]	2010
Silberstein 2011	21	136	24	126	4.1%	0.81 [0.48, 1.38]	2011
Mirza 2011	26	191	21	92	4.2%	0.60 [0.36, 1.00]	2011
Martinschek 2012	3	19	3	19	1.0%	1.00 [0.23, 4.34]	2012
Froehner 2013	33	252	242	1925	5.5%	1.04 [0.74, 1.46]	2013
Choo 2013	30	77	70	176	5.6%	0.98 [0.70, 1.37]	2013
Silberstein 2013	74	493	147	961	6.2%	0.98 [0.76, 1.27]	2013
Total (95% CI)		**6136**		**7418**	**100.0%**	**0.94 [0.80, 1.10]**	
Total events	1172		1384				

Heterogeneity: Tau² = 0.09; Chi² = 80.23, df = 21 (P < 0.00001); I² = 74%
Test for overall effect: Z = 0.79 (P = 0.43)

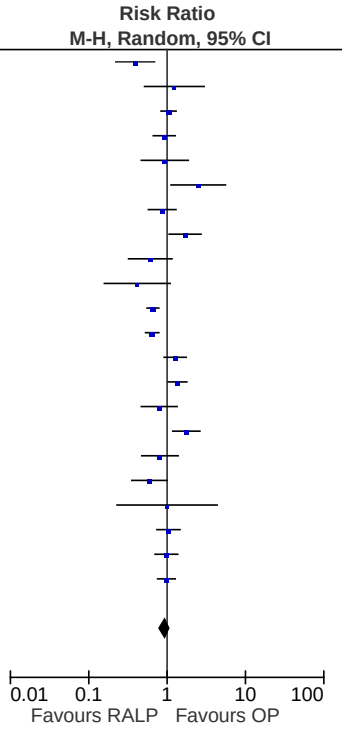


Figure 39 Risk of positive surgical margins following robot-assisted laparoscopic (RALP) versus laparoscopic (LP) prostatectomy

Study or Subgroup	RALP Events	RALP Total	LP Events	LP Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Menon 2002	7	40	10	40	5.6%	0.70 [0.30, 1.66]	2002
Sundaram 2004	2	10	2	10	2.5%	1.00 [0.17, 5.77]	2004
Rozet 2007	26	133	21	133	7.5%	1.24 [0.73, 2.09]	2007
Joseph 2007	99	754	246	800	8.9%	0.43 [0.35, 0.53]	2007
Trabulsi 2008	3	50	35	190	4.3%	0.33 [0.10, 1.02]	2008
Drouin 2009	12	71	16	85	6.6%	0.90 [0.46, 1.77]	2009
Stolzenburg 2010	1	25	1	25	1.2%	1.00 [0.07, 15.12]	2010
Magheli 2010	102	522	68	522	8.7%	1.50 [1.13, 1.99]	2010
Kasraeian 2011	27	200	24	200	7.5%	1.13 [0.67, 1.88]	2011
Willis 2011	22	121	22	161	7.4%	1.33 [0.77, 2.29]	2011
Asimakopoulis 2011	8	52	6	60	5.0%	1.54 [0.57, 4.15]	2011
Silberstein 2011	21	136	9	78	6.3%	1.34 [0.65, 2.78]	2011
Fiori 2012	16	60	12	60	6.7%	1.33 [0.69, 2.57]	2012
Wolanski 2012	9	73	12	87	5.9%	0.89 [0.40, 2.00]	2012
Koutlidis 2012	30	175	14	104	7.1%	1.27 [0.71, 2.29]	2012
Suzuki 2012	1	8	2	12	1.7%	0.75 [0.08, 6.96]	2012
Stolzenburg 2013	19	100	14	100	6.9%	1.36 [0.72, 2.55]	2013
Total (95% CI)		**2530**		**2667**	**100.0%**	**1.02 [0.73, 1.40]**	
Total events	405		514				

Heterogeneity: Tau² = 0.29; Chi² = 74.00, df = 16 (P < 0.00001); I² = 78%
Test for overall effect: Z = 0.09 (P = 0.93)

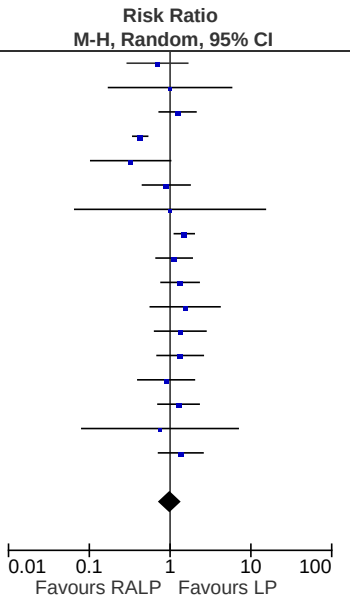


Table 91 Summary of included study characteristics

Abbreviations: Pca = prostate cancer; PSA = prostate specific antigen; RCT = randomised controlled trial; NR = not/none reported

Study	Country/ies	Re-cruit-ment period	Type of study	No. of patients	Median follow-up	Inclusion criteria	Exclusion criteria	Intervention	Comparator
Open versus laparoscopic									
Akito 2011	Japan	2004 – 2010	Retrospective cohort	579	35 months	Clinically localised Pca (T1-T2) with PSA < 25 ng/ml	Patients who underwent immediate adjuvant radiation therapy &/or hormone therapy	Open: retropubic	Laparoscopic: intraperitoneal approach
Crisan 2010	Romania	2005 – 2009	Prospective cohort	108	NR	Localised Pca	NR	Open	Laparoscopic
Narita 2013	Japan	2005 – 2009	Prospective cohort	165	NR	Clinically localised PCa patients undergoing RP	NR	Open	Laparoscopic
Sugihara 2013	Japan	2007 – 2010	Retrospective cohort	3,254	NR	Patients undergoing RP	Colorectal cancer	Open	Laparoscopic
Vassil 2010	US	1996 – 2005	Retrospective cohort	979	65 months	Intermediate risk Pca: T2b-T2c; Gleason =7; or PSA 10-20 ng/ml	Patients with > 1 risk factor (T2b-T2c; Gleason = 7; PSA 10-20 ng/ml); < 2 years follow-up; < 4 PSA tests; adjuvant radiation therapy	Open: retropubic	Laparoscopic
Vickers 2011	US	1987 – 2007	Retrospective cohort	8,389	NR	Clinically localised Pca	Patients censored within 2 years	Open	Laparoscopic
Open versus robot-assisted laparoscopic									
Choo 2013	Korea	2003 – 2010	Retrospective cohort	253	NR	Clinically localised (T1-T2) Pca undergoing RP	First 100 OP & first 25 RALP patients due to learning curve	Open: retropubic	Robot-assisted laparoscopic: transperitoneal approach
Froehner 2012	Germany	2007 – 2011	Cohort	2,177	NR	Pca patients undergoing RP	NR	Open: retropubic	Robot-assisted laparoscopic
Williams 2010	US	2005 – 2008	Prospective cohort	950	NR	Clinically localised Pca	Patients with missing data	Open: retropubic	Robot-assisted laparoscopic: transperitoneal approach
Minniti 2011	Italy	2007 – 2008	Retrospective cohort	115	NR	Patients undergoing RP	Large primary tumour invading other organs by direct extension before surgery (T4)	Open	Robot-assisted laparoscopic
Martinschek 2012	Germany	2008 – 2010	Case-control	38	NR	Prior prostate surgery & TURP	NR	Open	Robot-assisted laparoscopic
Mirza 2011	US	2005 – 2009	Retrospective cohort	463	NR	Clinically localised Pca	Prior adjuvant therapy or patients undergoing salvage prostatectomy	Open: retropubic	Open: perineal and Robot-assisted laparoscopic
Silberstein 2013	US	2007 – 2010	Retrospective cohort	1,454	NR	Non-metastatic Pca patients undergoing RP	RP performed by surgeons with low volume (not defined); salvage RP; adjuvant therapy	Open	Robot-assisted laparoscopic
Open versus laparoscopic and robot-assisted laparoscopic									
Magheli 2011	US	2000 – 2008	Prospective cohort	1,566	NR	Clinically localised Pca	Prior neoadjuvant hormonal therapy; stage T1a-T1b; incomplete preoperative informa-	Open: retropubic	Laparoscopic and Robot-assisted laparoscopic

Study	Country/ies	Recruitment period	Type of study	No. of patients	Median follow-up	Inclusion criteria	Exclusion criteria	Intervention	Comparator
							tion		
Silberstein 2012	US	2010 – 2010	Retropective cohort	330	NR	Localised Pca with predicted risk of lymph node involvement ≥ 2%	History of radiation therapy	Open: retropubic	Laparoscopic and Robot-assisted laparoscopic
Williams 2010	US	2004 – 2006	Retrospective cohort	4247	NR	Men aged ≥ 65 years with Pca	Stage T3b-T4; missing data	Open: retropubic	Minimally invasive (with or without robot)
Laparoscopic versus robot-assisted laparoscopic									
Asimakopoulos 2011	European	2007 – 2008	RCT	128	NR	Clinically localised Pca	Missing data	Laparoscopic: transperitoneal	Robot-assisted laparoscopic: transperitoneal
Berge 2013	Norway	2006 – 2008	Prospective cohort	420	36 months (total)	Localised PCa	NR	Laparoscopic: transperitoneal	Robot-assisted laparoscopic: transperitoneal
Fiori 2012 & Porpiglia 2012 & Porpiglia 2013	Italy	2010 – 2011	Prospective cohort	120	NR	Clinically localised Pca (T1-T2)	NR	Laparoscopic	Robot-assisted laparoscopic
Kasraeian 2011	France	2005 – 2008	Cohort	400	NR	NR (99.7% T1-T2)	NR	Laparoscopic: extraperitoneal	Robot-assisted laparoscopic: extraperitoneal
Koutlidis 2012	France	2004 – 2009	Prospective cohort	279	NR	Pca patients stage T1c-T2 undergoing RP with neurovascular bundle preservation	NR	Laparoscopic: intraperitoneal	Robot-assisted laparoscopic: intraperitoneal
Stolzenburg 2010	NR	NR	Prospective cohort	50	NR	Localised Pca	NR	Laparoscopic	Robot-assisted laparoscopic
Stolzenburg 2013	Germany	2011 – 2012	Prospective cohort	200	NR	PCa patients undergoing RP	First 10 RALP	Laparoscopic: extraperitoneal unless high risk	Robot-assisted laparoscopic: transperitoneal unless high risk
Suzuki 2012	Japan	1998 – 2006	Retrospective cohort	20	96 months	Prior TURP for benign prostatic hyperplasia followed by RP for PCa	NR	Laparoscopic: transperitoneal	Robot-assisted laparoscopic
Willis 2011	US	2003 – 2007	Cohort	282	NR	Clinically localised PCa (T1-T2)		Laparoscopic	Robot-assisted laparoscopic
Wolanski 2012	Australia	2009 - 2011	Retrospective cohort	160	NR	Patients undergoing RP	NR	Laparoscopic: extraperitoneal	Robot-assisted laparoscopic: transperitoneal

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Health Economic Evidence

Information sources and eligibility criteria

The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, COCHRANE, NHS EED. Studies conducted in OECD countries other than the UK were considered (Guidelines Manual 2009).

Studies were selected for inclusion in the evidence review if the following criteria were met:

Both cost and health consequences of interventions reported (i.e. true cost-effectiveness analyses)

Conducted in an OECD country

Incremental results are reported or enough information is presented to allow incremental results to be derived

Studies that matched the population, interventions, comparators and outcomes specified in PICO

Studies that meet the applicability and quality criteria set out by NICE, including relevance to the NICE reference case and UK NHS

Note that studies that measured effectiveness using quality of life based outcomes (e.g. QALYs) were desirable but, where this evidence was unavailable, studies using alternative effectiveness measures (e.g. life years) were considered.

Selection of studies

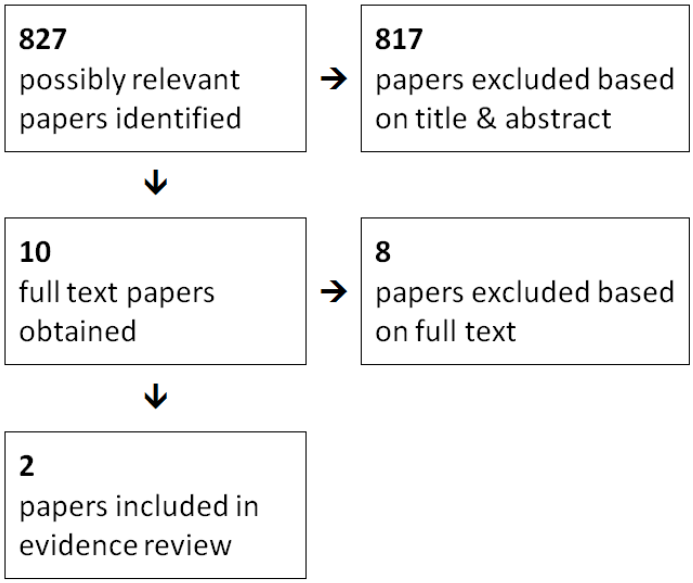
The health economist screened the literature search results obtained by the information specialist by checking the article's title and abstract for relevance to the review question. The full articles of non-excluded studies were then attained for appraisal and compared against the inclusion criteria specified above.

Results

The diagram below shows the results of the search and sifting process. It can be seen that 827 possibly relevant papers were identified. Of these, 10 full papers relating to this topic were obtained for appraisal. A further 8 papers were excluded based on the full text as they were not applicable to the PICO or did not include an incremental analysis of both costs and health effects. Therefore two papers (Hohwu et al. 2011 and Ramsay et al. 2012) were included in the current review of published economic evidence for this topic.

Ramsay et al. 2012 was a comprehensive report conducted as part of the NIHR HTA programme. Both papers were cost-utility analyses that quantified health effects in terms of quality adjusted life years (QALYs)

Figure 40: Summary of evidence search and sifting process for this topic



Quality and applicability of the included studies

Hohwu et al was deemed only partially applicable to the guideline, primarily because it considered a country other than the UK (Denmark). Ramsay et al. 2012, on the other hand, was deemed to be directly applicable because it considered a UK setting and there were no other applicability issues.

Potentially serious limitations were identified in the study by Hohwu et al. The one year time horizon was possibly too short to capture all the relevant costs and benefits (as a comparison, Ramsay et al. 2012 considered a ten year time horizon). Also, while numerous one-way sensitivity analyses were conducted, additional analyses could have been conducted in other important areas. No serious limitations were identified with Ramsay et al. 2012. However, there were a few minor limitations with some important information not being reported (e.g. price year) and an important (and uncertain) parameter left out of the probabilistic sensitivity analysis (PSA).

The table below summarises the quality and applicability of the included studies.

Table 92 Table showing methodological quality and applicability of the included study

Methodological quality	***Applicability***	
	Directly applicable	**Partially applicable**
Minor limitations	Ramsay et al. 2012	
Potentially serious limitations		Hohwu et al. 2011
Very serious limitations		

Modified GRADE table

The primary results of the analyses by Hohwu et al. 2011 and Ramsay et al. 2012 are summarised in the modified GRADE table below.

Table 93 Modified GRADE table showing the included evidence (Hohwu et al. 2011 and Ramsay et al. 2012) comparing methods of radical prostatectomy

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
Hohwu et al. 2011	Men with clinically localised prostate cancer who underwent radical prostatectomy.	Retropubic radical prostatectomy (RRP)	€3,863 (direct costs only) €12,465 (incl. Indirect costs)	27% successful operation 0.0116 QALYs	Reference			One-way sensitivity analysis was conducted on numerous variables. The ICERs ranged from €20,000 TO €150,000 per QALY. Probabilistic sensitivity analysis was not required as the analysis was not based on a model.	Partially applicable Not a UK study (Denmark). Potentially serious limitations Many inputs were not sourced through systematic review. Time horizon may be too short to capture all outcomes. Further sensitivity analyses could have been conducted.
		Robot assisted laparoscopic prostatectomy (RALP)	€8,369 (direct costs only) €13,411 (incl. Indirect costs)	34% successful operation 0.0103 QALYs	€4,506 (direct costs only) €946 (incl. indirect costs)	7% successful operation -0.0013 QALYs	€64,343 per successful operation (direct costs) €13,514 per successful operation (indirect costs) RRP is dominant when considering QALYs		
Ramsay et al. 2012 (NIHR HTA on radical prostatectomy)	Men with localised prostate cancer requiring radical prostatectomy.	Laparoscopic prostatectomy	£7,628	6.44 QALYs	Reference			Numerous one-way sensitivity analyses were conducted. As in the base case, results were presented according to throughput and robotic systems. ICERs ranged from £1,436 to £50,502 per QALY with robotic surgical capacity = 200.	Directly applicable Minor limitations
		Robot assisted prostatectomy (Numerous surgical capacity scenar-	**Capacity = 200:** £9,040 **Capacity = 150:** £9,799	6.52 QALYs	**Capacity = 200:** £1,412 **Capacity = 150:** £2,171	0.08 QALYs	**Capacity = 200:** £18,329 **Capacity = 150:** £28,172		

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
		ios were considered).	**Capacity = 100:** £11,312 **Capacity = 50:** £15,859 **Capacity = 200 with cheaper equipment cost:** £8,186		**Capacity = 100:** £3,684 **Capacity = 50:** £8,231 **Capacity = 200 with cheaper equipment cost:** £540		**Capacity = 100:** £47,822 **Capacity = 50:** £106,839 **Capacity = 200 with cheaper equipment cost:** £7,009	A two-way sensitivity analysis was also conducted whereby two of the most influential variables (cost per procedure and positive margin rates) were altered simultaneously. The results of this analysis were presented graphically. Probabilistic sensitivity analysis was also conducted. Robotic surgery was found to have a 95% probability of being cost-effective with robotic surgical capacity = 200.	
	Comments:								

Evidence statements

The conclusions of in the two studies were markedly different. Hohwu et al. found robot assisted laparoscopic prostatectomy (RALP) to be dominated by radical retropubic prostatectomy (RRP) i.e. RRP was both more effective and less costly. Conversely, Ramsay et al. found robot assisted prostatectomy to be cost-effective in at least some scenarios when compared to laparoscopic prostatectomy. Given the better applicability and fewer limitations associated with Ramsay et al. 2012, more weight is attached their results.

The results of the sensitivity analysis in Ramsay et al. suggest that the cost-effectiveness of robot assisted prostatectomy is highly dependent upon the number of procedures conducted per year (thereby affecting the cost per procedure) and the positive margin rates.

References

Hohwu L. "A short-term cost-effectiveness study comparing robot-assisted laparoscopic and open retropubic radical prostatectomy." Journal of Medical Economics 14.4 (2011): 403-09.

Ramsay C, Pickard R, Robertson C, Close A, Vale L, Armstrong N. et al. Systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of laparoscopic surgery and robotic surgery for removal of the prostate in men with localised prostate cancer." Health Technology Assessment 2012;16(41).

Full evidence table

The full details of the studies included in the evidence review are presented in the evidence table below.

Table 94 Full evidence table showing the included evidence (Hohwu et al. 2011 and Ramsay et al. 2012) that compared the methods of radical prostatectomy

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Study 1						
Author: Hohwu et al. **Year:** 2011 **Country:** Denmark	**Type of analysis:** Cost-effectiveness analysis (considering successful treatment and QALYs as effectiveness measures). **Model structure:** No model was constructed. Economic analysis was performed alongside retrospective cohort study. **Cycle length:** Not applicable **Time horizon:** 1 year **Perspective:** Third party payer and societal perspective are considered (societal includes indirect costs) **Source of base-line data:** Retrospective cohort study of 231 men aged 50-69 years with clinically localised prostate cancer who underwent radical prostatectomy. **Source of effectiveness data:** Retrospective cohort study described above. **Source of utility data:** SF-36 scores were collected from patients enrolled in the retrospective cohort study. Scores were collected at baseline and one year postoperatively. These scores were converted to SF-6D using a published conversion algorithm (Brazier). **Source of cost data:** Surgical equipment costs were obtained	**Inclusion criteria:** The study included patients with clinically localised prostate cancer. **Exclusion criteria:** The study excluded patients with stage cT3 disease because of the higher risk of urinary incontinence and recurrence postoperatively. **Base case (population):** Men with clinically localised prostate cancer **Sample size:** 231 **Age:** 50-69 years **Gender:** Men **Subgroup analysis:** None reported.	G. Robot-assisted laparoscopic prostatectomy (RALP) H. Retropubic radical prostatectomy (RRP)	**Effectiveness (proportion with successful operation):** RRP RALP **Effectiveness (QALYs):** RRP RALP **Total direct costs:** RRP RALP **Total indirect costs:** RRP RALP **ICER (cost per successful operation):** Direct costs scenario Indirect costs scenario **ICER (cost per QALY):** **Uncertainty:** One-way sensitivity analysis was conducted on the following variables : Lifetime for the da Vinci robot RALPs produced yearly Costs for the da Vinci robot Difference in effect Absence from work Hotel costs **Note** Exact ICER values were not reported but are displayed graphically using a tornado chart. ICERs reported here have been estimated to the nearest €10,000.	 27% 34% 0.0116 0.0103 € 3,863 € 8,369 € 12,465 € 13,411 € 64,343 € 13,514 RALP was dominated **Estimated ICER range** €50,000 - €150,000 €20,000 - €120,000 €50,000 - €80,000 €40,000 - €90,000 €20,000 €60,000	**Funding:** No funding or other financial relationships

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	from a published costing study by a Urology department in a hospital in Denmark. The lifetime of the Da Vinci Robot was assumed to be 5 years and was depreciated by 3% to estimate annual cost. The use of staff resources was estimated by interview. Average hourly rates for staff were obtained from gross annual salary rates published by the hospital in Denmark. Medical treatment costs were obtained from Medicin an online resource. All other costs were obtained from published studies. **Currency unit:** Euros (€) **Cost year:** Not reported **Discounting:** Not necessary given time horizon.					
Study 2						
Author: Ramsay et al. (NIHR HTA on radical prostatectomy) **Year:** 2012 **Country:** UK **Setting:**	**Type of analysis:** Cost-effectiveness analysis **Model structure:** Discrete event simulation (DES) model **Cycle length:** 3 months **Time horizon:** 10 years from the time of surgery **Perspective:** Third party payer perspective (NHS) **Source of base-line data:**	**Inclusion criteria:** Men with localised prostate cancer. **Exclusion criteria:** None stated **Base case (population):** Men with localised prostate cancer requiring radical prostatectomy. **Sample size:** 5,000	A. Robot-assisted prostatectomy B. Laparoscopic prostatectomy	Numerous base case analyses are presented according to throughput and robotic systems: **Effectiveness (mean total QALYs):** Robotic Laparoscopic **Cost (mean total costs):** Laparoscopic Robotic (Surgical capacity = 200) Robotic (Surgical capacity = 150) Robotic (Surgical capacity = 100) Robotic (Surgical capacity = 50) Robotic (Surgical capacity = 200 with cheaper equipment cost)	 6.517 6.440 £7,628 £9,040 £9,799 £11,312 £15,859 £8,186	**Funding:** NIHR HTA Programme No competing interests were declared.

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
NHS	All data were sourced according to the following hierarchy. 1. Associated systematic review 2. From other available and relevant literature 3. Consultation with relevant experts. Most of the baseline values, such as patient age were sourced from the systematic review. **Source of effectiveness data:** The data informing clinical parameters were sourced from systematic review. One of the key clinical parameters was the positive margin rates associated with robotic surgery and laparoscopic surgery (identified through systematic review). These rates were then used in conjunction with the patient's gleason score and tumour stage, to decide upon the subsequent care pathway for individuals using a decision matrix. Linked values of gleason score and postoperative tumour stage were sourced from a database including 4669 individuals at the Vanderbilt-ingram Cancer Centre. The decision matrix was formulated by rounds of consensus building with an expert panel. **Source of utility data:** Utility values were sourced from published studies (Cowen 1998, Volk 2004 and Korfage 2005) that were identified through a systematic literature review. Utility values encompassed the cancer management state (surveillance, biochemical recurrence, localised cancer and systematic cancer) and the longer term adverse event state (bladder neck contracture, urinary incontinence and erectile dys-	**Age:** 61.5 years old for patients undergoing robotic surgery 63 years old for patients undergoing laparoscopic surgery **Gender:** Men **Subgroup analysis:** None reported		**ICER (cost per QALY):** Surgical capacity = 200 Surgical capacity = 150 Surgical capacity = 100 Surgical capacity = 50 Surgical capacity = 200 with cheaper equipment cost **Uncertainty:** Numerous one-way sensitivity analyses were conducted. As in the base case, the results were presented according to throughput and robotic systems. However, for the purpose of brevity, only the results associated with the Robotic (surgical capacity = 200) scenario are presented here. **One-way sensitivity analyses** Lifetime horizon Positive margin rate Lower credible limit Upper credible limit Alternative rate of biochemical recurrence Biochemical recurrence rates twice that estimated in the base case **Two-way sensitivity analysis** Two-way sensitivity analysis was conducted on, what appears to be, the two most significant input parameters in the model; positive margin rates and the cost per procedure. The results of these analyses are represented graphically. The results show that the ICER increases as the number of procedures per year decreases or the odds ratio for relative difference in positive margin rate increases. In instances where these two effects are combined, the ICER value becomes very large (i.e. robotic surgery not cost-effective).	£18,329 £28,172 £47,822 £106,839 £7,009 **ICER** £1,436 £11,731 £50,502 £16,859 £11,890	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	function). **Source of cost data:** The unit costs of drugs were obtained from the British National Formulary (BNF). Some treatment costs were obtained using the tariffs applied to the relevant Healthcare Resource Group (HRG) codes. For the robotic system, various permutations of payment and leasing plans were considered. Furthermore, variations in the cost per procedure were considered by making changes to surgical capacity (i.e. number of procedures performed per year). The cost of surgical equipment was obtained from the manufacturer of the Da Vinci system (Intuitive Surgical Inc.). **Currency unit:** UK pound sterling (£) **Cost year:** Not reported **Discounting:** Costs and utilities were discounted at 3.5% per year			Probabilistic sensitivity analysis (PSA) also appears to have been conducted (although not described as such). **PSA** Probability of robotic surgery (capacity = 200) being cost-effective	**Proportion CE** 95%	

3.5 Radical radiotherapy

Conventional versus conformal radiotherapy

Short summary

Three randomised trials were identified (Dearnaley *et al.* 1999; Koper *et al.* 2004; Pollack *et al.* 2002). Two were direct comparisons of conformal and conventional radiotherapy (Dearnaley *et al.* 1999; Koper *et al.* 2004) and the other examined conventional radiotherapy with or without an 8 Gy conformal boost (Pollack *et al.* 2002). The evidence suggested reduced gastrointestinal and urinary toxicity with conformal radiotherapy. Follow-up was insufficient to compare overall survival. There was no evidence of a difference in biochemical failure rate in the trials that directly compared conformal with conventional radiotherapy (Dearnaley *et al.* 1999; Koper *et al.* 2004).

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOMES
Men with localised or locally advanced prostate cancer, of any age, with no prior treatment.	Conformal Radiotherapy	Conventional radiotherapy	• overall survival • disease-specific survival • biochemical disease-free survival • time until next intervention • 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)

Evidence summary

Conventional versus conformal radiotherapy

Three randomised trials (with six publications) were identified. Two trials were direct comparisons of conformal and conventional radiotherapy and the other one examined conventional radiotherapy with or without an 8 Gy conformal boost.

Table 95 Characteristics of the randomised trials comparing conventional and conformal RT.

Trial	Clinical T stage	Radiotherapy techniques	Number of patients
(Dearnaley *et al.* 1999; Tait *et al.* 1997a)	T1–T2 46% T3 53%	64 Gy conventional 64 Gy conformal 2Gy fractions	111 conventional 114 conformal
(Koper *et al.* 2004; Koper *et al.* 1999)	T1–T2 59% T3 38%	66 Gy conventional 66 Gy conformal 2Gy fractions	125 conventional 123 conformal
(Pollack *et al.* 2002; Storey *et al.* 2000)	T1–T2 80% T3 20%	70 Gy conventional 70 Gy conventional with 8 Gy conformal boost 2Gy fractions	150 conventional 151 nventional

Overall survival

The length of follow-up in the published trials is insufficient to allow conclusions about overall survival. The all cause mortality rates are shown below. Dearnaley and co-workers (Dearnaley *et al.* 1999) did not observe a significant difference in overall survival using actuarial analysis (p = 0.57).

Table 96 Overall mortality in the conventional vs. conformal RT trials

		All cause mortality		
Trial	Median follow-up	Conventional	Conformal	p (Chi Square)
Dearnaley (1999)	3.6 years	12/111	12/114	p = 0.94
Pollack (2002)	5 years	17/150	15/151	p = 0.84

Biochemical disease-free survival

Dearnaley and co-workers (Dearnaley *et al.* 1999) observed better biochemical control (PSA < 2 or 4 ng/ml) in the conformal radiotherapy group (p = 0.02), but when stratified using a pretreatment PSA cut-off of 20 ng/ml, the difference was no longer significant.

The overall biochemical failure rate in the MD Anderson trial (Pollack *et al.* 2002) was 48/150 in the conventional RT group and 32/151 in the conformal (p = 0.03) RT group. A multivariate regression showed treatment failure (either clinical or biochemical) was less likely in the conformal (higher dose) radiotherapy group: relative risk of freedom from failure (conventional vs. conformal) = 0.55 (95% C.I. 0.35 to 0.87; p = 0.009).

Acute radiation toxicity

Earlier publications from the three trials reported acute radiation toxicity (Tait *et al.* 1997a; Koper *et al.* 1999; Storey *et al.* 2000). (Tait *et al.* 1997a; Koper *et al.* 1999) were direct comparisons of conformal and conventional radiotherapy and (Storey *et al.* 2000) compared conventional radiotherapy with or without a conformal boost.

Table 97 Acute toxicity in the conventional vs. conformal RT trials

		Acute GU toxicity			Acute GI toxicity		
Trial	Scale	Conventional	Conformal	p	Conventional	Conformal	p
(Tait *et al.* 1997a)	Ad hoc	78/133	76/133	p=0.89	126/133	128/133	p=0.76
(Koper *et al.* 1999)	RTOG*	23/134	23/129	p=1.00	43/134	25/129	p=0.03
(Storey *et al.* 2000)	RTOG*	35/98	27/91	p=0.21	40/98	39/91	p=0.89

*Grade 2 or higher

One trial reported less grade 2 or higher acute gastrointestinal (GI) toxicity in the group treated with conformal radiotherapy. The other trials did not observe a significant difference in acute GI toxicity. None of the trials reported a significant difference in acute genitourinary (GU) toxicity.

Late radiation toxicity

Three randomised trials reported late radiation toxicity (Dearnaley *et al.* 1999; Pollack *et al.* 2002; Koper *et al.* 2004)

Table 98 Late toxicity in the conventional vs. conformal RT trials

			Late GU toxicity			Late GI toxicity		
Trial	Scale	Minimum follow-up	Conventional	Conformal	p	Conventional	Conformal	p
(Dearnaley *et al.* 1999))	RTOG*	2 years	23/111	20/114	p=0.34	15/111	5/114	p<0.01
(Koper *et al.* 2004)	RTOG*	2 years	14/125	11/123	p=0.70	20/125	16/123	p=0.63
(Pollack *et al.* 2002)	RTOG*	5 years (median)	8/150	13/151	p=0.63	12/150	26/151	p<0.01

*Grade 2 or higher

None of the trials reported a difference in grade 2 or higher late GU toxicity. One of the trials (Dearnaley *et al.* 1999) reported significantly less late GI toxicity when conformal radiotherapy was used. In the trial that compared 78 Gy conformal radiotherapy to 70 Gy conventional radiotherapy, an increase in late GI toxicity was seen in the higher dose group.

Three dimensional conformal radiotherapy (3DCRT) vs. intensity modulated radiotherapy (IMRT)

No randomised trials comparing 3DCRT with IMRT were found. Hummel and co-workers (Hummel *et al.* 2003) summarised evidence from six retrospective case series comparing the two techniques in men with prostate cancer. There was insufficient evidence to draw conclusions about the relative effectiveness of the two techniques. Evidence from one large case series suggested that, at the same dose, treatment with IMRT is associated with less late GI toxicity than standard 3DCRT.

Evidence tables

(Tait *et al.* 1997b)

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

Country: United Kingdom, setting: Tertiary care

Inclusion criteria Patients receiving CT planning for pelvic radiotherapy with four or less fields. 52% of patients had prostate cancer.

Exclusion criteria -

Population number of patients = 266.

Interventions Conventional or conformal radiotherapy, 64 Gy in 2 Gy fractions

Outcomes Acute GI or GU toxicity during treatment. Symptom severity was coded as 1 to 4, 1 was not at all, and 4 was very much.

Follow up Symptoms were assessed using a questionnaire at the start of treatment, weekly during treatment, and then monthly for two months after treatment.

Results -

COMPARISON IN PATIENTS DURING RADICAL PELVIC RADIOTHERAPY	CONVENTIONAL RT	CONFORMAL RT	OVERALL RESULT
Acute GU toxicity	78/133	76/133	No sig. difference, p=0.89
Acute GI toxicity	126/133	128/133	No sig. difference, p=0.76

General comments -

(Dearnaley *et al.* 1999

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

Country: United Kingdom, setting: Tertiary care

Inclusion criteria Men who were candidates for radical radiotherapy for histologically confirmed prostate cancer. Clinical disease stage T1-T4, G1 -G3, N0 and M0. Life expectancy at least 5 years. All were treated between 1988 and 1995.

Exclusion criteria -

Population number of patients = 225.

Interventions Conventional or conformal radiotherapy. Radiotherapy was delivered using a three field technique, to a dose of 60 to 64 Gy in 2 Gy fractions. 69% of the men received neoadjuvant hormone deprivation (LHRH agonist).

Outcomes Overall survival, biochemical recurrence free survival and late radiation toxicity.

Follow up Minimum follow up was 2 years, median was 3.6 years. Less than 2% of men were lost to follow up.

Results -

COMPARISON IN MEN AFTER EBRT FOR PCA	CONVENTIONAL RT	CONFORMAL RT	OVERALL RESULT
Death due to any cause	12/111	12/114	No significant difference in overall survival using actuarial analysis (p = 0.57)
Biochemical progression free survival			The authors biochemical control (PSA < 2 or 4 ng/ml) in the conformal radiotherapy group (p = 0.02), but when stratified using a pretreatment PSA cut-off of 20 ng/ml, the difference was not significant.
Late GI toxicity	15/111	5/114	Favours conformal RT (p=0.006)
Late GU toxicity	23/111	20/114	No significant difference (p=0.34).

General comments -

(Koper *et al.* 1999)

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

Country: Netherlands, the, setting: Tertiary care

Inclusion criteria Men with T1 to T4 N0 and M0 prostate cancer.

Exclusion criteria Prior pelvic radiotherapy. Other malignancies.

Population number of patients = 266.

Interventions All men were treated to a dose of 66 Gy, using the same planning procedure, treatment technique, linear accelerator, and portal imaging procedure. However, patients were randomised to either conventional or conformal dose distribution. No neoadjuvant hormonal therapy was given.

Outcomes Acute GI and GU radiation toxicity. The RTOG scale was used.

Follow up The report looks at acute toxicity during or very soon after treatment.

Results -

COMPARISON IN PATIENTS RECEIV-ING PELVIC EBRT FOR PROSTATE CANCER	CONVENTIONAL RT	CONFORMAL RT	OVERALL RESULT
Acute GU toxicity	23/134	23/129	No sig. difference, p=1.00
Acute GI toxicity	43/134	25/129	Favours conformal RT, p = 0.03

General comments -

(Koper *et al.* 2004)

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

Country: Netherlands, the, setting: Tertiary care

Inclusion criteria Men with T1 to T4 N0 and M0 prostate cancer.

Exclusion criteria Prior pelvic radiotherapy. Other malignancies.

Population number of patients = 266.

Interventions All men were treated to a dose of 66 Gy, using the same planning procedure, treatment technique, linear accelerator, and portal imaging procedure. However, patients were randomised to either conventional or conformal dose distribution. No neoadjuvant hormonal therapy was given.

Outcomes Late GI and GU radiation toxicity. The RTOG scale was used

Follow up Toxicity data at 2 years post treatment were available for all surviving patients

Results -

COMPARISON IN PATIENTS RECEIVING PELVIC EBRT FOR PROSTATE CANCER	CONVENTIONAL RT	CONFORMAL RT	OVERALL RESULT
Late GU toxicity	14/125	11/123	No sig. difference
Late GI toxicity	20/125	16/123	No sig. difference

General comments -

(Pollack *et al.* 2002)

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

Country: United States, setting: Tertiary care

Inclusion criteria Men with stage T1-T3, Nx/N0, M0 prostate cancer.

Exclusion criteria No prior pelvic radiotherapy, prostatectomy or hormonal therapy.

Population number of patients = 301.

Interventions All men were initially treated with a 4-field box to an isocenter dose of 46 Gy at 2 Gy per fraction. Men were randomised to either the 70 Gy treatment arm or 78 Gy treatment arm. In the 70-Gy arm, treatment was continued to a reduced volume using a 4-field box technique. In the 78-Gy arm, treatment was continued to a reduced volume using a conformal 6-field arrangement.

Outcomes Overall survival, biochemical recurrence free survival, late radiation toxicity (RTOG scale).

Follow up 301/305 enrolled patients were assessable, with a median follow-up of 60 months.

Results A multivariate regression showed treatment failure (either clinical or biochemical) was less likely in the conformal radiotherapy group: relative risk of freedom from failure (conventional vs. conformal) = 0.55 (95% C.I. 0.35 to 0.87; p = 0.009).

COMPARISON IN PATIENTS RECEIVING RADICAL PELVIC EBRT	CONVENTIONAL RT	CONFORMAL RT	OVERALL RESULT
Death due to any cause	17/150	15/151	No sig. difference
Biochemical recurrence	48/150	32/151	Favours conformal RT, p=0.03
Late GU toxicity	8/150	13/151	No sig. diff. (p=0.63)
Late GI toxicity	12/150	26/151	Favours conventional / lower dose RT, (p=0.006)

General comments -

(Storey *et al.* 2000)

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

Country: United States, setting: Tertiary care

Inclusion criteria Men with stage T1b-T3 prostate cancer

Exclusion criteria Salvage prostatectomy

Population number of patients = 189.

Interventions All men were initially treated with a 4-field box to an isocenter dose of 46 Gy at 2 Gy per fraction. Men were randomised to either the 70 Gy treatment arm or 78 Gy treatment arm. In the 70-Gy arm, treatment was continued to a reduced volume using a 4-field box technique. In the 78-Gy arm, treatment was continued to a reduced volume using a conformal 6-field arrangement.

Outcomes Acute GI and GU toxicity (RTOG scale).

Follow up 11/189 had incomplete follow up. Median follow up was 40 months, although only acute outcomes are listed in this appraisal.

Results -

COMPARISON IN PATIENTS RECEIVING RADICAL PELVIC EBRT	CONVENTIONAL RT	CONFORMAL RT	OVERALL RESULT
Acute GU toxicity	35/98	27/91	No sig. diff. p=0.21
Acute GI toxicity	40/98	39/91	No sig. diff. p=0.89

General comments -

Health Economics

The health economics analysis relating to this topic can be found at the end of section 4.2.

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Dose escalation in external beam radiotherapy

Short summary

Randomised trials have examined dose escalation in conformal radiotherapy for prostate cancer (Peeters *et al.* 2006; Dearnaley *et al.* 2007a; Dearnaley *et al.* 2005; Pollack *et al.* 2002), although Pollack and co-workers only used a conformal radiotherapy boost. There was consistent evidence of improved biochemical progression free survival in the higher dose groups, at the cost of increased late bowel toxicity. Longer follow-up is needed before overall or disease specific survival can be compared.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOMES
Men with localised or locally advanced prostate cancer, of any age, with no prior treatment.	Conformal Radiotherapy standard dose	Conformal Radiotherapy escalated dose	• overall survival • disease-specific survival • biochemical disease-free survival • time until next intervention • 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)

Evidence Summary

Four randomised trials compared low and high dose radiotherapy (Dearnaley *et al.* 2005; Pollack *et al.* 2002). The MD Anderson trial (Storey *et al.* 2000; Pollack *et al.* 2002) trial was also a comparison of conventional and conformal radiotherapy. The Dearnaley and co-workers (Dearnaley *et al.* 2005) trial included a comparison of treatment margins and was published as a pilot study for a larger multicentre trial (MRC RT01).

Two systematic reviews (Hummel *et al.* 2003; van Tol-Geerdink *et al.* 2006) examined the effect of conformal radiotherapy dose on outcome.

Table 99 Characteristics of randomised trials of radiotherapy dose escalation.

Trial	Clinical T stage	Radiotherapy doses	Number of patients
(Dearnaley *et al.* 2007a)	T1 – T2 81% T3 18%	64 Gy 74 Gy 2 Gy fractions	421 standard dose 422 escalated dose
(Peeters *et al.* 2006)	T1 – T4, % not reported	68 Gy 78 Gy 2 Gy fractions	331 standard dose 333 escalated dose
(Dearnaley *et al.* 2005)	T1 – T2 61% T3 39%	64 Gy 74 Gy	64 standard dose 62 escalated dose

		2 Gy fractions	
(Pollack *et al.* 2002)	T1 – T2 80%	70 Gy conventional	150 standard dose
	T3 20%	70 Gy conventional with 8 Gy conformal boost 2Gy fractions	151 calated dose

Overall and disease specific survival

At median follow-up of 50 months, Peeters and co-workers (Peeters *et al.* 2006) did not observe a significant overall survival difference between the dosage groups. The other randomised trials did not report overall or disease specific survival, either because they were not trial endpoints or because survival data were immature.

The review of Hummel and co-workers (Hummel *et al.* 2003) included a retrospective matched-pair analysis of 1306 patients comparing low dose (<74Gy) and high dose (>74 Gy) conformal radiotherapy. Men in the high dose group had significantly better overall and disease specific survival than those in the lower dose group.

In their systematic review, Van Tol-Geerdink and co-workers (van Tol-Geerdink *et al.* 2006) used logistic regression to model the relationship between dose and 5 year overall survival (also incorporating prognostic risk and treatment margins). The data for the models were drawn from observational studies. For an increase in radiotherapy dose from 70 to 80 Gy, their model predicted a corresponding increase in survival of around 11%.

Biochemical disease-free survival

Dearnaley and co-workers (Dearnaley *et al.* 2007a) reported significantly better biochemical recurrence free survival in men treated with the escalated dose, HR = 0.67 (95% C.I. 0.53 – 0.85). Similarly Peeters and co-workers (Peeters *et al.* 2006).reported better biochemical or clinical recurrence free survival in the escalated dose group, HR = 0.74 (95% C.I. 0.58 – 0.96).

The biochemical failure rate in (Dearnaley *et al.* 2005) was 33/64 in the standard dose group and 23/62 in the higher dose group RT (Log-rank test: p = 0.10; HR = 0.64, 95% CI 0.38 to 1.10). Five year disease free survival was 59% (95% CI 45 to 70%) for the standard dose group compared with 71% (95% CI 58 to 81%) for the high dose group, suggesting improved biochemical control with higher dose radiotherapy.

The biochemical failure rate in the Pollack and co-workers trial (Pollack *et al.* 2002) was 48/150 for standard RT and 32/151 for conformal (higher dose) RT (p = 0.03). A multivariate regression showed treatment failure (either clinical or biochemical) was less likely in the conformal (higher dose) radiotherapy group: relative risk of freedom from failure (conventional vs. conformal) = 0.55 (95% C.I. 0.35 to 0.87; p = 0.009).

The logistic regression model of Van Tol-Geerdink and co-workers (van Tol-Geerdink *et al.* 2006) predicted an increase in 5 year biochemical recurrence free survival of around 20% for moderate or high risk patients when radiotherapy dose was increased from 70 to 80 Gy. For low risk patients the corresponding predicted increase in biochemical recurrence free survival was around 6%.

The review of Hummel et al (Hummel *et al.* 2003) included four observational studies comparing biochemical disease free survival in standard and high dose groups. The evidence suggested a benefit of dose escalation, but not for low risk patients.

Acute radiation toxicity

Table 100 Acute radiation toxicity (RTOG Grade 2 or higher) in trials of radiotherapy dose escalation.

		Acute GU toxicity			Acute GI toxicity		
Trial	Scale	Standard dose	High dose	p	Standard dose	High dose	p
(Dearnaley *et al.* 2007b)	RTOG	38%	39%	–	30%	33%	–
(Dearnaley *et al.* 2005)	RTOG	23/64	28/62	p=0.34	28/64	29/62	p=0.81
(Storey *et al.* 2000)	RTOG	35/98	27/91	p=0.21	40/98	39/91	p=0.89

*Group differences in the rates of grade two or higher acute toxicity were not statistically significant.

Late radiation toxicity

Table 101 Rate of late radiation toxicity (RTOG grade 2 or more) in trials of radiotherapy dose escalation.

			Late GU toxicity			Late GI toxicity		
Trial	Scale	Follow-up	Standard dose	High dose	p	Standard dose	High dose	p
(Dearnaley *et al.* 2007a)	RTOG	5 years	32/421	46/422	p=0.14	83/421	119/422	p<0.01
(Peeters *et al.* 2006).	RTOG	5 years	41%	39%	p=0.40	27%	32%	p=0.20
(Dearnaley *et al.* 2005)	RTOG	5 yrs	7/64	11/62	p=0.38	7/64	14/62	p=0.12
(Pollack *et al.* 2002)	RTOG	Median 3.6 yrs	8/150	13/151	p=0.63	12/150	26/151	p<0.01

Two of the four trials reported increased grade two or more gastrointestinal toxicity with higher radiotherapy dose (Dearnaley *et al.* 2007a; Pollack *et al.* 2002). Dearnaley and co-workers (Dearnaley *et al.* 2005) reported significantly increased bowel toxicity with the higher radiotherapy dose, if all grades of toxicity were included.

Van Tol-Geerdink and co-workers (van Tol-Geerdink *et al.* 2006) predicted an increase in late GI morbidity of around 15% when radiotherapy dose increased from 70 to 80 Gy. The corresponding predicted increases in GU morbidity and erectile dysfunction were around 9% and 22% respectively.

Evidence tables

Randomized controlled trials

(Dearnaley *et al.* 2005)

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

Country: United Kingdom, setting: Tertiary care

Inclusion criteria Men with histologically confirmed prostate cancer, clinical state T1b to T3b, N0, M0.

Exclusion criteria Medical history which made radical radiotherapy inappropriate. Previous androgen suppression or pelvic radiotherapy

Population number of patients = 126, median age = 67 years.

Interventions Men were randomised to received either 64 Gy

74 Gy conformal radiotherapy in 2 Gy fractions. Another factor (treatment margins of 1 or 1.5 cm) was also examined in this trial.

Men had neoadjuvant hormone suppression with an LHRH analogue for 3 to 6 months, initially with cyproterone acetate to prevent testosterone flare.

Outcomes Biochemical failure free survival (biochemical failure was PSA more than 2 ng/ml). Acute and late side effects (RTOG and LENT SOM scales).

Follow up Acute side effects were assessed weekly during therapy (weeks 1 to 6), and at weeks 8, 10 and 18. Clinical examinations and PSA test were done at 6 weekly intervals during hormonal therapy. 10/126 patients were lost to follow-up.

Results Although there was no overall significant difference in biochemical failure free survival, five year disease free survival was 59% (95% CI 45 to 70%) for the standard dose group compared with 71% (95% CI 58 to 81%) for the high dose group, suggesting improved biochemical control with higher dose radiotherapy.

Toxicity rates in the table below are the number of patients who experienced RTOG scale 2 or higher adverse events. Including all grades of toxicity, there was significantly increased bowel toxicity with the higher radiotherapy dose (p=0.02).

COMPARISON IN MEN AFTER EBRT FOR PCA	64 GY DOSE	74 GY DOSE	OVERALL RESULT
Biochemical progression free survival	Biochemical failure rate was 33/64	Biochemical failure rate was 23/62	Log-rank test: p = 0.10; HR = 0.64, 95% CI 0.38 to 1.10
Acute GI toxicity	28/64	29/62	p=0.81
Acute GU toxicity	23/64	28/62	p=0.34

Late GI toxicity	7/64	14/62	p=0.12
Late GU toxicity	7/64	11/62	p=0.38

(Dearnaley *et al.* 2007)

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

Country: UK and New Zealand, setting: Tertiary care

Inclusion criteria Men with histologically confirmed T1b to T3a, N0, M0 prostate cancer, with PSA<50ng/ml. WHO performance status of 0 or 1; normal blood count.

Exclusion criteria Previous pelvic radiotherapy or radical prostatectomy. Previous androgen deprivation. Substantial past medical history which precluded pelvic radiotherapy.

Population number of patients = 843, median age = 67 years.

Interventions All men had neoadjuvant androgen suppression (LHRHa plus antiandrogen for tumour flare). Men were randomly assigned to receive either 64 Gy in 32 fractions (the standard group) or 74 Gy in 37 fractions (the escalated group), by conformal radiotherapy.

Outcomes Biochemical progression free survival, freedom from local progression, metastases free survival, overall survival and late toxicity. Toxicity was assessed using physician completed RTOG questionnaires, LENT/SOM questionnaires and Royal Marsden Hospital (RMH) scores.

Follow up Men were assessed every 6 months until 2 years after the start of radiotherapy and once a year thereafter. 831/843 received radiotherapy. Median follow-up was 63 months overall, 71% of surviving patients had at least 5 years of follow-up.

Results -

COMPARISON IN MEN WITH LOCALISED OR LOCALLY ADVANCED PROSTATE CANCER, WITH NO METASTASES	74 GY DOSE	64 GY DOSE	OVERALL RESULT
Biochemical progression free survival	108/422 cumulative biochemical progression events at 5 years	179/421 cumulative biochemical progression events at 5 years	favours escalated dose, HR for bPFS escalated to standard group was 0.67 (95% CI 0.53 to 0.85)
Clinical progression	35/422 cumulative clinical progression	49/421 cumulative clinical progression	not significantly different, HR=0.69 (95% CI

free survival	events at 5 years	events at 5 years	0.47 to 1.02)
Local progression free survival	14/422 cumulative local progression events at 5 years	18/421 cumulative local progression events at 5 years	not significantly different, HR=0.65 (95% CI 0.36 to 1.18)
Metastases free survival	rate not reported	rate not reported	not significantly different, HR=0.74 (95% CI 0.47 to 1.18)
Overall survival	rate not reported	rate not reported	94 men died overall, but groups are not compared
Late GI toxicity (RTOG 2 or more)	119/422 men reported RTOG grade 2 or higher by 5 years	83/421 men reported RTOG grade 2 or higher by 5 years	favours standard dose HR=1.47 (95% CI 1.12 to 1.92)
Late GU toxicity (RTOG 2 or more)	46/422 men reported RTOG grade 2 or higher by 5 years	32/421 men reported RTOG grade 2 or higher by 5 years	not significantly different, HR=1.36 (95% CI 0.90 to 2.06)

(Peeters *et al.* 2006)

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

Country: Netherlands, the

Inclusion criteria Men with prostate cancer, stage T1b to T4. PSA less than 60 ng/ml. Karnofsky performance score of 80 or more.

Exclusion criteria Men with metastases, cytologically or histologically confirmed lymph node involvement, previous pelvic radiotherapy, previous malignancy (other than BCC).

Population number of patients = 669.

Interventions Men were randomly assigned to either the standard dose of 68 Gy or the escalated dose of 78 Gy, delivered in 2 Gy fractions using 3D conformal radiotherapy. The protocol specified that hormonal therapy was permitted but not recommended.

Outcomes Freedom from failure (biochemical or clinical progression free survival). Clinical progression free survival, overall survival and toxicity (RTOG criteria slightly modified).

Follow up Median follow up was 50.7 months (range 9.6 to 94.2 months). 664/669 men were included in the statistical analysis.

Results -

COMPARISON IN MEN WITH LOCALISED OR LOCALLY ADVANCED PROS-	78 GY DOSE	68 GY DOSE	OVERALL RESULT

TATE CANCER, WITH NO METASTASES			
Biochemical or clinical recurrence	107/337	136/332	Favours escalated dose, HR=0.74 (95% C.I. 0.58 to 0.96)
Clinical failure	69/337	66/332	No significant difference
Overall survival	83% at 5 years	82% at 5 years	No significant difference
Late GI toxicity (RTOG 2 or more)	32% at 5 years	27% at 5 years	No significant difference
Late GU toxicity (RTOG 2 or more)	39% at 5 years	41% at 5 years	No significant difference

Systematic review of cohort studies

(van Tol-Geerdink *et al.* 2006)

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

Country: , setting: Other

Inclusion criteria Studies published between 1990 and 2003 about conformal radiotherapy dosage and patient outcomes in prostate cancer

Exclusion criteria IMRT

Population -

Interventions Three dimensional conformal radiotherapy.

Outcomes Overall survival at 5 years. Five year biochemical recurrence free survival. Late GI and GU morbidity. Erectile dysfunction.

Results A total of 38 studies were included. Logistic regression was used to form a model combing prognostic risk, treatment margin, dose and outcome.

5 year overall survival

For an increase in radiotherapy dose from 70 to 80 Gy the model predicted a corresponding increase survival of around 11%.

5 year biochemical recurrence free survival

The model predicted an increase in 5 year biochemical recurrence free survival of around 20% for moderate or high risk patients when radiotherapy dose was increased from 70 to 80 Gy. For low risk patients the corresponding predicted increase in biochemical recurrence free

survival was around 6%.

Late treatment toxicity

The model predicted an increase in late GI morbidity of around 15% when radiotherapy dose increased from 70 to 80 Gy. The corresponding predicted increases in GU morbidity and erectile dysfunction were around 9% and 22% respectively.

Health Economics

The health economics analysis relating to this topic can be found at the end of section 4.2.

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Hypofractionated versus conventionally fractionated radiotherapy

Short summary

Two randomised controlled trials (Lukka *et al.* 2005; Yeoh *et al.* 2003) have compared hypofractionated (fractions of 2.6 Gy or more) with conventionally fractionated (2Gy fractions) radiotherapy in this population, but at doses lower than currently used. One trial (Lukka *et al.* 2005) reported overall survival, and found no significant difference between groups at a median follow-up of 5.7 years. There was no evidence about the effect of hypofractionation on disease specific survival, but the evidence suggests an increased risk of biochemical failure and acute treatment toxicity with hypofractionated radiotherapy.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOMES
Men with localised or locally advanced prostate cancer, of any age, with no prior treatment.	Hypofractionated radiotherapy	Conventionally fractionated radiotherapy	• overall survival • disease-specific survival • biochemical disease-free survival • time until next intervention • 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)

Evidence summary

Overall and disease specific survival

One of the trials reported overall mortality rates (Lukka *et al.* 2005). At median follow-up of 5.7 years, there was no statistically significant difference in overall mortality: hazard ratio for overall mortality for conventional versus hypofractionated radiotherapy was 1.12 [95% CI 0.87–1.59]. The rate of death from prostate cancer was 18/470 (3.8%) in the conventional fractionation arm compared with 13/466 (2.7%) in the hypofractionation arm, but there was no formal analysis of disease specific survival.

Biochemical failure

In Lukka and co-workers (Lukka *et al.* 2005), the overall rate of biochemical failure was 56% in men treated with hypofractionated radiotherapy compared with 50% in men treated with the conventional fractionation. The hazard ratio for biochemical failure (conventional fractionation versus hypofractionation) was 0.85 [95% C.I. 0.71 to 1.01].

Yeoh and co-workers (Yeoh *et al.* 2003) estimated the rate of biochemical failure at four years as 14%, for both treatment groups.

Acute gastrointestinal toxicity

Yeoh and co-workers (Yeoh *et al.* 2003) reported the rates of each LENT-SOMA grade 2 or higher gastrointestinal side effect (diarrhoea, frequency of bowel movements etc.) at one month after treatment separately. While they found no significant differences, there was a clear trend in favour of conventional fractionation: in all cases, the rate of each side effect was approximately twice as high in the hypofractionated as in the conventionally fractionated treatment arm.

Lukka and co-workers (Lukka *et al.* 2005) grouped all acute NCIC grade 3 or 4 GI side effects in their analysis. The rate of acute GI side effects was 4.1% for the hypofractionation group compared with 2.6% in the conventional fractionation group, but the difference was not statistically significant.

Pollack and co-workers (Pollack *et al.* 2006) reported acute toxicity in the first 100 men enrolled in a randomised trial of hypofractionated versus conventionally fractionated radiotherapy in men with prostate cancer. There were no statistically significant differences between treatment arms in the overall maximum acute gastrointestinal or genitourinary toxicity. In a longitudinal analysis, however, there was a significant increase in gastrointestinal toxicity in the hypofractionated EBRT group during weeks two, three and four of treatment, compared with the conventionally fractionated group. The greatest mean difference was half a toxicity grade (on the RTOG scale), during week three

Acute genitourinary toxicity

Yeoh and co-workers (Yeoh *et al.* 2003) did not publish the rates of acute grade 2 or higher genitourinary side effects but reported that no statistically significant differences were found.

Lukka and co-workers (Lukka *et al.* 2005) the rate of acute GU side effects was 8.6% for the hypofractionation group compared with 4.9% in the conventional fractionation group (risk difference of -4.4%, conventional vs. hypofractionated, [95% C.I. -0.6 to -8.1%]).

Late treatment toxicity

Lukka and co-workers (Lukka *et al.* 2005) found no group differences in late NCIC grade 3 or 4 treatment toxicity. The rate of late gastrointestinal toxicity was the same in both treatment groups at 1.3%. The rate of late genitourinary toxicity was 1.9% in both treatment groups.

Yeoh and co-workers (Yeoh *et al.* 2003) did not report any significant differences between groups in late grade two or more GI or GU toxicity. At two years after treatment, the rates of urgency of defecation in the conventional and hypofractionation groups were 22% and 27% respectively. The corresponding rates of rectal bleeding were 14% and 20%.

Evidence Tables

Yeoh, Fraser, McGowan, Botten, Di Matteo, Roos, Penniment & Borg . Evidence for efficacy without increased toxicity of hypofractionated radiotherapy for prostate carcinoma: Early results of a Phase III randomized trial. Int J Radiat. Oncol Biol. Phys. 55[4]. 2003.

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

Country: Australia, setting: Tertiary care

Inclusion criteria Consecutive men with clinically localised prostate cancer, referred to one of 5 clinical oncologists for radical radiotherapy.

Exclusion criteria Serum PSA > 80 ng/ml, antiandrogen therapy.

Population number of patients = 120, age range 44 to 83 years, median age = 64 years.

Interventions Men were randomised to receive either conventional or hypofractionated EBRT. The conventional dose was 64 Gy in 32 fractions within 6.5 weeks. The hypofractionated dose was 55 Gy in 20 fractions within 4 weeks.

EBRT dose was prescribed to the isocentre of either a three field or four field plan encompassing the prostate only.

Outcomes Gastrointestinal symptoms (LENT-SOMA scale), genitourinary symptoms (LENT-SOMA scale) and sexual function (assessed using EORTC questionnaire). Outcomes were reported before treatment and at 1 month, 1 year and 2 years after treatment.

Follow up Minimum 2 years, median follow-up 43.5 months (3.6 years). Follow-up interval after EBRT was monthly for 3 months, then 3 monthly until 2 years post-therapy, and from then on 6 monthly.

Results Rate of grade 2 or higher GI symptoms on the LENT-SOMA scale (grade 2 or higher symptoms require treatment).

Rates of grade 2 or higher GU symptoms were not reported, however rates of grade 1 of higher GU symptoms did not differ statistically between treatment groups at any time point.

COMPARISON IN MEN AFTER EBRT FOR PCA	HYPOFRACTIONATED EBRT	CONVENTIONALLY FRACTIONATED EBRT	OVERALL RESULT
Frequency of bowel movements	10 (17%) at 1 month after EBRT and 2 (4%) at 2 years	4 (6%) at 1 month after EBRT and 4 (6%) at 2 years	Difference not significant, figures not reported
Diarrhoea	3 (5%) at 1 month after EBRT and none at 2 years	1(1%) at 1 month after EBRT and none at 2 years	Difference not significant, figures not reported
Pain on using bowels	11 (19%) at 1 month post-EBRT and none at 2 years	7 (11%) at 1 month post-EBRT and none at 2 years	Difference not significant, figures not reported
Mucous discharge from bowel	15 (27%) at 1 month post-EBRT and 4 (7%)	9 (14%) at 1 month post-EBRT and 7	Difference not significant, figures not re-

	at 2 years	(12%) at 2 years	ported
Urgency of defecation	23 (37%) at 1 month post-EBRT and 14 (27%) at 2 years	16 (26%) at 1 month post-EBRT and 12 (22%) at 2 years	Difference not significant, figures not reported
rectal bleeding	9 (16%) at 1 month post-EBRT and 10 (20%) at 2 years	2 (3%) at 1 month post-EBRT and 8 (14%) at 2 years	Difference not significant, figures not reported

(Pollack *et al.* 2006)

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

Country: United States, setting: Tertiary care

Inclusion criteria Men with intermediate to high risk prostate cancer. Intermediate risk was Gleason score 7, PSA 10 to 20 ng/mL, or at least 3 biopsy cores of Gleason score at least 5.

Exclusion criteria More than 4 months of androgen deprivation before treatment, initial PSA more than 80 ng/ml, prior pelvic radiotherapy, prior RP, prior malignancy (excluding skin cancers).

Population number of patients = 100.

Interventions All men were treated with intensity modulated external beam radiotherapy. Men were randomised to receive either 76 Gy in 38 fractions at 2 Gy per fraction (conventional fractionation) or 70.2 Gy in 26 fractions at 2.7 Gy per fraction (hypofractionation).

Outcomes Acute side effects of radiotherapy, measured using the RTOG and LENT-SOMA scales.

Follow up Men were assessed weekly during radiotherapy and at 3 months after treatment.

Results There were no statistically significant differences between treatment arms in the overall maximum acute gastrointestinal (GI) or genitourinary (GU) toxicity.

A longitudinal analysis, however, showed a significant increase in GI toxicity in the hypofractionated EBRT group during weeks 2, 3, and 4 of treatment, compared with the conventionally fractionated group. The greatest mean difference was half a toxicity grade, during week three.

COMPARISON IN MEN WITH INTERMEDIATE OR HIGH RISK PCA	CONVENTIONALLY FRACTIONATED EBRT	HYPOFRACTIONATED EBRT	OVERALL RESULT
Grade 2 or more GI toxicity during radiotherapy	4/50 (8%)	9/50 (18%)	No statistically sig. difference

Grade 2 or more GU toxicity during radio-therapy	28/50 (56%)	24/50 (48%)	No statistically sig. difference
Grade 2 or more GI toxicity at 3 months after EBRT	1/50 (2%)	0/50 (0%)	No statistically sig. difference
Grade 2 or more GU toxicity at 3 months after EBRT	4/50 (8%)	3/50 (6%)	No statistically sig. difference

General comments Results are for the first 100 men only, (an intermediate analysis) unclear whether this sample size is sufficient to make comparisons of acute toxicity.

Lukka, Hayter, Julian, Warde, Morris, Gospodarowicz, Levine, Sathya, Choo, Prichard, Brundage & Kwan . Randomized trial comparing two fractionation schedules for patients with localized prostate cancer. J Clin Oncol 23[25]. 2005.

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

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

Inclusion criteria Men with clinical stage T1 to T2 prostate cancer, treated at one of 8 institutions.

Exclusion criteria PSA > 40 ng/ml. Previous therapy for prostate cancer. Prior or active malignancy (with some exceptions). Prior treatment or comorbidity that would preclude pelvic radiotherapy.

Population number of patients = 936, age range 53 to 84 years, mean age = 70 years.

Interventions Men were randomised to receive either hypofractionated EBRT or conventionally fractionated EBRT. The hypofractionated group received 52.5 Gy in 20 fractions over 28 days. The conventionally fractionated group received 66 Gy in 33 fractions over 45 days.

Outcomes Treatment failure (biochemical or clinical failure or start of androgen deprivation), overall survival, positive prostate biopsy at 2 years post-EBRT, radiation toxicity

Follow up Men were assessed at 1 month and 6 months post-EBRT and then at 6 monthly intervals. Median follow-up was 5.7 years (minimum 4.5 years, maximum 8.3 years). 7 men did not receive EBRT and 3 men had EBRT that violated the trial protocol.

Results Rates of grade 3 or 4 toxicity are shown below. Acute toxicity was within 5 months of the end of radiotherapy. Late toxicity was at least 5 months after the end of radiotherapy.

COMPARISON IN MEN AFTER EBRT FOR PCA	HYPOFRACTIONATED EBRT	CONVENTIONALLY FRACTIONATED EBRT	OVERALL RESULT

Overall mortality	77/466 (17%)	89/470 (19%)	From Cox regression, conv. vs. hypo, HR = 1.12 [95% C.I. 0.87-1.59]
Treatment failure	263/466 (56%)	236/470 (50%)	Favours conventional, from Cox regression, conv. vs. hypo, HR = 0.85 [95% C.I. 0.71 to 1.01]
Positive prostate biopsy	50.9%	53.2%	Risk difference 2.3% [95% CI -5.1% to 9.8%]
Acute GI toxicity	19/466 (4.1%), grade 3 or 4	12/470 (2.6%), grade 3 or 4	Risk difference -1.5% [95% CI -4.0% to 0.8%]
Acute GU toxicity	40/466 (8.6%), grade 3 or 4	23/470 (4.9%), grade 3 or 4	Favours conventional, risk difference -3.7% [95% CI -7.0% to -0.5%]
Late GI toxicity	6/466 (1.3%), grade 3 or 4	6/470 (1.3%), grade 3 or 4	Risk difference 0.0% [95% CI -1.7% to 1.6%]
Late GU toxicity	9/466 (1.9%), grade 3 or 4	9/470 (1.9%), grade 3 or 4	Risk difference 0.0% [95% CI -1.7% to 1.6%]

General comments -

Health Economics

The health economics analysis relating to this topic can be found at the end of section 4.2.

Reference List

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Brachytherapy versus watchful waiting or other radical therapies

Short summary

There were no randomised trials comparing brachytherapy with other radical therapies or with watchful waiting. Five systematic reviews of observational studies found insufficient evidence to compare overall and disease specific survival after brachytherapy with that after other radical therapies. Although some of the reviews contained evidence from high dose rate brachytherapy series, the majority of studies were of low dose rate brachytherapy. Evidence from these systematic reviews suggests that, at least for low risk patients, biochemical recurrence free survival after brachytherapy is equivalent to that after external beam radiotherapy or prostatectomy. Systematic reviews comparing the toxicity of radical therapies for prostate cancer suggest brachytherapy has a similar adverse event rate to prostatectomy or external beam radiotherapy, but such comparisons use evidence from observational studies. Some reports of brachytherapy case series suggest lower rates of impotence and incontinence than seen with surgery or EBRT but higher rates of obstructive and irritative urinary symptoms.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOMES
Men with localised or locally advanced prostate cancer, of any age, with no prior treatment.	Brachytherapy	• Watchful waiting also • Radical prostatectomy • EBRT • Conformal Radiotherapy • Conventional radiotherapy • Cryosurgery • HIFU	• overall survival • disease-specific survival • biochemical disease-free survival • time until next intervention • 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)

Evidence summary

No randomised trials compared brachytherapy with watchful waiting or with other radical therapies. Evidence about the clinical effectiveness of brachytherapy came from systematic reviews of observational studies, randomized controlled trials comparing brachytherapy isotopes, and observational studies. Although some of the reviews contained evidence from high dose rate brachytherapy series, the majority of studies were of low dose rate brachytherapy.

Overall and disease specific survival

Hummel and co-workers (Hummel 2003) reported overall survival rates of between 77% and 90% at five years after treatment. Disease specific survival was not reported separately in the systematic reviews, and there was insufficient evidence to compare overall or disease specific survival after brachytherapy with that after other radical therapies.

Biochemical disease free survival

Systematic reviews of institutional case series (Hummel, 2003; Doust, 2004) suggest that brachytherapy is less effective than external beam radiotherapy or prostatectomy for intermediate or high risk patients. Other systematic reviews (Norderhaug et al. 2003; Vicini, 2005; Nilsson, 2004) concluded that, if risk group is accounted for, biochemical disease free survival is similar for men treated with brachytherapy,

external beam radiotherapy or prostatectomy. In a randomised trial comparing prostate brachytherapy isotopes in men with low risk prostate cancer, around 90% of the men were free from biochemical failure at three years after treatment (Wallner, 2003).

Treatment toxicity and quality of life

A systematic review of observational studies concluded that that treatment toxicity was acceptable. (Nilsson et al. 2004). There was some evidence to that brachytherapy results in lower rates of impotence, and incontinence than surgery or EBRT but higher rates of obstructive and irritative urinary symptoms (Hummel et al. 2003; Doust et al. 2004; Downs et al. 2003; Buron et al. 2007; Soderdahl et al. 2005; Namiki et al. 2006).

Evidence tables

Norderhaug, Dahl, Høisæter, Heikkilä, Klepp, Olsen, Kristiansen, Wæhre, Johansen. Brachytherapy for prostate cancer: A systematic Review of Clinical and Cost Effectiveness. European Urology 44(2003) 40-46			
Design: Systematic Review evidence level 1++			
Country: International			
Setting: Other			
Inclusion criteria: RCTs with comparable patient groups, with the populations covered comparable, similar methods used in the investigation, outcome measures comparable and the variability in effect size between studies is less than would be expected by chance alone.			
Exclusion criteria: studies that did not have the required evidence level			
Population: number of studies: 5			
Intervention: Brachytherapy (BT) compared with radical prostatectomy (RP); BT. versus external beam radiation therapy (EBRT); BT plus EBRT;			
Outcomes: Disease free survival based on PSA; Biochemical no evidence of disease (bNED) cf. ASTRO definition.			
Follow-up: -			
Results: Strong evidence that there is no difference in the disease-free survival based on PSA (5 year bNED) or in rates of complications, between comparable patient groups treated with BT, RT, EBRT, BT + EBRT.			
OUTCOME	COMPARISON		RESULT
BT vs. RT	**BT**	**RT**	
Stokes et. al	n= 186 median age 74 stage T1c, T2a Gleason ≤ 6/10 PSA < 10ng/ml	n= 222 66 40% stage T1c, T2a ≤ 6/10 < 10ng/ml	No difference in 5 year bNED; 70% for patients with 79% low or intermediate risk
BT vs. EBRT	**BT**	**EBRT**	
Beyer & Brachman	n= 695 median age 74 stage T1-T2 21% Gleason <5 19% PSA < 4 ng/ml	n= 1527 64 stage T1-T2 28% Gleason <5 9% PSA < 4 ng/ml	No difference in 5 year bNED; BT 69%; EBRT 71%
Zelefski et al	n=145 median age 74 stage T1c-T2b Gleason <6 PSA median 6.1 ng/ml	n= 137 64 stage T1c-T2b Gleason <6 PSA median 6.6 ng/ml	No difference in 5 year bNED; BT 82%; EBRT 88% proctitis 11% vs. 6% ED 53% vs. 43% urethral stricture 12% vs. 2%

Stokes et al	n=186	n= 132	No difference in 5 year bNED;
	median age 74	72	BT 69%;
	79% stage T1c-T2a	72% stage T2c-T3	EBRT 71%
	Gleason ≤6/10	Gleason >7/10	rectal complications
	PSA < 10 ng/ml	PSA > 20 ng/ml	
BT plus EBRT	**BT + EBRT**	**EBRT**	
Kestin et al	n= 1615	n= 161	5 year bNED;
	median age 69	74	BT + EBRT 67%;
	median stage T2b	median stage T2b	EBRT 44%
	median Gleason 7	median Gleason 9.9	
	BT + EBRT	**BT**	
Geldblum et al	age not specified stage T1c T2b	(52-89) for both groups stage T1c T2b	5 year bNED; BT + EBRT 10.5%; BT 8.9%

General comments: No studies comparing the cost effectiveness of BT vs. other therapies were included due to poor description of cost component, disease severity, co-morbidity and socio-demographic factors. Costs seem to vary depending on the country.

Hummel, Paisley, Morgan Currie, Brewer. Clinical and Cost-effectiveness of New and Emerging Technologies for Early Localised prostate Cancer: A Systematic Review. Health Technology Assessment, Vol. 7 : No.33, 2003
Design: Systematic Review evidence level 1++
Country: International
Setting: hospital based (secondary care)
Inclusion criteria: 104 studies evaluating 12 interventions: Neoadjuvant Hormonal Therapy (NHT); Adjuvant Hormonal Therapy (AHT); Hormonal Monotherapy; Brachytherapy; 3D-CRT; Intensity-modulated Conformal Radiotherapy (IMRT); Cryotherapy; High-intensity Focused Ultrasound (HIFU); Interstitial Microwave Thermal Therapy (IMTT); Transperineal Radiofrequency Interstitial Tumour Ablation (RITA); Laser Photocoagulation; Gene Therapy.
Exclusion criteria: -
Population: Biological abstracts; CDSR and CCTR; CINAHL; Citation indexes; CRD databases; EMBASE; HEED; HMIC; MEDLINE
Intervention: Evaluate clinical and cost-effectiveness of new technologies for early localised prostate cancer.
Outcomes: Clinical effectiveness and cost-effectiveness
Follow-up: -
Results: • For Neoadjuvant hormonal therapy, no evidence of benefit was seen in terms of biochemical disease-free survival. • For adjuvant hormonal therapy, there was no evidence of benefit in terms of survival, but some conflicting evidence that higher risk patients may benefit. • The largest number of studies reported results for Brachytherapy, where some evidence suggested that it may be more effective than standard treatments for lower risk patients, although less effective for intermediate and high-risk patients, in terms of biochemical disease-free survival. • Lower quality evidence reported fewer complications than for standard treatments. • Higher quality evidence suggested that disease-specific quality of live (QoL) for brachytherapy patients was slightly higher than for patients receiving standard treatments. • The review of three-dimensional conformal radiotherapy (3D-CRT) considered treatment-related morbidity, where significantly fewer gastrointestinal complications occurred than with standard radiotherapy. It was suggested that higher radiation doses achieved better disease control, although patient characteristics were often reported as independent indicators of control. • The review of intensity-modulated conformal radiotherapy suggested that late gastrointestinal toxicity may be reduced compared with 3D-CRT. • For cryotherapy, high rates of impotence were reported. Owing to the paucity and poor quality of evidence identified for other interventions, conclusions regarding their clinical effectiveness cannot be drawn. • Cost-effectiveness estimates were based on the impact of adverse events on quality-adjusted life-years and the assessment was restricted to Brachytherapy, 3D-CRT and cryotherapy compared with standard treatments. Of the new treatments included, only cryotherapy appeared not

to be potentially cost-effective compared with traditional treatments, owing to the associated high incidence of impotence.

COMPARISON	OUTCOME OF INTEREST
NHT	bDFS: no difference (p=0.663) at 36, 38 and 48 months follow up.
	Rate of organ confined disease: no difference.
	Rate of positive surgical margins: 23% vs. 41% (p=0.013) in favour of the NHT patie
	Mean preoperative PSA: Patients receiving NHT, PSA levels significantly red operatively. 57% lower in the 8-month therapy group (p=0.0141).
AHT	Positive biopsy (residual disease): 62% vs. 30% in favour of AHT; 4% in patient (p=0.0005) at 12 months.
	PSA levels: similar advantage at 12 months, but by 24 months, PSA differences b groups were not statistically significant.
	bNED rates at 5 years: in favour of AHT patients 55% vs. 31% (p=0.02).
	OS + DSS at 5 years: no difference.
	PSA failure rates:
	Low Risk Group – no difference.
	Intermediate and High Risk – reduction in risk of failure 5-fold [relative risk 0.2 w and 2.5-fold 0.4 with 95% CI respectively, in favour of EBRT + AHT.
	QoL: patients receiving AHT are more likely to be impotent and have ejaculator than those receiving EBRT only.
Hormonal Mono-therapy	PSA dropped to ≤0.1 ng/mL in 95% of patients after 3 months
	Remained stable at 36 months
Brachytherapy	Reported bDFS at: 5 years – range 57-94%; 10 years – range 66-92%; 15 years -
	Overall actuarial survival at 5 years: 77-90%
	No difference in terms of failure-free survival at 5 years when compared with EB 69%, respectively).
	Intermediate and high risk patients significant difference in favour of EBRT.
	No differences in actuarial bDFS for low and intermediate risk patients when con EBRT and RP. Significance difference in favour of RP for high risk patients.
	No difference in overall 5 year PSA relapse-free survival between Pd-103 and I-125
	Better biochemical control for Pd-103 + NHT.
	General and disease-specific QoL better for Brachytherapy compared with BT + EB activity, urinary incontinence and cystitis).
	No long-term GI complications, fewer side-effects compared with EBRT or RP.
3D-CRT	Higher doses appear to achieve better disease control. Fewer GI complications tha

	radiotherapy.
IMRT	Reduced late GI toxicity compared with 3D-CRT at the same dose.
Cryotherapy	High complication rates, particularly impotence and outlet obstruction 9-15%. bDFS rate at 5 years: Low Risk Group – 80% High Risk Group – 45% Overall survival rate at 5 years: 90%
HIFU	bNED: 55% vs. 29% in favour of HIFU only. Biochemical Freedom at 3 years: 80% Reported Complications: temporary obstruction; mild stress incontinence; decrease potency.
IMTT	Insufficient evidence to draw conclusions
RITA	Insufficient evidence to draw conclusions.
Photocoagulation	Insufficient evidence to draw conclusions.
Gene Therapy	Insufficient evidence to draw conclusions.

General comments:

Nilsson, Norlen and Widmark. A systematic Overview of Radiation Therapy Effects in Prostate Cancer. Acta Oncologica vol. 43, no 4 pp. 316-381, 2004
Design: systematic review evidence level 1++
Country: International
Setting: Hospital based
Inclusion criteria: One meta-analysis, 30 randomised trials, 55 prospective trials, 210 retrospective studies
Exclusion criteria: Lack of original data, insufficient data for analysis, lack of pre-treatment prognostic factors and/or outcome criteria, incomplete reviews of the literature, earlier reports on individual studies, conference reports, laboratory data, technical data, case reports, other diagnoses, other questions than outcome total 4317 studies.
Population: 152614 patients
Intervention: Conventional external beam radiation therapy (EBRT), 3D conformal radiation therapy (3DRCT), radiation induced toxicity and quality of life, adjuvant and salvage radiotherapy after prostatectomy (RP), androgen suppression with adjuvant radiotherapy after RP, high-dose-rate (HDR) brachytherapy as a radiation boost to EBRT, seed implantation BT with or without EBRT before the introduction of dedicated BT dose planning systems, BT with transperineal seed implantation and dedicated BT dose planning systems, BT with seed implantation combined with EBRT and with the use of dedicated BT dose planning systems, particle beam radiotherapy (hadron therapy), neoadjuvant and adjuvant hormonal therapy.
Outcomes: DFS, OS, PSA reduction, urinary and rectal toxicity
Follow-up: -

Results:

- No randomised trials have been identified that compare the outcome (disease free survival (DFS) and overall survival) of surgery - radical prostatectomy (RP) with either external beam radiation therapy (EBRT) of Brachytherapy (BT) for patients with localised low-risk prostate cancer (iPSA <10, GS≤ 6, stage ≤ T2b)
- There is substantial evidence from case series in large single institutional or multi-institutional studies showing that the outcome of EBRT and BT are similar to those of RT.
- There is reasonable evidence that patients with localised intermediate-risk and high-risk (iPSA ≥ 10 and/or GS ≥ 7 and/or T2) disease (i.e. patients normally not suited for surgery) benefit (freedom form failure and freedom form distant metastases) from higher than conventional dose. No overall survival benefit was shown.
- Substantial support for the conclusion that dose escalation for patients with localised intermediate-risk and high-risk disease can be performed with 3D conformal radiotherapy (photon or proton) boost with Ir 192 high dose rate brachytherapy boost, or brachytherapy boost with permanent seed implantation. Despite increased risk of urinary tract and/or rectal side effects dose escalated therapy can generally be safely delivered with all three techniques.
- Some evidence that £D conformal radiotherapy results in reduced late rectal toxicity and acute anal toxicity compared with radiotherapy administered with non-conformal treatment volumes.
- There is some evidence that postoperative EBRT after RP in patients with pT3 disease prolongs biochemical disease free survival (bDFS) and that the likelihood of achieving long term DFS is higher when treatment is given in an adjuvant rather than salvage setting. A breakpoint seems to exist around PSA level of 10 ng/ml, above which the likelihood for eradication of the recurrence diminishes (ongoing studies)
- After RP, endocrine therapy prior to and during adjuvant radiotherapy may result in longer bDFS than if only adjuvant radiotherapy is given. No impact on overall survival (OS) shown.
- Fairly strong evidence that short term endocrine therapy prior to and during radiotherapy results in increased DFS, increased local control, reduced incidence of distant metastases and reduced cause-specific mortality in patients with locally advance disease.
- There is some evidence that short term endocrine therapy prior to and during radiotherapy results in increased OS in a subset (GS 2-6) of patients with locally advanced disease.
- There is strong evidence that adjuvant endocrine treatment after curative radiotherapy results in improved local control, increased freedom form distant metastases and increased DFS in patients with loco-regionally advanced and/or high-risk disease.
- There is moderately strong evidence that adjuvant endocrine treatment after radiotherapy results in longer OS compared with radiotherapy alone in patients with loco-regionally advanced disease.

COMPARISON	OUTCOME OF INTEREST				
Conventional EBRT	Conventional ERBT with curable intent can be safely administered. Outcome data (bNED) are predictable when corrected for pre-treatment PSA levels. The rate of bNED control decreases with pre-treatment PSA level increase.				
	The 5-year DFS	PSA <4ng/mL	4-10ng/mL	10-20ng/mL	>20ng/mL
		85%	55%	45%	15%
	The 10-year DSS	well differentiated	moderately well differ-entiated	poorly differenti-ated prostate cancer	
		90%	75%	50%	
3DCRT ± dose escalation IMRT	3DCRT can be given safely. The portion of normal tissue exposed is reduced. Great demands on the positioning of the patient are imposed.				
	3DCRT reduces GI toxicity markedly. Fewer patients develop rectal/anal side-effects than those treated with conventional RT.				
	Radiation doses ≥74 Gy can be delivered with acceptable acute toxicity.				
	Patients most likely to benefit from increasing doses seem to be those in the low risk group (iPSA ≥10, GS ≥7, tumour stage ≥T2b).				
	IMRT makes high demands on patient and organ positioning during therapy. Effect on local control reported a high percentage of local failures promoting development of metastatic disease and the increasing hazard of distant metastasis overtime from local tumour persistence.				
	RT dose escalation has been advocated. Rising PSA and disease progression after RT requires patients to undergo hormonal therapy. Association between de-differentiation of locally recurrent post RT cancer and tumour progression has been reported. The aggressiveness of recurrent cancers is reflected by p53 protein over expression associated with increased cell proliferation.				
Adjuvant and Salvage Radio-therapy	After RP with adverse factors adjuvant RT seems to result in better DFS than salvage or no postoperative RT.				
	Similarly salvage RT probably results in a marginally better outcome than conserva-tive treatment. Lower pre-treatment PSA values enhance long-term bDFS				
	Toxicity data are inadequate				
	Androgen suppression combined with adjuvant RT may result in better bNED than sole adjuvant RT				
High-dose Rate Brachytherapy as Radiation Boost to EBRT	HDR BRT has mainly been used as a boost with conventional RT or in 3D-conformal radiation therapy (3DCRT) to achieve high-dose RT to the entire prostate.				
	The minimum total dose to the prostatic gland generally exceeds the maximum doses yet delivered with modern 3DCRT dose escalation and exceeds by far the doses achievable with conventional EBRT and Pd-103 or I-125 seed implantation BRT.				
	Toxicity is acceptable.				

	HDR BRT given as a boost to EBRT induces local sure in the majority of patients with favourable and intermediately favourable disease.
	The HDR BRT boost in combination with EBRT induces local cure in most patients with unfavourable (PSA ≥10, T-stage ≥ T2b, GS ≥ 7) disease.
Seed-implantation Brachytherapy with or without EBRT	Digital retropubic low-dose seed implantation should be replaced by TRUS-directed transperineal seed placement with dedicated dose-planning systems.
	Long-term (>5 years) treatment outcome with TRUS-guided permanent seed implantation BRT appears to be similar to that of RP and 3DCRT in patients with favourable risk (PSA < 10, T0-T2a,k GS ≤ 6) disease.
	Permanent seed implantation BFT appears less effective than the combination of HDR BRT with external beam RT and the 3DCRT technique with doses ≥ 74 Gy in patients with unfavourable risk (PSA ≥ 10, T-stage ≥ T2b, and GS ≥ 7) disease but the precise role of combination therapy with EBRT and neo-adjuvant HT needs to be determined by prospective studies.
	Outcome data reveal no major differences between I-125 and Pd-103 permanent seed implantation BRT.
	Toxicity from low-dose seed implantation BRT with modern techniques.

Particle Beam Radiotherapy (Hadron Therapy)	Treatment with pions induces clinical and local control and OS in the same range as conventional EBRT. In one controlled study on neutron RT in unfavourable risk patients, improved 5-year local control and DFS as compared with conventional EBRT was observed. OS remained unaffected. Severe side effects were more frequent after neutrons but when treatment was guided by modern neutron beam shaping systems toxicity was reduced. Photon beam RT (50 Gy) plus a boost with protons (25 Gy) results in improved local control when compared with EBRT (67 Gy) in patients with poorly differentiated tumours. The role of proton therapy remains to be determined.
Neoadjuvant and Adjuvant Hormonal Therapy	Short-term neoadjuvant therapy results in increased local control and DFS OS is improved by short-term neoadjuvant and concomitant HT in a subset of patients with unfavourable disease characteristics. A benefit is seen in OS after adjuvant HT.

Doust, Miller, Duchesne, Kitchener and Weller. A systematic review of brachytherapy: is it an effective and safe treatment for localised prostate cancer. Australian Family Physician, vol. 33, no. 7 pp. 525-529, 2004	
Design: Systematic review evidence level 1++	
Country: Australia	
Setting: hospital based	
Inclusion criteria: studies with permanent seed impanation – effectiveness and safety of BT	
Exclusion criteria: combination therapy with EBRT studies, studies with less than 40 patients.	
Population: Effectiveness - 2 systematic reviews, 7 retrospective cohort studies, 22 case series Safety – 2 systematic reviews, 1 RCT, one prospective cohort study, 7 retrospective cohort studies, 27 case series	
Intervention: -	
Outcomes: Effectiveness - failure free survival (no biochemical or clinical evidence of disease) Safety - complications following BT	
Follow-up: -	
Results: Effectiveness: Brachytherapy appears to be as effective as prostatectomy for men with 'low risk' localised prostate cancer, but there are no studies to demonstrate better survival rates than 'watchful waiting'. Safety: Brachytherapy results in lower rates of impotence, and incontinence than surgery or EBRT but higher rates of obstructive and irritative urinary symptoms	
OUTCOME OF INTEREST	**COMPARISON**
Effectiveness	Similar rates of survival for BT and EBRT for low risk patients (T2a, GS≤6 ≤10 ng/ml) No difference in biochemical progression free survival rates for RP, BT or for low risk patients but lower survival rates for intermediate or high risk p treated with BT than those with RP or EBRT. Survival rates are higher for all treatment modalities for low risk group (>90%
Safety	The most common complication for immediate post-treatment period is acu nary retention, which may require temporary catheterisation (15%-38% of pa Approx. 1% of seeds migrate to the lung – but no harmful side-effects have reported Urinary symptoms such as frequency, nocturia and dysuria occur common rise to a peak of about 80% of patients complaining of symptoms 2-3 month treatment and then declines. Later complications include urethral stricture, impotence and incontinence median time to develop a stricture has been reported as 18 months to 27 m Approx. 7% of patients require a TURP for obstruction.

	Generally lower rates of impotence for BT. Median time to impotency is repo as 14 months. Incontinence occurred mainly in patients who had a TURP either prior or after E Comparisons with EBRT have shown fewer grade 2 and 3 urinary and rectal sy toms but worse urinary bother, bowel function and bowel bother scores than treated with RP.
General comments: Good study, accounts well for confounding factors, etc., but this seems to be an abstract and no references are given, therefore there is no evidence of what studies have been used.	

Neal. A Systematic Review of Minimally Invasive Therapies for BPH and prostate Cancer. ReFeR, Summary number 135, June 2000.
Design: Systematic Review evidence level 1-
Country: UK
Setting: hospital based (secondary care)
Inclusion criteria: Clinical Trials; Effectiveness of Minimally Invasive Techniques for the Treatment of Prostate Cancer and Benign Prostatic Hyperplasia (BPH).
Exclusion criteria: Not reported
Population: -
Intervention: Comparing results with "gold standard" treatment of TURP for BPH.
Outcomes: Morbidity; Changes in Symptoms and Flow Rates, PSA, Biopsy.
Follow-up: -
Results: There is some evidence that for BPH, medium term results of new technology show a tendency to return towards pre-treatment values. Longer term results may demonstrate increased rates of re-treatment. For prostate cancer, a prospective audit of Brachytherapy is recommended to monitor early results on PSA and complications. For other new technology, their use should ideally be limited to open trials in men who have failed conventional treatment with monitoring of complications. There is insufficient evidence to recommend the use of such treatments as standard therapy.

OUTCOME OF INTEREST

BPH

New technologies have lower short term major morbidity compared with transurethral prostatectomy (TURP), but they are less effective as measured by symptom scores, flow rates and residual urine measurements.

There are no good studies reporting cost effectiveness of new treatments compared with TURP, and though stays in hospital are shorter, the costs of capital and disposables are frequently not taken into account.

Rates of ejaculatory failure in most types of new technology (excepting Holmium laser treatment) are lower than following TURP.

There are no large scale prospective randomised studies that have used urodynamics to stratify men with lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH) into those with outlet obstruction, weak detrusor contraction and un-obstructed detrusor instability.

No long-term studies are available so we do not know rates of re-treatment.

Balloon dilatation has a significant re-treatment rate in the medium term; Prostatic stents may have a role in the treatment of very unfit men who would otherwise require a permanent indwelling catheter.

Prostate Cancer

Treatments can be classified as local treatments directed at (1) men with potentially curable, locally confined disease, (2) men with locally advanced and incurable disease, (3) men with systemic disease. For men with locally confined and potentially curative disease conventional treatment options include radical prostatectomy, radiotherapy of various types and conservative treatment (watchful waiting). There is still controversy over which is the best treatment, making it difficult to compare with new treatments.

New minimally invasive therapies include microwave thermo-therapy, brachytherapy, cryotherapy, laser therapy and high intensity focused ultrasound (HIFU). At present only brachytherapy is being used widely. The other treatments have mainly been used in elderly patients with co-morbidity or in the treatment of men with local disease that has failed to respond to conven-

	tional treatments or those who have relapsed. Several large-scale trials of brachytherapy have been done, but once again these were non-randomised. Short-term response rates were comparable to contemporary external beam radiotherapy. Trials in thermotherapy were non-randomised and only one included a control arm. Trials of laser treatment have shown high rates of persistent local disease and once again were non-randomised. Trials of cryotherapy have shown encouraging local response rates, but in men with persistent disease after radiotherapy high rates of incontinence were found.
General Comments: Not sufficient details for the study to be used as evidence as this publication is only a summary and the full review has not been published. It is impossible to extract data regarding the population, the comparison and the basis for the conclusions. This study should be rejected.	

Wallner, Merrick, True, Sutlief, Cavanagh, Butler. ^{125}I vs. ^{103}Pd for low risk prostate cancer: preliminary PSA outcomes from a prospective randomised multicentre trial. Int. J. Radiation Oncology Biol. Phys, vol. 57, no 5 pp. 1297- 1303, 2003

Design: RCT evidence level 1++

Country: USA

Setting: hospital based (secondary care)

Inclusion criteria: Stage T1c- T2a prostatic carcinoma, Gleason score 5-6, PSA 4-10 ng/ml

Exclusion criteria: Upgraded Gleason score, death of unrelated causes, social issues, and short course pre-implant hormonal therapy not continued post implant.

Population: total number of patients: 115

	^{125}I	^{103}Pd	*p*=
Patients (*n*)	57	58	
Age (*years*)	65 ± 7	66 ± 6	0.38
Gleason Score	5.9 ± 0.24	5.9 ± 0.29	0.54
Initial PSA (ng/mL)	7.0 ± 1.9	6.7 ± 1.7	0.46
TRUS volume (cm^3)	34 ± 15	34 ± 10	0.75
Hormonal therapy (*n*)	9	11	

Intervention: ^{125}I (144 Gy) vs. ^{103}Pd (125 Gy) implantation

Outcomes: freedom from biochemical failure – serum PSA level ≤ 0.5 ng/ml at last follow-up

Follow-up: 2.0 to 4.9 years (median 2.9)

Results: Strong evidence that the 3 year actuarial biochemical control rates for low-risk early stage prostate cancer are similar after ^{125}I or ^{103}Pd.

OUTCOME OF INTEREST	**COMPARISON**		
biochemical freedom-from-failure rate at 3 years	^{125}I arm	^{103}Pd arm	*p*=
	89%	91%	0. 76
	D_{90} < 100%	D_{90} ≥ 100%	
	82 %	97%	0.01
	V_{100} < 90%	V_{100} ≥ 90%	
	87 %	97%	0.01

Narayana, Troyer, Evans, Winfield, Robertson and McLaughlin. Randomised Trial of High and Low-Source Strength ^{125}I Prostate Seed Implants. Int. J. Radiation Oncology Biol. Phys, vol. 61, no. 1 pp. 44-51, 2005

Design: Prospective RCT evidence level 1+

Country: USA

Setting: hospital based (secondary care)

Inclusion criteria: Candidates for permanent prostate implantation

Exclusion criteria: Not reported

Population:

	High source strength arm	**Low-source strength arm**
number of patients:	20 (15 combination therapy + 5 brachytherapy alone)	20 (15 combination therapy + 5 brachytherapy alone)
prostate volume average:	39.0 ± 13.3 cm^3	41.4 ± 13.8 cm^3
Seeds:	60.1 ±15.6 seeds	95.7 ± 23.2 seeds

Intervention: High source strength 0.76 μGy/m^2/h of ^{125}I compared with Low-source strength 0.4 μGy/m^2/h of ^{125}I

Outcomes:

Post implant dosimetric evaluation (using CT -seed position, and T_2 - weighed MRI scans)

Implant quality parameters (assessed by dose indexes - ratio of achieved / planned dose)

Follow-up: not reported

Results: Strong evidence that implants planned with high-source strength seeds improved the probability of excellent implant quality at a lower cost than those planned with low-source strength seeds.

OUTCOME OF INTEREST

	High source strength 0.76 μGy/m^2/h of ^{125}I	**Low-source strength 0.4 μGy/m^2/h of ^{125}I**	***P* value**
Dose coverage	Better		
V_{100} of prescribed dose	larger (96.3%± 3.5%)	90.4 ± 5.3%	p < 0.0002
Seeds	less 60.1 ±15.6 seeds	95.7 ± 23.2 seeds	
Seed cost	lower ($ 2,400)	$ 3,840	
Operating room time	less (67 ± 16 min)	85 ± 20 min	p < 0.004
Differences in rectal and urethral doses not statistically significant			

General comments: Small study, follow-up not reported, possible differences in long term toxicity.

Sathya, Davis, Julian, Guo, Daya, Dayes, Lukka and Levine. Randomised trial comparing Iridium implant plus External Beam Radiotherapy (EBRT) with EBRT alone in node-negative locally advanced cancer of the prostate Journal of Clinical Oncology, vol. 23, no pp. 1192-11996, 2005

Design: RCT evidence level 1+

Country: Canada

Setting: hospital based (secondary care)

Inclusion criteria: histologically proven adenocarcinoma of the prostate, clinical stage T2 or T3, N0, M0. (TNM classification)

Exclusion criteria: prior history of pelvic radiotherapy, radical prostatectomy, androgen ablation, transurethral resection of prostate, evidence of metastatic disease (CT scan and bone scan), positive lymph nodes at the time of lymphadenectomy

Population: number of patients: 104

	Arm IM + EBRT	**EBRT alone**
n=	51	53
age range	range 49 - 74 (mean 65)	range 57-74 (mean 66)
PSA µg/l	range 3.4 –71(mean 19.0)	range 1.2-93 (mean 20.2)
Gleason score	range 4 – 9 (mean 6.7)	range 4 – 9 (mean 6.8)
Tumor stage T2	n=31	n=32
Tumor stage T3	n=20	n=21
Intermediate risk	n=21	n=21
High risk	n=30	n=32

Intervention: pelvic lymphadenectomy, Transperineal Iridium implant (35 Gy) plus External Beam Radiotherapy (40 Gy) compared with EBRT (66 Gy to 100% isodose line) alone

Outcomes: biochemical or clinical failure (BCF), post radiation biopsy, overall survival, toxicity

Follow-up: median 8.2 years

Results: There is strong evidence that in combination IM plus EBRT was superior to EBRT alone in terms of BCF, and post radiation biopsy positivity. Higher doses of radiation delivered in a shorter duration result in better local as well as biochemical control in locally advanced prostate cancer.

Toxicity, overall survival and sexual function did not have statistically significant differences.

Comparison:

	IM+EBRT arm	**EBRT arm**	**Hazard / Odds ratio**	***P*=**	**95% CI**
BCF	17 (29%)	33 (61%)	0.42	0.0024	0.23 – 0.75
post radiation biopsy +	n=42 10 (24%)	n=45 23 (51%)	0.30	0.015	0.12 – 0.75
overall survival	94%	92%	1.36	0. 54	0.50 - 3.65
toxicity	7	2		0.09	
sexual function	16	17		0.00	

General comments:

Wallner, Merrick, True, Sherertz, Sutlief, Cavanagh & Butler. 20Gy versus 44Gy supplemental beam radiation with Pd-103 prostate brachytherapy: preliminary biochemical outcomes from a prospective randomised multi-centre trial. Radiotherapy and oncology (2005) p. 307-310

Design: RCTs, evidence level 1+

Country: USA

Setting: hospital based

Inclusion criteria: men with 1997AJC clinical stage T1c-T2a prostatic carcinoma, Gleason grade 7-10 and/or PSA 10-20 mg/ml

Exclusion criteria: not mentioned

Population: number of patients: 156

	20Gy arm	**44Gy arm**	
mean age:	83 patients	76 patients	*P* value
PSA (ng/mL)	67 (± 7)	67 (± 7)	0.38
Average Gleason score	7 (± 1.9)	6.7 (±1.7)	0.46
Co-morbidity not addressed	7.0 (±0.58)	7.0 (±0.64)	0.54

Intervention: 44 Gy (standard) vs. 20 Gy pre-implant supplemental beam radiation, combined with Pd-103 Brachytherapy 90 vs. 115 Gy (NIST 1999)

Outcomes: Freedom from biochemical failure (serum PSA ≤ 0.5 ng/ml) at last follow-up (0.5 to 4.9 years, median 2.9 years)

Follow-up: For non- failing patients 2.0 to 4.9 years, median 2.9 years. Loss to follow-up not reported.

Results: There is strong evidence that the likelihood of biochemical cure is similar with standard (44 Gy) or lower dose (20 Gy) supplemental radiation beam. Study suggests that a supplemental beam radiation is un-necessary, in the setting of a high degree of prostate coverage by the Brachytherapy prescription dose.

OUTCOME OF INTEREST	**COMPARISON**		
Freedom from progression at 3 years	**20Gy arm**	**44 Gy arm**	
Overall	83%	88%	*P* = 0.64
Initial PSA < 10 ng/mL	84%	94%	*P* = 0.16
Initial PSA >10 ng/mL	82%	72%	*P* = 0.38

General comments: Randomised groups differed in V100 values (4% higher in the 44 Gy arm), gap interval from external beam radiation to implant (4 days longer in 44 Gy arm), short course adjuvant hormonal therapy (41% of the patients in the 44 Gy arm vs. 23% in the 20 Gy arm)

Retrospective Cohort Studies

Vicini, Martinez, Hanks, Hanlon, Miles, Kernan, Beyers, Ragde, Forman, Fontanesi, Kestin, Kovacs, Denis, Slawin, Scardino. An Interinstitutional and Interspecialty Comparison of Treatment Outcome Data for Patients with Prostate Carcinoma on Predefined Prognostic Categories and Minimum Follow-up. Cancer, no. 95 pp. 2126-35, 2005
Design: cohort study evidence level 2++
Country: International
Setting: hospital based
Inclusion criteria: clinically localised prostate cancer
Exclusion criteria: -
Population: number of patients: 6877 Primary prognostic group 1: PSA ≤ 10 ng/ml; GS ≤6, median age range 62-73; Primary prognostic group 2: PSA 10-20 ng/ml; GS ≤6, median age range 64-74; Primary prognostic group 3: PSA ≥ 20 ng/ml; GS ≤6, median age range 64-76 Primary prognostic group 4: PSA ≤ 10 ng/ml; GS ≥ 7, median age range 63-77 Primary prognostic group 5: PSA 10-20 ng/ml; GS ≥ 7, median age range 65-77 Primary prognostic group 6: PSA > 20 ng/ml; GS ≥ 7, median age range 62-70 Secondary prognostic group 1: Tumour stage T1c/T2a, PSA ≤ 10 ng/ml; GS ≤6, median age range 61-73 Secondary prognostic group 2: Tumour stage T1c/T2a, PSA >10 ≤ 20 ng/ml; GS ≤6, median age range 64-74 Secondary prognostic group 3: Tumour stage T1c/T2a, PSA > 20 ≤ 40 ng/ml; GS ≤6, median age range 70-74 Secondary prognostic group 4: Tumour stage T1c/T2a, PSA ≤ 10 ng/ml; GS ≥ 7, median age range 62-76 Secondary prognostic group 5: Tumour stage T1c/T2a, PSA > 10 ≤ 40 ng/ml; GS ≥ 7, median age range 69-74 Secondary prognostic group 6: Tumour stage T2b/T3, PSA ≤ 10 ng/ml; GS ≤6, median age range 64-74 Secondary prognostic group 7: Tumour stage T2b/T3, PSA > 10 ≤ 40 ng/ml; GS ≤6, median age range 64-74 Secondary prognostic group 8: Tumour stage T2b/T3, PSA ≤ 20 ng/ml; GS ≥ 7, median age range 63-77 Secondary prognostic group 9: Tumour stage T2b/T3, PSA > 20 ≤ 40 ng/ml; GS ≥ 7, median age range 62-76
Intervention: Permanent Radioactive Seed Implant; Temporary HDR Implant; 3D conformal EBRT; Neutrons/EBRT; EBRT alone; Radical Prostatectomy
Outcomes: 5 year outcome: clinical failure (CF), biochemical control (BC), disease free survival (DFS), overall survival (OS)
Follow-up: minimum median 36 months;
Results: There is good evidence that 5 years PSA are similar for patients in low risk and intermediate risk groups, regardless of the form of therapy, when all three pre-treatment variables were used to define prognostic categories. For patients in the high-risk group, PSA outcomes were suboptimal, regardless of the treatment used. Substantial differences in outcome are observed for the same type of treatment (in the same institution) depending on the number of prognostic variable used to define treatment groups.

COMPARISON OUTCOME OF INTEREST

Institution/treatment	**Primary prognostic group 1:**			**5 year outcome %**	
	n=	**CF**	**BC**	**DFS**	**OS**
Arizona (seeds)	345	-	85	-	-
Seattle (seeds)	431	-	88	-	-
Kiel (HDR)	57	70	95	-	83
WBH (HDR)	26	63	100	100	100
FCCC (3D-EBRT)	409	73	83	-	-
WSU (neutrons)	80	-	84	-	-
WBH (EBRT)	372	66	71	77	83
Baylor (surgery)	758	-	94	-	97
WBH (surgery)	157	-	84	80	95
Institution/treatment	**Primary prognostic group 2:**			**5 year outcome %**	
	n=	**CF**	**BC**	**DFS**	**OS**
Arizona (seeds)	95	-	58	93	83
Seattle (seeds)	137	-	83	-	-
FCCC (3D-EBRT)	203	-	77	-	-
WBH (EBRT)	156	10	59	63	74
Baylor (surgery)	142	4	87	-	97
Institution/treatment	**Primary prognostic group 3:**			**5 year outcome %**	
	n=	**CF**	**BC**	**DFS**	**OS**
Arizona (seeds)	54	-	59	-	55
Seattle (seeds)	52	-	75	-	-
Kiel (HDR)	31	13	68	87	68
FCCC (3D-EBRT)	101	-	32	-	-
WBH (EBRT)	100	22	24	45	79
Baylor (surgery)	34	19	54	-	93
Institution/treatment	**Primary prognostic group 4:**			**5 year outcome %**	
	n=	**CF**	**BC**	**DFS**	**OS**
Arizona (seeds)	51	-	63	91	70
Seattle (seeds)	69	-	80	-	-
WBH (HDR)	44	7	83	81	85
FCCC (3D-EBRT)	107	-	75	-	-
WSU (neutrons)	69	-	73	-	-
WBH (EBRT)	133	15	61	54	70
Baylor (surgery)	249	11	74	-	94
Institution/treatment	**Primary prognostic group 5:**			**5 year outcome %**	
	n=	**CF**	**BC**	**DFS**	**OS**

Arizona (seeds)	29	-	33	-	82
Seattle (seeds)	40	-	75	-	-
WBH (HDR)	31	38	67	39	86
FCCC (3D-EBRT)	61	-	62	-	-
WSU (neutrons)	37	-	56	-	-
WBH (EBRT)	85	20	24	49	71
Baylor (surgery)	90	6	73	-	91
Institution/treatment	**Primary prognostic group 6:**			**5 year outcome %**	
	n=	**CF**	**BC**	**DFS**	**OS**
Kiel (HDR)	29	35	39	66	62
FCCC (3D-EBRT)	60	-	36	-	-
WSU (neutrons)	52	-	34	-	-
WBH (EBRT)	87	28	25	23	72
Baylor (surgery)	33	24	40	-	85
Institution/treatment	**Secondary prognostic group 1:**			**5 year outcome %**	
	n=	**CF**	**BC**	**DFS**	**OS**
Arizona (seeds)	207	-	82	-	83
Seattle (seeds)	330	-	89	-	-
FCCC (3D-EBRT)	357	-	85	-	-
WBH (EBRT)	313	7	71	77	85
Baylor (surgery)	491	1	97	-	97
Institution/treatment	**Secondary prognostic group 2:**			**5 year outcome %**	
	n=	CF	BC	DFS	OS
Arizona (seeds)	58	-	69	-	85
Seattle (seeds)	82	-	85	-	-
FCCC (3D-EBRT)	163	-	74	-	-
WBH (EBRT)	109	10	65	70	80
Baylor (surgery)	80	0	96	-	100
Institution/treatment	**Secondary prognostic group 3:**			**5 year outcome %**	
	n=	CF	BC	DFS	OS
FCCC (3D-EBRT)	43	-	43	-	-
WBH (EBRT)	39	15	38	49	77
Institution/treatment	**Secondary prognostic group 4:**			**5 year outcome %**	
	n=	**CF**	**BC**	**DFS**	**OS**
Arizona (seeds)	26	-	86	-	72
Seattle (seeds)	43	-	81	-	-
FCCC (3D-EBRT)	75	-	80	-	-

WBH (EBRT)	95	13	66	58	71
Baylor (surgery)	121	1	80	-	94
Institution/treatment	**Secondary prognostic group 5:**			**5 year outcome %**	
	n=	**CF**	**BC**	**DFS**	**OS**
WBH (HDR)	25	29	78	62	90
FCCC (3D-EBRT)	65	-	58	-	-
WBH (EBRT)	78	23	24	47	74
Institution/treatment	**Secondary prognostic group 6:**			**5 year outcome %**	
	n=	**CF**	**BC**	**DFS**	**OS**
Arizona (seeds)	113	-	84	-	85
Seattle (seeds)	75	-	85	-	-
Kiel (HDR)	39	3	95	98	85
WBH (HDR)	25	0	100	100	100
WBH (EBRT)	59	9	69	72	76
Baylor (surgery)	218	1	91	-	98
Institution/treatment	**Secondary prognostic group 7:**			**5 year outcome %**	
	n=	**CF**	**BC**	**DFS**	**OS**
Arizona (seeds)	52	-	85	-	86
Seattle (seeds)	65	-	77	-	-
Kiel (HDR)	38	16	84	84	74
WBH (EBRT)	77	16	36	49	70
Baylor (surgery)	62	4	77	-	90
Institution/treatment	**Secondary prognostic group 8:**			**5 year outcome %**	
	n=	**CF**	**BC**	**DFS**	**OS**
Arizona (seeds)	38	-	73	-	75
Seattle (seeds)	46	-	67	-	-
Kiel (HDR)	28	21	75	79	71
WBH (HDR)	29	33	64	49	89
WSU (neutrons)	122	-	66	-	-
WBH (EBRT)	69	16	41	47	68
Baylor (surgery)	136	13	65	-	91
Institution/treatment	**Secondary prognostic group 9:**			**5 year outcome %**	
	n=	**CF**	**BC**	**DFS**	**OS**
WBH (EBRT)	26	22	33	20	57
Baylor (surgery)	14	35	39	-	97

General comments:

Kupelian, Potters, Khuntia, Ciezki, Reddy, Reuther, Carlson, and Klein. Radical Prostatectomy, External Beam Radiotherapy <72 Gy, External Beam Radiotherapy ≥72 Gy, Permanent Seed Implantation or combined Seeds/ External Beam Radiotherapy for stage T1-T2 Prostate Cancer. Int. J. Radiation Oncology Biol. Phys, vol. 58, no. 1 pp. 25-33, 2004

Design: cohort study evidence level 2++

Country: USA

Setting: hospital based (secondary care)

Inclusion criteria: clinically localised prostate cancer

Exclusion criteria: not reported

Population: number of patients: 2991 consecutive patients mean age: 67

	RP	ldEBRT	hd EBRT	COMB	PI
n=	1034	484	301	222	950
Mean age	63	70	68	69	70
iPSA≤ 4	12%	9%	4%	3%	6%
>4 and ≤10	60%	43%	57%	38%	55%
>10 and ≤20	21%	29%	26%	38%	22%
>20	7%	18%	13%	21%	6%
GS ≤6	74%	66%	57%	39%	76%
7	20%	24%	33%	47%	21%
≥ 8	6%	10%	10%	14%	3%

Intervention: Radical Prostatectomy (RP), External Beam Radiotherapy <72 Gy (low dose EBRT) External Beam Radiotherapy ≥72 Gy (high dose EBRT), Permanent Seed Implantation (PI) or combined Seeds/ External Beam Radiotherapy (COMB)

Outcomes: biochemical relapse free survival (bRFS) rates after treatment

Follow-up: median 56 months **(**range 12 – 145)

Results: There is good evidence that biochemical failure rates are similar among, PI, high dose EBRT, COMB and RP. Significantly worse outcomes for low dose EBRT (<72 Gy).

iPSA, bGS and year of therapy are independent predictors of relapse.

Clinical stage, treatment modality and androgen deprivation are not independent predictors of failure.

OUTCOME OF INTEREST **COMPARISON**

	RP	ldEBRT	hd EBRT	COMB	PI	*p* value
5 year bRFS	81%	51%	81%	77%	83%	< 0.001
7 year bRFS	76%	48%	81%	77%	75%	

Predictors:	iPSA	bGS	Year of therapy	Treatment modality	Clinical stage	Androgen deprivation

	$p < 0.001$	$p<0.001$	$p=0.001$	$p=0.95$	$p=0.09$	$p=0.56$
General comments:						

Meng, Elkin, Latini, DuChane, Carroll. Treatment of Patients With High Risk Localized Prostate Cancer: Results From Cancer Of The Prostate Strategic Urological Research Endeavour (C_APSURE). The Journal of Urology, Vol. 173, pp 1557-1561. 2005.

Design: Cohort Study Evidence Level 2++

Country: USA

Setting: Hospital Based

Inclusion criteria: **C**linically localised prostate cancer on CaPSURE database nonmetastatic, high risk disease based on T stage, tumor grade and PSA

Exclusion criteria: Not reported

Population: number of patients: 6,074

Primary Treatment	**Low Risk**	**Intermediate Risk**	**High Risk**
n=6,074	2079 (34%)	2402 (40%)	1,593 (26%)
RP	1,170	1,371	577
EBRT	186	342	346
BT	305	187	75
BT + EBRT	19	93	71
AD	202	267	459
WW	197	142	65

Intervention: Radical Prostatectomy (RB), External Beam Radiation Therapy (EBRT), Brachytherapy (BT), EBRT and BT in combination, Hormonal Therapy (AD), Watchful Waiting (WW), Neoadjuvant or Adjuvant Hormonal Treatment.

Outcomes: Efficacy of treatment, based on risk group; need for neoadjuvant and adjuvant AD

Follow-up: 9 months

Results: There is good evidence that men with high risk but nonmetastatic prostate cancer are more likely to received radiation therapy as well as androgen deprivation with the latter as primary therapy or in conjunction with local treatment. These data stress the importance or pre-treatment risk stratification, education regarding appropriate combinations of local and systemic therapies, and the consideration of novel clinical trials in patients at higher risk.

Differences in primary treatment type among the 3 risk groups were statistically significant ($p < 0.0001$) with increasing external beam radiation therapy and androgen deprivation, and decreased surgery, brachytherapy and surveillance in men with high risk cancers. In this group older age, higher PSA and non-private insurance were associated with decreased use of radical prostatectomy. More than half of the men at high risk receiving radiation therapy also received androgen deprivation, which was significantly higher than in the low and intermediate risk groups ($p < 0.0001$). factors associated with androgen deprivation in high risk disease were primary therapy, PSA, Gleason sum, T stage, body mass index, insurance status and ethnicity. PSA and Gleason sum were the primary determinants of adjuvant radiation after prostatectomy.

OUTCOME OF INTEREST **COMPARISON**

Model predicting primary treatment	Adjusted OR (95% CI)				
	EBRT vs. RP	**BT vs. RP**	**BT+EBRT vs. RP**	**AD vs. RP**	**WW vs. RP**
Age:					
<70	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
>70	1.9 (6.9-17.2)	7.2 (3.1-16.7)	6.6 (2.8-15.5)	17.2 (10.7-27.7)	49.9 (13.2-185.4)
PSA:					
≤10	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
10.1-20	1.9 (1.1-3.3)	0.7 (0.2-2.4)	1.9 (0.8-4.9)	1.9 (1.1-3.5)	2.7 (0.9-7.8)
>20	2.9 (1.7-4.9)	1.2 (0.4-3.7)	1.4 (0.5-4-0)	8.3 (4.8-14.3)	4.6 (1.7-12.8)
bGS:					
<7	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
7	1.7 (1.0-3.0)	1.2 (0.4-3.9)	1.3 (0.3-5.1)	2.0 (1.1-3.6)	1.1 (0.4-3.0)
8-10	1.9 (1.0-3.4)	0.9 (0.2-3.5)	1.1 (0.3-4.9)	3.9 (2.1-7.2)	0.6 (0.2-1.9)
Clinical Stage:					
T1	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
T2	0.8 (0.5-1.3)	0.5 (0.2-1.2)	2.4 (0.9-6.9)	1.0 (0.6-1.7)	0.4 (0.2-0.9)
T3a	1.6 (0.8-3.3)	0.1 (0.01-1.1)	0.1 (0.01-1.3)	2.2 (1.0-4.5)	1.8 (0.6-5.7)

Model predicting neoadjuvant AD	**AD vs. No AD Adjusted OR (95% CI)**
Primary Treatment:	
RP	1.0 (reference)
EBRT	7.1 (4.1-12.3)
BT	4.0 (1.6-9.9)
BT + EBRT	8.0 (3.4-18.9)
PSA:	
≤10	1.0 (reference)
10.1-20	1.7 (1.0-3.0)
>20	2.2 (1.3-3.6)
Clinical Stage:	
T1	1.0 (reference)
T2	2.2 (1.3-3.7)
T3a	2.1 (1.0-4.5)

Model predicting adjuvant AD	AD vs. No AD Adjusted OR (95% CI)
Primary Treatment:	
RP	1.0 (reference)
EBRT	3.5 (2.1-5.9)
BT	1.4 (0.5-3.5)
BT + EBRT	2.0 (0.9-4.5)
PSA:	
≤10	1.0 (reference)
10.1-20	1.3 (0.8-2.1)
>20	2.3 (1.4-3.9)
Clinical Stage:	
T1	1.0 (reference)
T2	1.9 (1.0-3.4)
T3a	2.9 (1.5-5.3)

General comments:

Vargas, Martinez, Boike, Spencer, Goldstein, Gustafson, Krauss, Gonzales. High dose irradiation for prostate cancer via a high-dose-rate brachytherapy boost: results of phase I and II study. Int. J. Radiation Oncology Biol. Phys, vol. 66, no. 2 pp. 416-423, 2006

Design: cohort study evidence level 2++

Country: USA

Setting: hospital based (secondary care)

Inclusion criteria: clinically localised prostate cancer, intermediate and high risk factors, PSA >10 ng/ml; Gleason score ≥ 7 or clinical stage ≥T2B

Exclusion criteria: -

Population: number of patients: 197 median age 68 (47-85)

T stage	T1	T2	T3	
n=	39 (19.8%)	143 (72.6%)	15 (7.6%)	
Initial PSA ng/ml	< 4	4 to < 10	10 to <20	≥ 20
n=	14 (7.1%)	110 (55.8%)	53 (26.9%)	20 (10.2)
Gleason score	2-6	7	8-10	
n=	65 (33%)	100 (50.8%)	32 (16.2%)	

Intervention: pelvic EBRT (46 GY) plus two or three HDT boost treatments

Outcomes: biological failure (BF) clinical failure - local failure or distant metastasis (CF) clinical event free survival (cEFS), cause specific survival (CSS), overall survival (OS)

Urinary toxicity; gastrointestinal toxicity.

Follow-up: median 4.9 years

Results: there is a strong dose-response relationship for intermediate to high risk prostate cancer. Improved loco-regional control with higher radiation doses alone can significantly decrease biochemical and clinical failures. Higher dose per fraction will increase the therapeutic window allowing better tumour control and decrease toxicity

OUTCOME OF INTEREST		**COMPARISON**			
		Low dose	**High dose**	*p*=	**all cases**
5 year outcome	n=	67	130		197
	BF	32.7%	14.0%	0.006	21.6%
	CF	15.6%	6.1%	0.04	9.8%
	cEFS	75.5%	91.7%	0.003	84.8%
	CSS	95.4 %	100%	0.02	98.3%
	OS	86.2%	97.8%	0.002	92.9%
Urinary Toxicity	Dysuria	6.0%	20.8%	0.01	
	Retention	14.9%	32.8%	0.7	

	Frequency/urgency	28.4%	40%	0.09
	Bleeding	10.4%	12.3%	0.3
	Incontinence	11/67	14/130	0.3
	Urethral stricture	10.4%	6.2%	0.7
	Highest GU	56.7%	47.7%	0.2
GI Toxicity	Diarrhoea	16.4%	16.7%	0.4
	Tenesmus	9.0%	10%	0.2
	Bleeding	10.4%	17.7%	0.1
	Proctitis	1.5%	6.2%	0.4
	Perineal pain	0%	1.5%	0.3
	Ulceration	1.5%	0%	0.2
	Highest GI	68.7%	6.3%	0.5

Demanes, Rodriguez, Schour, Brandt and Altieri. High-dose-rate intensity-modulated brachytherapy with external beam radiotherapy for prostate cancer: California Endocurietherapy's 10 year results. Int. J. Radiation Oncology Biol. Phys, vol. 61, no. 5 pp. 1306-1316, 2005

Design: cohort study evidence level 2++

Country: USA

Setting: hospital based (secondary care)

Inclusion criteria: clinically localised prostate cancer

Exclusion criteria: patients who declined or delayed completion of treatment, or died without disease

Population: number of patients: 209 Median age: 69 (range 44-87) stratified by risk groups

		Gleason score	iPSA ng/ml	n=
Low	Stage ≤ T2a	≤ 6	≤ 10	70
Intermediate	T2b,c	7	10-20	92
High	T3	8-10	> 20	47

Intervention: high-dose-rate brachytherapy (HDR-BT) combined with external beam radiotherapy (EBRT)

Outcomes: general clinical failure (PSA progression); late GU and lower GI morbidity (RTOG criteria)

Follow-up: 7.25 years (range 5-12)

Results: There is good evidence that HDR-BT plus EBRT is a proven treatment for all stages of localised prostate cancer. Low morbidity. Transurethral resection post RT should be avoided.

OUTCOME OF INTEREST **COMPARISON**

	Overall	Low	Intermed.	High	*p* valu
General clinical control rate	90%	-	-	-	-
5 years cases at risk	-	59	73	37	-
8 years	-	16	32	22	-
10 years	-	4	9	10	0.16
General clinical failure rate	10%	-	-	-	-
Overall survival rate	79%	-	-	-	-
Cause specific survival rate	97%	-	-	-	-
PSA progression free survival (ASTRO)					
5 years	-	90%	91%	74%	-
8 years	-	90%	87%	69%	-
10 years	-	90%	87%	69%	0.002

		Grade 3	Grade 4
urinary morbidity	**-**	6.7%	1%
rectal morbidity	-	nil	nil
Sexual potency preservation	67%		

General comments: -

Galalae, Martinez, Mate, Mitchell, Edmundson, Nuernberg, Eulau, Gustafson, Gribble, Kovacs. Long term outcome by risk factors using conformal high dose brachytherapy (HDR – BT) boost with or without neoadjuvant androgen suppression for localised prostate cancer. Int. J. Radiation Oncology Biol. Phys, vol. 58, no 4 pp. 1048- 1055, 2004

Design: cohort study evidence level 2+

Country: International

Setting: hospital based (secondary care)

Inclusion criteria: patients with clinically localised prostate cancer

Exclusion criteria: not reported

Population: number of patients: 611, stratified by risk factors for failure:

	Group 1	**Group 2**	**Group 3**
n=	46	188	359
Stage:	≤ T2a	≥ T2b	any two
Gleason score:	≤ 5	≥ 7	risk factors
initial PSA:	≤ 10ng/ml	≥10ng/ml	higher

Intervention: conformal high dose brachytherapy (HDR – BT) boost with or without neoadjuvant androgen deprivation therapy (ADT); EBRT with dose escalating HDR brachytherapy (BT) boost

Outcomes: long term outcome

Follow-up: 5 years (range 0.2 - 15.3)

Results: Good evidence that EBRT with HDR – BT produced excellent long-term outcomes in terms of BC, DFS, and CSS even in patients from high risk group.

Conformal HDR – BT is precise dose delivery system and effective treatment for all groups.

The addition of a shot course ADT failed to improve outcome

OUTCOME OF INTEREST **COMPARISON**

		All	**Group 1**	**Group 2**	**Group 3**
Biochemical control at 5 years	Overall Survival (OS)	85%	81%	86%	85%
	Cause Specific Survival (CSS)	96%	100%	99%	95%
	Biochemical Control (BC)	77%	96%	88%	69%
	Disease Free Survival (DFS)	67%	83%	75%	61%
	Local Recurrence (LR)	7.4%	0%	3.5%	10%

			Group 2			Group 3	
		No ADT	**ADT**	***p*=**	**No ADT**	**ADT**	***p*=**
Survival analysis of risk factors with or without ADT	n=	137	51		240	119	
	(OS)	86%	90%	0.661	87%	80%	0.057
	(CSS)	100%	97%	0.083	97%	90%	0.002
	(BC)	87%	91%	0.524	69%	68%	0.437
	(DFS)	73%	85%	0.235	60%	61%	0.542

General comments: -

Martinez, Gonzalez, Spencer, Gustafson, Kestin, Kearney and Vicini. Conformal high dose rate brachytherapy improves biochemical control and cause specific survival in patients with prostate cancer and poor prognostic factors. The Journal of Urology vol. 169, 974-980, 2003

Design: Case Series evidence level 3

Country: USA

Setting: hospital based (secondary care)

Inclusion criteria: PSA ≥10 ng/ml; Gleason score ≥7; clinical stage ≥ T2b (T1c, TA if Gleason score ≥7)

Exclusion criteria: age ≥85; prostate volume >65 cc; prostate length >5.5 cm; hormonal therapy

Population: number of patients: total 207; median age 69 years

Stage	***n***	**Initial PSA**	***n***	**Gleason score**	***n***	**Prognostic factors**	***n***	**Age**	***n***	**Gland volume**	***n***
T1c	36	**<4.0**	14	**≤6**	81	**1**	97	**<65**	68	**<30**	58
T2a	34	**4.0-10.0**	107	**7**	85	**2**	75	**65-75**	108	**30-40**	88
T2b, T2c	118	**10.1-20.0**	65	**≥8**	41	**3**	35	**>75**	31	**>40**	61
T3a-T3c	19	**>20.0**	21								

Intervention: EBRT with conformal HDRBT dose escalation; % of dose level = low <92Gy, high >92Gy

Outcomes: overall survival (OS), Cause specific survival (CSS) Disease free survival (DFS) biochemical control (BC)

Follow-up: mean 4.7 years (range 0.6 to 10.4)

Results: There is some evidence that for patients with poor prognostic factors, EBRT with conformal HDRBT improved biochemical control, resulting in a high cause specific survival rate (CSS) with low toxicity.

Advantage: Patient is not radioactive after the high dose implant.

OUTCOME OF INTEREST

		OS	**CSS**	**DFS**	**BC**
% total		92	98	68	74
% poor prognostic factors	1	92	100	77	85
	2	93	97	72	75
	3	91	97	41	50
p value (log rank)		0.706	0.327	0.001	0.001
% dose level	Low	93	95	50	52
	High	91	100	70	87
p value (log rank)		0.745	0.014	<0.001	<0.001

General comments:

Retrospective case series

Kollmeier, Stock and Stone. Biochemical outcomes after prostate brachytherapy with 5 year minimal follow-up: importance of patient selection and implant quality. Int. J. Radiation Oncology Biol. Phys, vol. 57, no3 pp.645-653, 2003

Design: case series study evidence level 3

Country: USA

Setting: hospital based (secondary care)

Inclusion criteria: clinically localised prostate cancer, with radioactive seed implantation (treated with brachytherapy without EBRT). Disease stage 1992 AJC criteria T2a, T2b, T2c, Gleason score ≤ 9, PSA ≤ 20 ng/ml; available post implant dosimetric data for review

Exclusion criteria: lack of adequate PSA follow-up, absence of dosimetry data; death before the fifth post-implant year.

Population: total number of patients: 243 median age: 68

	Low Risk	Intermed. Risk	High Risk
Stage	**≤ 2TA**	**T2b-T2c**	
n=	120 (49%)	123 (51%)	
Gleason score	**≤ 6**	**= 7**	**8-10**
n=	189 (78%)	35 (14%)	19 (8%)
Initial PSA	**≤ 10**	**10.1 -20**	**> 20**
n=	149 (61%)	63 (26%)	31 (13%)

	Suboptimal	Optimal
Implant dose	**^{125}I D_{90} ≤140 Gy**	**^{103}Pd D_{90} ≥ 100Gy**
n=	138	105

Intervention: follow-up observational group comparison to determine **outcome** (biochemical failure freedom) in Correlation between **initial prognostic** (stage, Gleason score and PSA) and **quality of implant** (primary treatment) and **hormonal therapy**

Outcomes: Actuarial 8 year freedom from biochemical failure bFFF (ASTRO defined) PSA

Follow-up: 61 to 135 months (median 75)

Results: Some evidence that disease related factors are significant predictors of biochemical failure and the quality of the implant (dose) is a significant in optimal outcomes. Data supports the use of implantation alone in low risk prostate cancer patients and demonstrate the impact of implant quality (dose) in achieving optimal outcomes. Low risk patients who receive an optimal dose implant have a 94% bFFF rate at 8 years.

OUTCOME: **COMPARISON:**

bFFF rate at 8 years for:	Low risk	Intermediate risk	High risk	*P* value
	88%	81%	65%	0.0009
	Stage: ≤ 2TA	**T2b-T2c**		
	85%	69%		0.013
	Gleason score: ≤ 6	**= 7**	**8-10**	
	81%	67%	53%	0.0003

	Initial PSA: ≤ 10	**10.1 -20**	**> 20**	
	80%	86%	45%	0.0019
Dose:	**Suboptimal ^{125}I D_{90} ≤140 Gy**	**Optimal dose ^{103}Pd D_{90} ≥ 100Gy**		
	82%	68%		0.007
Hormonal therapy not significant				0.27
General comments: -				

Sharkey, Chovnick, Behar, Perez, Otheguy, Rabinowitz, Steele, Webster, Donohue, Solc, Huff, Cantor. Minimally invasive treatment for localised adenocarcinoma of the prostate: review of 1048 patients treated with ultrasound guided Palladium 103 Brachytherapy. Journal of Endourology, vol. 14, no. 4, 2000
Design: case series study evidence level 3
Country: USA
Setting: hospital based (secondary care)
Inclusion criteria: clinically localised prostate cancer
Exclusion criteria: not reported
Population: stage T1 and T2 adenocarcinoma of the prostate number of patients: 780 of which: ^{103}Pd monotherapy n= 299;^{103}Pd + hormonal therapy n=481 mean age: 72.6 (range 44 - 88), 64% > 70 years old prior transurethral resection: n= 236 30.5% average initial PSA value: 7.2 ng/ml (range 0.0 - 93.0 ng/ml) 82% < 10 ng/ml of which initial PSA in ^{103}Pd monotherapy arm 90% <10 ng/ml ^{103}Pd + neoadjuvant arm 79% < 10 ng/ml Gleason scores range 2 to 10, 78% < 7
Intervention: assessing the effectiveness of ultrasound guided Palladium 103 Brachytherapy alone in comparison with Brachytherapy plus Hormonal Therapy (neoadjuvant leuprolide and flutamide - 3 month before and 2 months after)
Outcomes: effects on PSA values and tissue biopsy
Follow-up: every 6 months up to year 5
Results: Some evidence that brachytherapy is effective in reducing PSA concentrations to < 1.5 ng/ml and in producing negative biopsies 1 and 2 years postoperatively. The results are comparable to those of EBRT and RP while demonstrating a significant reduction in morbidity. Year 1 stable PSA < 1.5 ng/ml in 86% of patients. Year 5 stable PSA < 1.5 ng/ml in 86% of patients Year 2 negative biopsy in 92% of patients. Best outcomes in patients with initial PSA < 10 ng/ml Patients in ^{103}Pd + neoadjuvant arm achieved PSA reduction more rapidly. Principal morbidity: short term bladder and bowel irritation without permanent sequelae. Impotence occurred in 15% of the patients. Incontinence occurred in % of those who underwent prior transurethral resection

OUTCOME OF INTEREST **COMPARISON**

PSA <1.5ng/ml		**1 year**	**2 years**	**3 years**	**4 years**	**5 years**
^{103}Pd monotherapy arm	initial PSA					
	0-4.0	90%	91%	91%	95%	95%
	4.1-10.0	71%	74%	78%	81%	93%
	10.1-20.0	52%	65%	67%	60%	40%
	>20	43%	40%	33%	100%	83%
	Total	**77%**	**79%**	**80%**	**86%**	**91%**
^{103}Pd + neoadjuvant arm	0-4.0	98%	88%	95%	97%	100%
	4.1-10.0	91%	87%	89%	84%	76%
	10.1-20.0	85%	85%	86%	77%	50%
	>20	75%	85%	46%	62%	50%
	Total	**91%**	**87%**	**88%**	**86%**	**78%**
Negative biopsy						
^{103}Pd monotherapy arm	0-4.0	86%	92%			
	4.1-10.0	84%	88%			
	10.1-20.0	71%	100%			
	>20	83%	75%			
	Total	**84%**	**90%**			
^{103}Pd + neoadjuvant arm	0-4.0	96%	96%			
	4.1-10.0	95%	92%			
	10.1-20.0	94%	85%			
	>20	89%	100%			
	Total	**95%**	**93%**			

General comments:

Mate. High Dose Rate prostate brachytherapy with ^{192}Iridium: the Seattle Experience. Journal of Oncology, vol. 53, no. 1 pp. 34-37, 2003

Design: review evidence level 4

Country: USA

Setting: hospital based (secondary care)

Inclusion criteria: clinically localised prostate cancer, characteristics not reported

Exclusion criteria: not reported

Population: number of patients: 104

mean age: not reported

Intervention: HDR brachytherapy with ^{192}Iridium

Outcomes: Survival to 10 years

Follow-up: mean 76 months, median 75, maximum 124 months

Results: Very poor evidence that multifractioned HDR brachytherapy combined with EBRT is a well tolerated and effective treatment for localised prostate cancer. HDR brachytherapy as monotherapy is also effective (?) Independent risk factors identified: PSA>15, GS>6, tumour stage>T2b.

OUTCOME OF INTEREST		**COMPARISON**	
Overall bNED		5 years	83%
		10 years	77%
bNED	iPSA <10	10 years	95%
	iPSA 10-20		80%
	iPSA >20		42%
bNED	No risk factor	5 years	100%
		10 years	97%
	1 risk factor	5 years	78%
		10 years	69%
	2-3 risk factors	5 years	44%
		10 years	33%

Long term toxicity: grade 3 urethral stricture.

General comments: very poor evidence level, patient characteristics not reported, results are reported without evidence, conclusion based on literature review.

Robinson, Moritz, and Fung. Meta-analysis of rates of erectile function after treatments for localised prostate carcinoma. Int. J. Radiation Oncology Biol. Phys, vol. 54, no. 4 pp. 1063-1068, 2002

Design: meta-analysis evidence level 1++

Country: Canada

Setting: hospital based (secondary care)

Inclusion criteria: 54 study reports published from 1970 to 2002 reporting on EBRT, RT, BT and cryotherapy (combined neoadjuvant hormonal therapy permitted, reporting on primary discrete data sets, with known pre-treatment erectile status

Exclusion criteria: physician's assessment of EF, articles with no known pre-treatment erectile status, studies reporting on patients who already reported ED

Population:

Treatment	All studies	Follow-up
Brachytherapy	172	-
Brachytherapy + EBRT	58	58
EBRT	1343	731
Nerve sparing RP	485	128
Standard RP	3019	2673
Cryotherapy	264	198
Total	**5341**	**3788**

Intervention: data extracted (logistic regression model): experimental design, type of treatment, number of subjects and mean age, selection criteria, definition of normal erectile function, method of assessment, number of men with normal erectile function before and after treatment, duration of follow-up.

Outcomes: the probability of men with normal erectile function retaining erectile function.

Follow-up: -

Results: Treatment method: there is very strong evidence that there are statistically significant ($p<0.05$) differences in probabilities of retaining erectile function between treatments, with brachytherapy showing the highest probability. Brachytherapy plus EBRT and EBRT alone tied in second, followed by nerve-sparing radical prostatectomy, standard radical prostatectomy and finally cryotherapy.

Short vs. Long Follow-up: there is very strong evidence that Erectile Function decreased significantly ($p<0.05$) after nerve-sparing radical prostatectomy between 12 months and 24 months. The decline was non significant in all other methods.

Age adjusted results: there is very strong evidence that significant differences were present in age of men by treatment methods. Age adjustment increased probability of erectile function after radiotherapy methods, decreased for radical prostatectomy and did not change for cryotherapy.

COMPARISON **OUTCOME OF INTEREST**

Probability of maintaining erectile function after treatment of prostate cancer.

(age adjusted for a 65 year old patient)

Treatment	**1 year after treatment**		**2 years after treatment**		**Age adjus**	
	Probability	95% CI	Probability	95% CI	Probability	9
Brachytherapy	0.76	0.69-0.82	-	-	0.80	0
Brachytherapy + EBRT	0.60	0.48-0.73	0.60	0.48-0.73	0.69	0
EBRT	0.55	0.52-0.58	0.52	0.48-0.56	0.68	0
Nerve sparing RP	0.34	0.30-0.38	0.25	0.18-0.33	0.22	0
Standard RP	0.25	0.23-0.26	0.25	0.23-0.26	0.16	0
Cryotherapy	0.13	0.09-0.17	0.15	0.10-0.20	0.13	0

General comments:

Henderson, Laing, Langley. Quality of Life Following Treatment for Early Prostate Cancer: Does Low Dose Rate (LDR) Brachytherapy Offer a Better Outcome? A Review. European Urology no 45 pp 134-141, 2004.
Design: Systematic Review Evidence Level 1++
Country: UK
Setting: Other
Inclusion criteria: Quality of Life Studies of patients that have undergone BT, RP or EBRT.
Exclusion criteria: Not reported
Population: -
Intervention: Comparing the toxicity of low dose rate BT with other commonly utilised radical treatments for early prostate cancer. Assessment of Quality of Life with Health Related Quality of Life (HRQOL), Cancer Specific Quality of Life (CSQol), Prostate Cancer Specific Quality of Life (PCSQol), Symptom Index (SI), Short Form 36 (SF36), Functional Assessment of Cancer Therapies-General (FACT-G), FACT-Prostate (FACT-P), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQC30), EORTC Prostate-25 (EORTC PR-25), Technology Assessment Group Life/ Family (TAG Life/Family), University of California Los Angeles-Prostate Cancer Index (UCLA-PCI), Expanded Prostate Cancer Index Composite (EPIC), International Index of Erectile Function (IIEF), International Prostate Symptom Score (IPSS).
Outcomes: Patient reported outcome of treatment for early prostate cancer; (Acute morbidity, Late morbidity); Neoadjuvant and Adjuvant Androgen Deprivation Therapy in EBRT and Combined Brachytherapy Treatments.
Follow-up: -
Results: There is very strong evidence that radical prostatectomy, external beam radiotherapy and BXT either alone or in combination with supplementary external beam radiotherapy offer good long-term health-related quality of life. However, differences exist in the toxicity of treatment in terms of erectile function, voiding difficulty, incontinence and bowel function. These differences seem to persist for at least 3-5 years post-treatment though longer-term quality of life outcomes from modern techniques are unknown. Very strong evidence that BXT offers a high probability of maintaining continence, potency and normal rectal function though both storage and voiding urinary symptoms have been reported. Addition of androgen deprivation of EBRT to BXT may increase urinary, bowel and sexual toxicity of treatment. Quality of life outcome following brachytherapy compares favourably with other radical treatment options for the management of early prostate cancer.

OUTCOME OF INTEREST **COMPARISON**

Advantages and Disadvantages of Health Related Quality of Life Questionnaires in Prostate Cancer:

Name	Type	Items	Assesses	Advantages	Disadvantages
RAND SF36	HRQOL	36	HRQOL	Benchmark, well-validated questionnaire for assessment of general health-related QoL. Available in 44 languages	Insensitive in EPC, doesn't attempt to measure disease specific items
FACT-G	CSQol	34	CSQol	Well-validated instrument applied to cancers in general	No disease-specific items. Usually paired with disease-specific subscale (FACT-P)
EORTC QLQ C30	CSQol	30	CSQol	Well-validated instrument widely used in oncology trials. Validated in most European languages.	Like FACT, usually paired with a disease-specific module (PR-25)
TAG Life/ Family	CSQol	8	CSQol and impact on family	One of few questionnaires to capture the impact of treatment on family	Little used, insensitive. Instruments administered to spouse might be better.
FACT-P	PCSQol	13	Weight loss, role, ED, LUTS	Brief, designed to work with FACT-G and scored as a total with FACT-G	Assessment of LUTS but not urinary incontinence. May be insensitive to change in EPC.
EORTC PR-25	PCSQol	25	ED, bowel, urinary function, and toxicity from androgen deprivation	More comprehensive, suitable for assessment of localised and metastatic disease. Suitable for assessment of patients post-surgery, BXT or EBRT	Newer questionnaire, still awaiting publication of validation studies.
UCLA-PCI	PCSQol	20	Urinary, sexual and bowel function and bother	Comprehensive assessment of common side effects following RP and EBRT	Often paired with SF36 to assess HRQOL. Lack of brevity may decrease return rates. Urinary function assesses solely incontinence and does not include irritative LUTS

EPIC	PCSQol	50	ED, bowel, and urinary function, and toxicity from androgen deprivation	Designed to compare results of treating early disease with BXT, EBRT or RP. Expanded version of UCLA-PCI.	Validated in the USA only, lack of brevity limits clinical use. Does not assess HRQOL so usually paired with SF12 or SF36. Heavy weighting towards LUTS vs. incontinence.
IIEF	SI	15	ED	Well-validated, familiar, available in abbreviated form (sexual health index for men, comprises five erectile subscales of IIEF)	Concentrates on function and doesn't assess effect of ED on HRQOL.
IPSS	SI	8	LUTS	Well-validated index of LUTS, familiar to urologists.	Not exhaustive (doesn't assess incontinence or dysuria).

Health Related Quality of Life (HRQOL), Cancer Specific Quality of Life (CSQol), Prostate Cancer Specific Quality of Life (PCSQol), Symptom Index (SI), Short Form 36 (SF36), Functional Assessment of Cancer Therapies-General (FACT-G), FACT-Prostate (FACT-P), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQC30), EORTC Prostate-25 (EORTC PR-25), Technology Assessment Group Life/ Family (TAG Life/Family), University of California Los Angeles-Prostate Cancer Index (UCLA-PCI), Expanded Prostate Cancer Index Composite (EPIC), International Index of Erectile Function (IIEF), International Prostate Symptom Score (IPSS).

General comments:

Merrick, Butler, Wallner, Galbreath, Anderson, Kurko, Lief and Allen. Erectile Function after Prostate Brachytherapy. Int. J. Radiation Oncology Biol. Phys, vol. 62, no. 2, pp. 437-447, 2005

Design: RCT evidence level 1++

Country: USA

Setting: community

Inclusion criteria: patients from two prospective RCTs, permanent prostate brachytherapy, potent (erectile function determined preimplant by International Index of Erectile Function (IIEF) as ≥ 13)

Exclusion criteria: not reported

Population: number of patients: 132 patients

mean age: 62.6 (± 7.7)

	low risk trial	**high risk trial**
PSA	≤ 10 ng/ml	10.1 - 20 ng/ml
Gleason score	≤ 6	≥ 7
Disease stage	T1b-T2b	T2c
Dose	^{103}Pd - 125 Gy or ^{125}I - 145 Gy	^{103}Pd - 115 Gy or 20 Gy vs. 44 Gy arms – 90 G

Patients who maintained potency n= 69

Patients with post implant erectile dysfunction (ED) n= 59

Intervention: validated patient administered questionnaire to determine the effect of multiple clinical, treatment and dosimetric parameters on penile erectile function.

Outcomes: penile erectile function as defined by IIEF (Post implant potency vs. Post implant erectile dysfunction)

Follow-up: 13.1 to 42.8 months (mean 29.0 (± 8.3), median 29.1)

Results: Very strong evidence that Brachytherapy induced ED occurred in 50% of the patients at 3 years. Best predictors are preimplant erectile function (IIEF) and D_{50} to the proximal crura. Techniques to minimise the radiation dose to the proximal penis may result in improved rates of potency preservation. The use of neoadjuvant androgen deprivation therapy, supplemental EBRT, isotope, tobacco status, hypertension or Body mass index did not affect the 3 year rate of potency preservation.

OUTCOME OF INTEREST	**COMPARISON**		
	Patients who maintained potency	**Patients with post implant ED**	***P* value**
n	n= 69	n= 59	
Mean age	60.9 (± 7.2)	64.6 (± 7.9)	0.007
Mean Preimplant IIEF score	26.4 (± 4.6)	23.3 (± 5.6)	0.001
Mean time to onset of ED		2.6 months	
Median time to the onset of ED		5.4 months	

3 year actuarial rate of potency preservation	50.5%
Other parameters deemed without statistical significance	
Neoadjuvant androgen deprivation therapy	(p=0.828)
supplemental EBRT	(p=0.624)
stratification to supplemental EBRT	(p= 0.778)
isotope	(p=0.829)
tobacco status	(p=0.382)
hypertension	(p=0.315)
body mass index	(p=0.943)
diabetes mellitus	(p=0.100)

General comments: :

Herstein, Wallner, Merrick, Mitsuyama, Armstrong, True, Cavanagh and Butler. I-125 vs. Pd-103 for low risk prostate cancer: long term morbidity outcomes from a prospective multicentre randomised trial. Cancer Journal , vol. 11, no 5 pp. 385-9, 2005

Design: RCT evidence level 1++

Country: USA

Setting: hospital based

Inclusion criteria: clinically localised prostate cancer, T1c – T2a, GS 2-6, PSA 4-10 ng/mL

Exclusion criteria: GS>6, social issues

Population: total number of patients: 314

	I-125	**Pd-103**	p value
n=	159	155	
mean age:	65±7	66±6	0.38
PSA (ng/mL)	7.0 ± 1.9	6.7± 1.7	0.46
AUA score	7.6 ± 7	8.2 ± 7	0.54
TRUS volume (cc)	34±15	34±10	0.75
V100	94% ± 6%	89%± 10	< 0.0001
R100	1.8 cc ± 2.1	0.79 cc ± 0.9	< 0.0001
Hormonal Therapy	18%	17%	

Intervention: I-125 (144 Gy) vs. Pd-103 (125 Gy), treatment related morbidity monitored.

Outcomes: AUA scores (rectal morbidity, urinary morbidity, -modified RTOG criteria)

Follow-up: min 2 years, no patients lost to follow-up

Results: Strong evidence that AUA scores peaked at 1 month post-implant for both isotopes and gradually declined. Greatest difference between treatment arm at 1 and 6 months. At month 1, I125 arm patients had significantly lower AUA scores. Use of alpha-blockers similar in both groups. Radiation proctitis occurred in 9% of patients, more in the I125 arm (*p*=0.21). Only 2% of patients with R100 below 1.0cc developed bleeding, which did not differ between isotopes.

OUTCOME OF INTEREST **COMPARISON**

Average AUA scores	**I-125**	**Pd-103**	**p value**
Initial	7.6 (±6.7)	8.2 (±7.0)	0.51
1 month	14.8 (±9.5)	18.6 (±9.8)	0.0009
3 months	14.5 (±10)	13.5 (±9.2)	0.37
6 months	7.6 (±6.7)	8.2 (±7.0)	0.04
12 months	10.1 (±8.5)	9.7 (±8.3)	0.72
18 months	9.5(±8.6)	9.4 (±7.8)	0.9

24 months	8.8(±7.9)	8.9 (±7.6)	0.89

General comments: -

Merrick, Butler, Wallner, Galbreath, Kurko and Cleavinger. Rectal function following brachytherapy with or without supplemental beam radiation: results of two prospective randomised trials. Brachytherapy, 2 (2003) pp. 147-157
Design: RCT evidence level 1++
Country: USA
Setting: Community
Inclusion criteria: patients randomised into 2 RCTs evaluating the effect of isotope for low risk patients and different doses of supplemental XRT for higher risk features. Endpoints biochemical outcome and QOL parameters, urinary , bowel and sexual function See population
Exclusion criteria: not reported
Population: number of patients: 213 mean age: 66.2 ± 6.9 enrolled into 2 RCTs: Monotherapy for patients with low risk GS 5-6; iPSA 4-10 ng/ml, T1b T2a — ^{103}Pd (125Gy mpd) n=61 vs. ^{125}I (145 Gy mpd) n=57 XRT+ Brachytherapy for high risk GS 7-9; iPSA 10-0 ng/ml, T1b T2b — 20 Gy + ^{103}Pd n=61 vs. 44 Gy+ ^{103}Pd n=57
Intervention: evaluating treatment related rectal morbidity; clinical treatment and dosimetric parameters evaluated included patient age, diabetes, hypertension, tobacco consumption, clinical stage, prostate ultrasound volume, time since implant, hormonal manipulation, supplemental XRT, isotope, treatment planning volume and values of the minimum dose received by 90% of the prostate gland (D_{90}), the percentage of prostate volume receiving 100%, 150% and 200% of the minimum peripheral dose ($V_{100/150/200}$), rectal implant doses ($V_{75/100/125/150}$ and $D_{5/10/25/50}$), and rectal XRT doses ($D_{5/10/25/50/75}$).
Outcomes: rectal morbidity - using RTOG instrument (patient administered Quality of Life questionnaire) and multi-factorial R-FAS score.
Follow-up: at 1, 3, 6, 12, 24 and 36 moths (median 22 months)
Results: There is strong evidence that following permanent prostate brachytherapy, the ability to discern subtle changes in rectal function is dependent on the sensitivity of the survey instrument. Only the rectal dosimetry variable D_5 predicted for rectal dysfunction in R-FAS instrument. No clinical, treatment or dosimetric parameters predicted for bowel function when using the RTOG survey. Using the RTOG instrument rectal morbidity peaked at 1 month. The pre-and most recent post implant median RTOG scores were 0 and 0 respectively. The pre and post implant R-FAS scores were 2.41 and 3.83 respectively. With time rectal scores for both instruments improved and approached baseline. No patient required surgical intervention for rectal complications.

OUTCOME OF INTEREST

Rectal function assessment scores (R-FAS) overall and difference (Post-Pre) Mean ± SD

Overall			^{125}**I**	^{103}**Pd**	^{103}**Pd +20Gy**	^{103}**Pd +44Gy**	*p* value
Pre	post	Pre-post Diff	Pre- post Diff	Pre- post Diff	Pre- post Diff	Pre- post Diff	1 way* ANOVA
2.41±1.95	3.83±3.04	1.40±2.90	1.46±2.47	1.13±2.74	1.32±2.91	1.67±3.42	0.690

* probability across all arms using post implant-preimplant difference scores

** probability across all arms using individual post implant and preimplant scores

General comments:

Ghaly, Wallner, Merrick, True, Sutlief, Cavanagh, Butler. The effect of supplemental beam radiation on prostate brachytherapy-related morbidity: the outcomes from two prospective randomised multicentre trials. Int. J. Radiation Oncology Biol. Phys, vol. 55, no5 pp. 1288-1293, 2003

Design: RCT evidence level 1+

Country: USA

Setting: community

Inclusion criteria: patients enrolled in two prospective randomised trials, comparing implantation with I-125 vs. Pd-103 (in low risk patients) and implantation Pd-103 with 44 Gy vs. 20 Gy EBRT respectively (in intermediate risk patients)

Exclusion criteria: not reported

Population: total number of patients: 220

study	**low risk**		**intermediate risk**	
Gleason score	5-6		>7	
PSA	4-10 ng/ml		10/20 ng/ml	
randomised to	**I-125**	**Pd – 103**	**20 Gy EB + Pd**	**44 Gy EB + P**
n=	54	51	57	51
age	66 ± 7	65 ± 6	65 ± 11	64 ± 11
prostate volume	36 ± 12	35±10	33 ± 16	31 ±9
initial AUA score	7.5 ± 5.7	6.9 ± 6.1	6.8 ± 6.4	6.6 ± 6.1

Intervention: treatment related morbidity questionnaire

Outcomes: rectal morbidity and incontinence score (AUA and RTOG criteria) at 1,3, 6, 12 and 24 months

Follow-up: n/a

Results: Strong evidence that the addition of supplemental beam radiation has little effect on morbidity. Morbidity should not influence the decision whether or not to use supplemental beam radiation. AUA scores increases are higher at 1 month in patients treated with high dose radiation (Pd-103 alone or Pd-103 + 20Gy EBRT) by six months most returned to baseline AUA scores, and I-125 patients have declining scores. Patients treated with lower dose had lesser elevation at 1 and 6 months with inconsistent difference between 20 and 44 Gy arms.

Additional EBRT increased rectal morbidity at 1 month only

OUTCOME OF INTEREST	**COMPARISON**			
Rectal morbidity	**1 month**	**3 months**	**6 months**	**12 months**
I-125 vs. Pd-103	*p*= 0.0029*			
I-125 vs. Pd-103+ 20 Gy				
I-125 vs. Pd-103+ 44 Gy				
Pd-103 vs. Pd-103 + 20 Gy	*p*= 0.028			
Pd-103 vs. Pd-103 + 44 Gy	*p*= 0.019			
Pd-103 + 20 Gy vs. Pd-103 + 44 Gy				
Urinary morbidity				

I-125 vs. Pd-103	*p*= 0.035
* only significant values (p< 0.1) are reported	
General comments: the report has no other data in tabular form. All data is presented as plotted graphs and extracting precise figures would be highly speculative.	

Matzkin, Kaver, Stenger, Agai, Esna and Chen. Iodine 125 Brachytherapy for localised prostate cancer and urinary morbidity: a prospective comparison of two seed implant methods- preplanning and intraoperative planning. Urology 62: 497-502, 2003

Design: prospective follow-up on consecutive cohort, evidence level 2+

Country: Israel

Setting: hospital based (secondary care)

Inclusion criteria: clinically localised prostate cancer (biopsy confirmed), GS 2-6, PSA<20ng/ml, stage ≤T2b, completion of International prostate symptom scores questionnaire (IPSS) at all stages

Exclusion criteria: not reported

Population: number of patients: 300 consecutive patients allocated to 2 seed implant methods

	Preplanning (Group 1)	**Intraoperative planning (Group 2)**	***p* value**
Patients (n)	136	164	
mean age (yr)	67.2	68.4	>0.05
mean PSA (ng/mL)	8.69	7.95	= 0.04
mean gland volume (cm^3)	39.6	42.9	>0.05
GS 2-4 (n)	30	33	
GS 5-6 (n)	106	131	>0.05
T1c (n)	105	131	
T2a (n)	19	23	>0.05
T2b (n)	12	10	
Mean needles/case	19.8	16.1	>0.05
Mean seeds/case	91.6	79.1	>0.05
iIPSS 0-7 (n)	72	81	
iIPSS 8-19 (n)	54	72	>0.05
iIPSS 20-35 (n)	10	11	
mean iIPSS	8.6	7.8	>0.05
previous TURP	3	2	>0.05
hormone therapy	22	33	>0.05
Initial QoL value	1.5	1.7	

Intervention: comparing urinary morbidity outcomes in 2 different seed implant methods- preplanning and intraoperative planning.

Outcomes: urinary morbidity

Follow-up: mean 32, median 30 months

Results: Good evidence that in both treatment groups IPSS increases significantly for 9 to 12 months and then returned to baseline scores; reached a higher level and remained high for longer in the intraoperative group (mild clinical importance)Incidence of acute retention and need for surgery was very low in both groups. (2% and 1% respectively). Significantly better CT implant dosimetry parameters noted with the intraoperative method. Positive correlation (p<0.001) found between dosimetry parameter and symptom

severity.

OUTCOME OF INTEREST			COMPARISON			
	Group 1	**Group 2**		**Group 1**	**Group 2**	**p value**
Incontinence	0	0	**QoL**			
Prolonged retention	2	0	Month 6	3.4	4.3	*p*>0.05
IPSS values			Month 12	2.7	3.3	
Month 1	17	18				
Month 3	13	17	**Dosimetry**	**analysis**		
Month 6	10	14				
Month 9	9	13	Prostate D_{90}	55.3 ± 2.7	115±3.0	*p*<0.001
Month 12	8	11	Prostate V_{90}	57.5 ± 2.2	97.9±0.3	*p*<0.001
reached baseline value ±1	92%	-	Prostate V_{100}	60.0 ± 2.3	95.2±0.3	*p*<0.001
Month 18	< 9	< 9	Prostate V_{150}	22.5 ± 1.5	45.4±0.3	*p*<0.001
reached baseline value ± 1	-	95%	Urethral V_{150}	1.0 ± 0.5	1.7± 0.6	*p*>0.05
Month 24	< 9	< 9	Activity/case	36.0 ± 0.8	34.2±0.7	*p*>0.05

General comments: the IPSS results are presented as plotted graph, data extracted might not be 100% accurate.

Retrospective Cohort Studies

Speight, Elkin, Pasta, Silva, Lubeck, Carroll and Litwin. Longitudinal Assessment Of Changes In Sexual Function And Bother In Patients Treated With External Beam Radiotherapy Of Brachytherapy, With Or Without Neoadjuvant Androgen Ablation: Data From CaPSURE. Int. J. Radiation Oncology Biol. Phys, vol. 60, no. 4 pp. 1066-1075, 2004

Design: cohort study evidence level 2++

Country: USA

Setting: hospital based (secondary care)

Inclusion criteria: biopsy proven clinically localised prostate adenocarcinoma patients enrolled in the Cancer of the Prostate Strategic Urological Research Endeavour (CaPSURE) database.

Exclusion criteria: missing initial SF and SB scores, RP as primary treatment

Population: number of patients: 922

Characteristics	**BT**	**EBRT**	**EBRT + BT**
n	**365**	**460**	**97**
Receiving STAD	196	104	47
Median age / (range)	70 (46-87)	70 (48-83)	70 (53-80)
bGS 2-6	298	256	35
7	43	127	54
8-10	10	53	8
iPSA ≤ 4	56	37	7
4.1 – 10	254	323	51
10.1-20	33	122	30
>20	9	55	6
Stage T1	159	146	31
T2	204	290	65
T3a	2	24	1

Intervention: assessment of treatment related changes in sexual function (SF) and sexual bother (SB). Treatment subgroups were compared: EBRT-STAD; EBRT +STAD; BT-STAD; BT+STAD; EBRT+BT-STAD; EBERT+BT+STAD.

Outcomes: UCLA Prostate Cancer Index and SF-36; sexual function (SF) and sexual bother (SB).

Follow-up: median 24.6, 32.4 and 24.2 months respectively

Results: There is good evidence that each treatment for prostate cancer can negatively affect Sexual function (SF) and (SB). Initial difference between treatment groups exist but diminish with time. Changes associated with EBRT ± BT were statistically significant and those for BT are not. Patients receiving BT reported greater SF and the least change in SF overall. Those receiving EBRT ± BT reported greatest decline in SF. STAD appear to confer only temporary and recoverable impairment of erectile function. SF scores associates with STAD were initially lower than in patients without STAD; however, by 1 year no statistically significant difference in SF or SB was reported.

Overall, the greatest reported changes in SF occur during the first 2 years post-therapy.

OUTCOME OF INTEREST		COMPARISON		
		Treatment groups without STAD		
		EBRT mean (95%CI)	**BT** (95%CI)	**EBRT+BT** (95%CI)
Sexual function	Post treatment	38 (34-43)	36 (24-40)	32 (24-40)
	Year 1	32 (29-35)	33 (30-36)	24 (17-30)
	Year 2	29 (26-32)	34 (30-37)	27 (19-34)
	Year 3	27 (24-30)	32 (28-36)	24 (15-34)
	Year 3	24 (20-28)	29 (23-34)	14 (0-28)
Sexual bother	Year 1	51 (44-58)	48 (42-55)	59 (56-73)
	Year 2	43 (38-48)	44 (38-49)	37 (26-49
	Year 3	43 (37-48)	46 (39-52)	38 (24-51)
	Year 3	39 (34-45)	42 (34-49)	47 (27-66)
		45 (38-52)	44 (31-56)	40 (0-90)

Figures for SF and SB for the same treatment groups with STAD do not differ significantly; in all treatment groups the post-treatment measurements are lower but they follow the same curve after year 1, supporting the conclusion that effects of STAD on SF and SB are temporary and reversible. However, data appears only as plotted on the graph and data extraction would be speculative.

General comments: -

Downs, Sadetsky, Pasta, Grossfeld, Kane, Mehta, Carroll and Lubeck. Health Related Quality of Life in Patients Treated with Interstitial Prostate Brachytherapy for Localised Prostate Cancer: data From CaPSURE. The journal of Urology, vol. 170, pp. 1822-1827, 2003

Design: cohort study evidence level 2++

Country: USA

Setting: hospital based (secondary care)

Inclusion criteria: biopsy proven clinically localised prostate adenocarcinoma patients enrolled in the Cancer of the Prostate Strategic Urological Research Endeavour (CaPSURE) database.

Exclusion criteria: patients treated with neoadjuvant hormonal therapy or EBRT in combination to BT

Population:

Characteristics	**BT**	**RP**	***p* value**
n	**92**	**327**	
Mean age	68.7 ± 6.7	61.2 ± 7.1	<0.0001
bGS 2-6	93%	75%	0.002
7	5%	22%	
8-10	3%	4%	
iPSA ≤ 4	28%	25%	0.3
4.1 – 10	64%	60%	
10.1-20	7%	11%	
>20	1%	4%	
Stage T1	48%	49%	0.9
T2	51%	50%	
T3	1%	1%	

Intervention: assessment of disease specific health related quality of life (HRQOL) factors in patients undergoing Brachytherapy monotherapy (BT) compared to patients undergoing radical prostatectomy (RP)

Outcomes: disease specific health related quality of life factors (UCLA Prostate Cancer Index and SF-36) urinary function, bowel function, sexual function.

Follow-up: 24 months

Results: There is good evidence overall, that both RP and BT are well tolerated procedures that cause mild changes in general HRQOL. Disease specific HRQOL patterns are different between treatment groups. Baseline and serial HRQOL measurements can provide valuable information regarding expected quality of life outcome after treatment for prostate cancer.

Patients treated with BT or RP did not differ in HRQOL after treatment. Both groups showed early functional impairment in most general domains, with scores returning to/ approaching baseline in 18 to 24 months after treatment. Patients treated with BT had significantly higher urinary function scores at 0 and 6 months after treatment than patients treated with RP. Urinary bother cores did not differ between treatment groups. Both treatment groups had decreased sexual function that did not return to pre-treatment levels.

OUTCOME OF INTEREST **COMPARISON**

Disease specific heath related quality of life (HRQOL) cross-sectional means:

	Pre treat-ment	6 months	12 months	18 months	24 months
Urinary function					
BT	91.7±12.6	84.5±18.7	85.9±15.7	84.3±20.2	88.1±18.9
RP	92.4±13.8	63.3±26.6	75.1±23.3	76.0±22.8	75.5±22.2
Urinary bother					
BT	86.5±21.1	67.7±31.2	78.2±27.5	78.0±26.7	85.6±24.2
RP	85.3±23.6	67.4±29.1	79.8±24.8	81.8±23.2	83.6±21.7
Bowel function					
BT	89.0±12.6	83.2±20.4	86.2±14.6	90.2±12.0	89.5±11.8
RP	87.9±14.2	86.2±15.9	88.6±14.1	88.6±14.3	88.3±14.5
Bowel bother					
BT	90.6±17.8	79.2±30.5	83.1±22.8	88.0±19.1	87.1±20.8
RP	89.5±21.1	85.8±23.0	89.6±21.1	89.1±21.4	90.6±19.4
Sexual function					
BT	51.2±27.8	39.8±29.4	38.5±9.0	35.6±29.3	33.8±30.4
RP	59.9±26.2	19.5±19.8	24.2±21.3	28.3±23.5	28.0±25.1
Sexual bother					
BT	60.3±37.8	50.0±39.1	44.1±38.7	43.9±40.7	44.5±41.0
RP	67.7±34.6	31.5±35.0	32.4±34.6	35.4±33.7	38.8±36.2

Differences between baseline and post-treatment heath related quality of life (HRQOL) scores:

	6 months		12 months		18 months		24 months	
	BT	**RP**	**BT**	**RP**	**BT**	**RP**	**BT**	**RP**
Urinary function								
no. pts.	66	236	86	294	58	212	32	126
change score	-8.1	-28.8	-6.1	-17.2	-6.6	-16.4	-1.8	-16.4
p value	<0.0001		<0.0001		0.003		0.001	
Urinary bother								
no. pts.	64	237	85	295	57	210	21	127

change score	-21.0	-15.5	-9.1	-5.5	-5.3	-3.7	+8	0.0
p value	0.2		0.4		0.7		0.2	
Bowel function								
no. pts.	66	241	83	300	55	215	31	128
change score	-6.5	-1.4	-4.0	+0.7	+1.0	+0.8	-0.5	+0.1
p value	0.02		0.005		0.9		0.8	
Bowel bother								
no. pts.	64	241	82	300	55	212	32	127
change score	-13.6	-3.8	-8.5	+0.2	-4.1	0.0	-2.3	+0.3
p value	0.007		0.001		0.2		0.6	
Sexual function								
no. pts.	61	236	81	295	55	208	31	125
change score	-12.1	-40.5	-10.8	-34.4	-15.9	-30.4	-17.6	-29.3
p value	<0.0001		<0.0001		<0.0001		0.02	
Sexual bother								
no. pts.	58	226	73	285	51	203	28	117
change score	-12.9	-39.2	-14.7	-34.5	-16.1	-30.7	-16.0	-27.1
p value	<0.0001		0.0001		0.02		0.02	

General comments: Potential bias - younger patients in the RP group

Case Series

Mabjeesh, Chen, Beri, Stenger and Matzkin. Sexual function after permanent ^{125}I Brachytherapy for prostate cancer. Int. J. Imp. Res., no. 17, pp. 96-101, 2005

Design: case series study evidence level 3

Country: Israel

Setting: hospital based

Inclusion criteria: clinically localised prostate cancer, stage T1c-T2b, GS ≤7, PSA <20ng/ml, sexually active EF>11

Exclusion criteria: high risk patients, GS >7, receiving combined therapy with EBRT

Population: number of patients: 131

	BT only	**BT + neoadjuvant hormone therapy**	*p* value
n=	80	51	
Mean age	65.7 ± 6.1	67.3 ± 5.2	NS
Mean PSA	8 ± 3.25	8.7±3.2	NS
Prostate volume	36±8.1	42.2±11	< 0.01
Clinical stage T1c	77%	78%	NS
T2a, b	23%	22%	NS

Intervention: IIEF questionnaire before and after ^{125}I Brachytherapy; Patients allowed sildenafil

Outcomes: International Index of Erectile Function (IIEF) – Erectile Function (EF), Orgasmic Function (OF), Sexual Desire (SD), Intercourse Satisfaction (IS), Overall Satisfaction (OS)

Follow-up: range 2-5 years

Results: Some evidence that any detrimental effect of ^{125}I Brachytherapy with or without addition of neoadjuvant hormonal therapy on EF is reversible and recovery is expected at 1 year after the treatment in most patients. Effect of neoadjuvant is not significant and transient.

Mean EF dropped within 3 moths after brachytherapy, recovered at the end of the first year and remained unchanged for up the end of year 2 after treatment, regardless of the addition of neoadjuvant hormonal therapy. 80% of the patients were satisfied with their sexual function up to 3 years after brachytherapy.

The decline in EF is not correlated with pre-treatment EF status or age.

OUTCOME OF INTEREST **COMPARISON**

Domain	**Score range**	**Before**	**Year 1**	**Year 2**	p value
EF	1-30	22.5±6	14.7±10	16.8±10	<0.01
OF	0-10	7.3±2.8	4.9±3.6	5.6±3.4	<0.01

SD	2-10	7.2±1.5	5.5±2.3	6.0±2.3	<0.05
IS	0-15	11.0±2.7	7.3±5.5	8.1±4.9	<0.01
OS	2-10	8.1±1.9	5.8±3.0	6.3±2.8	<0.01

General comments: Patients may have been positively influenced by the use of sildenafil. Median follow-up not reported clearly.

Feigenberg, Lee, Desilvio, Winter, Pisansky, Bruner, Lawton, Morton, Baikadi and Sandler. Health related Quality of Life in men receiving Prostate Brachytherapy on RTOG 98-05. Int. J. Radiation Oncology Biol. Phys, vol. 62, no. 4 pp. 956-964, 2005

Design: case series evidence level 3

Country: USA

Setting: hospital based

Inclusion criteria: clinically localised prostate cancer receiving Brachytherapy alone (^{125}I 145 Gy) stage T1c-T2a, iPSA ≤ 10 ng/ml, GS < 7, maximum prostate volume 45 cm^3, IPSS <18.

Exclusion criteria: patients with transurethral resection of prostate.

Population: number of patients: 98

Age		**Erectile capability**		**FACT-G mean**
<70	66%	Assisted	8%	98.3± 11.5
≥70	33%	Unassisted	65%	
				SAQ mean
Urinary incontinence		**Ejaculation capability**		58.1 ± 10.7
Yes	7%	Assisted	7%	
No	91%	Unassisted	64%	**IPSS mean**
				5.4±4.0

Intervention: health related quality of life questionnaire (HRQOL), functional assessment of cancer therapy prostate (FACT-P), Sexual adjustment questionnaire (SAQ) and international prostate symptom score (IPSS) at baseline, 3, 6, 9 and 12 months.

Outcomes: standard error of the mean (SEM)

Follow-up: median 33.8 months

Results: Some evidence that patients undergoing prostate brachytherapy have a very high overall HRQOL.

More than 60% of men reported decreased urinary function at 1 year compared to baseline. The rate of incontinence after 1 year is very low (rate increased to 14% at 6 months and decreased to 1% at 1 year), but many patients continue to have obstructive symptoms at 1 year. Although 78% of patients report they can achieve an erection with or without assistance, almost 50% report a decrease in sexual function.

OUTCOME OF INTEREST **COMPARISON**

		Month 3	**Month 6**	**Month 9**	**Month 12**
Erectile capability	Assisted	13%	19%	18%	20%
	Unassisted	45%	37%	40%	39%
Urinary incontinence	No	92%	86%	95%	99%
	Yes	8%	14%	5%	1%

FACT –G (SEM 3.8)	Improved	39%	25%	33%	40%
	Stable	29%	41%	35%	40%
	Decline	32%	35%	32%	20%
FACT-P (SEM3.3)	Improved	10%	13%	22%	15%
	Stable	39%	43%	36%	51%
	Declined	51%	43%	42%	34%
SAQ (SEM5.1)	Improved	10%	7%	6%	12%
	Stable	47%	41%	40%	43%
	Declined	42%	53%	50%	45%
IPSS	Improved	4%	7%	8%	14%
	Stable	3%	14%	28%	22%
	Declined	93%	79%	64%	64%

General comments: -

Wahlgren, Nilsson, Ryberg, Lennernas and Brandberg. Combined curative radiotherapy including HDR brachytherapy and androgen deprivation in localised prostate cancer: a prospective assessment of acute and late treatment toxicity. Acta Oncological, 2005; 44:633-643

Design: case series study evidence level 3

Country: Sweden

Setting: hospital based (secondary care)

Inclusion criteria: clinically localised prostate cancer treated or in line for treatment with EBRT and HDR BT boost including neoadjuvant/ concurrent androgen deprivation therapy

Exclusion criteria: contributing to few questionnaires, multiple malignancies, treatment failure during study

Population:

Number of patients:	525
Mean age	69 (range 51-84)
Stage	T1-T3a
Gleason Score	4-7
iPSA	range 1.7 to 110
Free of recurrence PSA level	<1

Intervention: questionnaires looking at urinary, bowel and sexual functions

Outcomes: prevalence of urinary, bowel and sexual dysfunction

Follow-up: range 2-34 months after radiotherapy

Results: Some evidence that adding androgen deprivation before RT significantly worsened sexual function. During RT urinary, bowel and sexual problems increased and were reported at higher level up to 34 months. General tendency to decreasing irritative bowel and urinary tract symptoms over time. No side effects requiring surgery were reported. Classic late irradiation effects, such as mucosal bleeding reported mainly after the second year after RT but less pronounced than in dose escalated EBRT.

Urinary tract symptoms:

Baseline: regardless of hormonal treatment frequency and haematuria dominated.

After RT: increased dysuria and frequency. Increase incontinence persisted throughout the study period.

Bowel symptoms: acute and late mucosal radiation effects, rectal bleeding most pronounced between 6 and 10 months. No grade 4 (RTOG) bowel complications reported.

GI toxicity appears earlier than GU toxicity.

Sexual symptoms

Baseline without AD: sexual desire and satisfaction percentages were high, while erectile dysfunctions were reported by ½ of patients.

Adding AD worsened all symptoms ($\chi 2$-$p \Leftarrow 0.002$) Nadir at 2 months and gradually restored form 4 months. Erectile function and satisfaction increased but never reached baseline levels.

OUTCOME OF INTEREST **COMPARISON**

Prevalence of symptoms in % of n		**Urinary**	**Bowel**	**Sexual**
Before RT	no TAB	19	14	35
Before RT	with TAB	27	13	59
2 months		49	45	77
4 months		42	38	74
10 months		38	52	65
16 months		33	45	68
22 months		36	34	65
28 months		33	45	68
34 months		25	31	69

Urinary tract symptoms In % of n	**Dysuria** 0ften /Always	**Frequency** >1/h	**Haematuria** yes	**Incontinence** daily
Before RT	1	3	3	1
2 months	11	8	9	6
4 months	4	4	7	4
10 months	10	2	6	4
16 months	14	1	12	5
22 months	4	5	12	5
28 months	9	5	15	3
34 months	0	2	6	2

Bowel symptoms In % of n	**Urgency** 0ften /Always	**Frequency** >5/d	**Rectal pain** yes	**Rectal bleeding** >2/week
Before RT	4	3	1	1
2 months	12	7	4	1
4 months	6	7	2	3
10 months	7	4	3	5
16 months	9	7	3	6
22 months	5	4	0	1
28 months	3	3	2	3
34 months	4	4	2	7

Sexual symptoms	Durable erection in % often /Always	Desire in % yes	Satisfaction in % often /Always
Before RT no TAB	48	95	82
Before RT with no TAB	13	65	40
2 months	4	50	12
4 months	11	71	26
10 months	17	78	40
16 months	17	83	40
22 months	15	80	45
28 months	20	77	36
34 months	14	89	41

Tran, Wallner, Merrick, Seeberger, Armstrong, Mueller, Cavanagh, Lin and Butler. Rectal Fistulas after Pros-

General comments: -

tate Brachytherapy, Int. J. Radiation Oncology Biol. Phys, vol. 63, no 1 pp. 150-154, 2005
Design: case report from RCT evidence level 3
Country: USA
Setting: hospital based (secondary care)
Inclusion criteria: prostate brachytherapy no other characteristics reported
Exclusion criteria: not reported
Population: number of patients: 503 randomised to: implantation ^{125} I vs. ^{103} Pd alone n=290 or ^{103} Pd with 20 Gy vs. 44 Gy supplemental EBRT n=213 mean age: not reported
Intervention: implantation ^{125} I vs. ^{103} Pd alone, or ^{103} Pd with 20 Gy vs. 44 Gy supplemental external beam radiotherapy; treatment related morbidity monitored adequately
Outcomes: rectal bleeding and subsequent rectal fistulas
Follow-up: minimum 24 months
Results:: Some evidence that high radiation doses should be avoided to minimise the likelihood of rectal bleeding Persistent rectal bleeding (n=44) , 73% of whom (n= 32) underwent confirmatory endoscopy; rectal fistulas occurred in 0.4% of patients (n=2)
General comments: - no result of the RCT per se, only case reports for rectal bleeding and subsequent rectal fistulas

Chen, D'Amico, Neville & Earle . Patient and treatment factors associated with complications after prostate brachytherapy. J Clin Oncol. 24[33]. 2006.
Design: Retrospective cohort study (therapy), evidence level: 2+ Country: United States **Inclusion criteria** Men treated with interstitial prostate brachytherapy (IB) for clinically localised prostate cancer between 2002 and 2005 at a single institution. Gleason score <7, PSA < 15 ng/ml and no evidence of distant or nodal metastases. **Exclusion criteria** Men with T4 disease or distant metastases at diagnosis. Men with prior prostatectomy or external beam radiotherapy more than 1 year before brachytherapy. **Population** number of patients = 5621. **Interventions** Brachytherapy, some men had concomitant EBRT (60%), some had neoadjuvant hormonal therapy (39%). Predictive factors for complications were examined, factors included demographic, prostate cancer, treatment and risk factor variables. **Outcomes** Complications occurring within the first 2 years after treatment. Complications were recorded as: 1) complications that may or may not required an invasive procedure and 2) com-

plications that would require an invasive procedure.

Follow up Men had at least 2 years of follow-up.

Results 54.5% of men had a diagnosis or invasive procedure defining a complication, within 2 years of treatment. 14.1% of men had an invasive procedure to treat a treatment complication.

Multivariate analysis of predictive factors was done using logistic regression.

Factors associated with urinary complications:

Older age (P < .01), non-white race (odds ratio [OR], 1.30; P = .01), low income (OR, 1.74; P < .01), external-beam radiotherapy (EBRT; OR, 0.85; P = .01), androgen deprivation (OR, 1.31; P < .01), later year of brachytherapy (OR, 1.03/yr; P = .02), higher Charlson comorbidity score (P < .01), and prior transurethral resection of the prostate (OR, 1.65; P < .01).

Factors associated with bowel complications

Older age (P = .04), EBRT (OR, 1.46; P < .01), later year (OR, 1.04/yr; P < .01), higher Charlson score (P = .01), and inflammatory bowel disease (OR, 2.60; P < .01)

Factors associated with erectile complications

Younger age (P < .01), non-white race (OR, 1.37; P < .01), AD (OR, 1.18; P = .04), and later year (OR, 1.08/yr; P < .01)

COMPARISON IN MEN WITH LOCALISED OR LOCALLY ADVANCED PROSTATE CANCER, WITH NO METASTASES	BRACHYTHERAPY	BRACHYTHERAPY PLUS EBRT	OVERALL RESULT
Urinary complications	35.4%	32.7	favours brachytherapy plus EBRT (p=0.03)
Bowel complications	17.7%	23.2%	favours brachytherapy alone (p<0.01)
Erectile complications	16.4%	17.2%	no statistically significant difference (p=0.44)

Buron, Le, Cosset, Pommier, Peiffert, Delannes, Flam, Guerif, Salem, Chauveinc & Livartowski . Brachytherapy versus prostatectomy in localized prostate cancer: results of a French multicenter prospective medico-economic study. Int J Radiat.Oncol Biol. Phys. 67[3]. 2007.

Design: Prospective case series (therapy), evidence level: 3

Country: France, setting: Tertiary care

Inclusion criteria Men with localised prostate cancer treated with radical prostatectomy or interstitial prostate brachytherapy at one of 11 centres between 2001 and 2002.

Exclusion criteria -

Population number of patients = 435.

Interventions Radical prostatectomy (RP), retropubic in 86% of cases and laparoscopic for 14%. 6.3% of men had neoadjuvant hormonal therapy before RP.

Interstitial prostate brachytherapy (IB) with iodine-125 seeds, most men had real-time ultrasound planning. 43% of men had neoadjuvant hormonal therapy before brachytherapy.

Outcomes Health related quality of life and treatment related symptoms. Two patient-completed measures were used, The EORTC quality of life questionnaire QLQ-C30 version 3 and the prostate cancer specific EORTC QLQ-PR25 module.

Follow up Men completed HRQOL questionnaires before treatment, immediately after treatment and at 2,6,12,18 and 24 months after treatment. Questionnaire response was higher for the brachytherapy group than the prostatectomy group. Immediately after treatment the response rates were 70% for the RP group and 85% for the IB group, at 18 months after treatment the corresponding figures were 39% and 60%.

Results There were baseline differences in the patient groups. Men in the IB group were significantly older, had lower clinical stage, lower PSA level and lower pretreatment International Prostate Symptom Score than men in the RP group.

Only results up to 2 months after surgery are reported in this appraisal, due to high loss to follow-up beyond this period.

Just after treatment, the decrease of global HRQOL was less pronounced in the IB than in the RP group, with a 13.5 points difference ($p < 0.0001$). At two months after treatment there was no significant difference in global HRQOL between the two groups.

Side effect profiles (within the first 2 months after treatment) differed between the two groups. Radical prostatectomy was associated with greater urinary incontinence and erectile dysfunction, whereas brachytherapy was associated with greater urinary urgency, pain and frequency. Faecal incontinence and rectal bleeding were also more likely after brachytherapy.

General comments Poor return rate for questionnaires, particularly so for the RP group: considerable potential for bias.

Caffo, Fellin, Bolner, Coccarelli, Divan, Frisinghelli, Mussari, Ziglio, Malossini, Tomio & Galligioni . Prospective evaluation of quality of life after interstitial brachytherapy for localized prostate cancer. International Journal of Radiation Oncology, Biology, Physics 66[1]. 2006.

Design: Prospective case series (therapy), evidence level: 3

Country: Italy, setting: Tertiary care

Inclusion criteria Men treated with interstitial prostate brachytherapy (IB) for clinically localised prostate cancer between 2002 and 2005 at a single institution. Gleason score <7, PSA < 15 ng/ml and no evidence of distant or nodal metastases.

Exclusion criteria -

Population number of patients = 147.

Interventions All men were treated using interstitial prostate brachytherapy . Treatment was preplanned using a modified peripheral loading technique, and men were implanted using preloaded I-125 needles. All men with prostate volume of more than 60 ml received 3 to 6 months neoadjuvant hormonal therapy.

Outcomes Quality of life, assessed using a patient completed questionnaire (Caffo et al, 1996; Br J Urol; 78; 557 - 563).

The questionnaire had seven subscales: physical well-being (PHY), physical autonomy (POW), psychological well-being (PSY), relational life (REL), urinary function (URI), rectal function (REC), and sexual function (SEX). Higher scores on this questionnaire indicate poorer QOL.

Men with treatment failure were not asked to complete questionnaires.

Follow up Men completed questionnaires 1 week before IB treatment, 1 month, and 1,2, 3 and 4 years after treatment. All patients completed the baseline and 1 month questionnaire but only 31% completed the 3 year one and 10% completed the 3 year one.

Results There was no statistically significant differences in the PHY, POW, PSY, and REL dimensions of the questionnaire scores 1 month after IB or later, compared with baseline values.

Urinary function significantly worsened after IB. In men with poor baseline urinary function mean (95% CI) URI scores were 23.1 (20.8 to 25.4) and 37.0 (32.6 to 41.4) pre-IB and post-IB respectively. In men with good baseline urinary function mean (95% CI) URI scores were 6.3 (5.5 to 7.1) and 26.4 (22.9 to 29.9) pre-IB and post-IB respectively.

Sexual function significantly worsened after IB. Mean (95% CI) SEX scores were 33.0 (28.3 to 37.7) and 45.1 (39.7 to 50.5) pre-IB and post-IB respectively.

General comments Exclusion of men with treatment failure is a potential source of bias.

Soderdahl, Davis, Schellhammer, Given, Lynch, Shaves, Burke & Fabrizio . Prospective longitudinal comparative study of health-related quality of life in patients undergoing invasive treatments for localized prostate cancer. Journal of Endourology 19[3]. 2005.

Design: Prospective case series (therapy), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men with newly diagnosed localised prostate cancer, treated with curative intent at a single institution between 2001 and 2003.

Exclusion criteria Men with more than 50% of their questionnaire data missing.

Population number of patients = 452.

Interventions Men were treated with either open radical prostatectomy (ORP), laparoscopic radical prostatectomy (LRP), or palladium-103 (pd-103) brachytherapy.

Outcomes Health related quality of life, measured using patient completed questionnaires. Physical and emotional issues were measured with the Rand 36 item health survey (SF-36). Disease specific QOL was measured with the UCLA Prostate Cancer Index (PCI). Urinary symptoms were measured using the American Urological Association (AUA) Symptom Index.

Follow up The surveys were done before treatment and at 2, 3, 6, 9 and 12 months after treatment. Complete survey data were available for 46%, 80.2% and 47.3% of men treated with open radical prostatectomy, laparoscopic radical prostatectomy and palladium-103 brachytherapy respectively.

Results SF-36 (general HRQOL)

After treatment general QOL showed an initial decline from the baseline values, but returned to baseline over time. There were no significant differences between the general QoL scores in the different treatment groups.

PCI (disease related symptoms)

All treatment groups experienced disease related symptoms, but symptom profiles differed. The prostatectomy groups reported worse sexual function, sexual bother and urinary continence than the brachytherapy group. The brachytherapy group initially had worse bowel function than the prostatectomy group.

AUA symptom scores

Brachytherapy was associated with worse general urinary function (obstructive and irritative urinary symptoms) than prostatectomy.

Khaksar, Langley, Lovell & Laing . Interstitial Low Dose Rate Brachytherapy for Prostate Cancer - A Focus on Intermediate- and High-risk Disease. Clinical Oncology (Royal College of Radiologists) 18[7]. 2006.

Design: Retrospective case series (therapy), evidence level: 3

Country: United Kingdom, setting: Tertiary care

Inclusion criteria Men treated with low dose interstitial prostate brachytherapy for clinical stage T1c to T3a prostate cancer, between 1999 and 2003, at a single institution.

Population number of patients = 300.

Interventions All men received interstitial prostate brachytherapy with I-125 seeds. Men with prostates larger than 50 mL were offered neoadjuvant androgen deprivation (NAD) or EBRT. Men were stratified into low (n=146), intermediate (n=111) and high (n=43) risk groups based on their pretreatment PSA, biopsy Gleason score and clinical stage.

Outcomes Biochemical relapse free survival (ASTRO 1997 definition of biochemical relapse).

Follow up Men were assessed at 3 to 6 month intervals for the first year and then yearly. Median follow-up was 45 months (range 33 to 82 months).

Results 21 men experienced biochemical relapse.

Five year actuarial biochemical relapse (BCR) free survival was 96%, 89% and 93% in the low, intermediate and high risk groups respectively.

Stratifying outcome by treatment group and risk group did not reveal any obvious differences. On multivariate analysis, using Cox regression, risk group was not a significant prognostic factor for relapse (HR=1.32; 95% CI 0.58 to 3.01).

LOW RISK PROSTATE CANCER	BRACHYTHERAPY	BRACHYTHERAPY + NAD	BRACHYTHERAPY + NAD + EBRT
5 year biochemical failure free survival	94% (n=77)	92% (n=66)	100% (n=3)
INTERMEDIATE RISK PROSTATE CANCER	BRACHYTHERAPY	BRACHYTHERAPY + NAD	BRACHYTHERAPY + NAD + EBRT
5 year biochemical failure free survival	93% (n=15)	94% (n=67)	92% (n=25)
HIGH RISK PROSTATE CANCER	BRACHYTHERAPY	BRACHYTHERAPY + NAD	BRACHYTHERAPY + NAD + EBRT
5 year biochemical failure free survival	100% (n=2)	88% (n=7)	96% (n=29)

General comments Low event rate, longer follow-up needed.

Namiki, Satoh, Baba, Ishiyama, Hayakawa, Saito & Arai . Quality of life after brachytherapy or radical prostatectomy for localized prostate cancer: A prospective longitudinal study. Urology 68[6]. 2006.
Design: Retrospective case series (therapy), evidence level: 3 Country: Japan, setting: Tertiary care **Inclusion criteria** Men with newly diagnosed, early, localised prostate cancer treated with radical retropubic prostatectomy (RRP) or brachytherapy (BT) at two institutions between 2004 and 2005. **Exclusion criteria** - **Population** number of patients = 157. **Interventions** Men were treated with either brachytherapy (using iodine-125, prescription dose was 145 Gy) or radical retropubic prostatectomy (33% bilateral nerve sparing and 51% unilateral nerve sparing). No men received hormonal therapy. **Outcomes** Health related quality of life. General HRQOL was measured using patient completed SF-36 questionnaire Disease specific HRQOL was measured using the UCLA Prostate Cancer Index (UCLA-PCI). Urinary symptoms were measured using the International Prostate Symptom Score (IPSS). **Follow up** Baseline HQOL assessment was 1 month before treatment, with follow-up assessment at 1,3,6 and 12 months after treatment. The questionnaire return rate was 87% at baseline and 73% at 12 months. **Results** At baseline the brachytherapy group had significantly lower Gleason score than the prostatectomy group. General HRQOL The same pattern was seen in both groups, with a significant decline in general HRQOL after treatment which returned to baseline values at 12 months. A more pronounced reduction was seen with RRP than with BT, but only in the first month after treatment. UCLA-PCI Urinary function, sexual function and sexual bother were significantly worse with RRP than with BT. There were no group differences in bowel symptoms. IPSS Voiding symptoms were more likely with BT than with RRP

Stone & Stock . Long-Term Urinary, Sexual, and Rectal Morbidity in Patients Treated with Iodine-125 Prostate Brachytherapy Followed Up for a Minimum of 5 Years. Urology 69[2]. 2007.
Design: Retrospective case series (therapy), evidence level: 3 Country: United States, setting: Tertiary care **Inclusion criteria** Men with clinical stage T1 to T2 prostate cancer treated with I-125 brachytherapy between 1990 and 2000. **Exclusion criteria** - **Population** number of patients = 325, median age = 67 years. **Interventions** All men were treated with iodine-125 brachytherapy. 23% of men had 5 to 6 months of neoadjuvant hormonal therapy before brachytherapy, and 33% of men had TURP before implantation. **Outcomes** Urinary symptoms were measured using the patient completed AUA symptom score. Erectile function was measured using the patient completed Mount Sinai Erectile Function Score (MSEFS) and the IIEF questionnaire. Rectal bleeding was determined by interview, and the presence of ulcers by DRE or colonoscopy (and graded according to the RTOG scale). Any men using pads were classified as incontinent **Follow up** Median follow-up 7 years (range 5 to 15 years). 271/325 men were available for evaluation at 5 years after treatment. **Results** Urinary complications At 6 months the AUA score had increased significantly (worsened) from the baseline value but at 5 years was no longer significantly different from the baseline value. Erectile function Before treatment 77.2% of men reported at least adequate erectile function. At 5 years after treatment this proportion decreased to 50.6%. Rectal morbidity 78/325 men (24%) experienced rectal bleeding at 1 to 3 years after treatment. There were no reported cases of rectal ulcers or fistula.

Health Economics

The health economics analysis relating to this topic can be found at the end of section 4.2.

3.6 Combined external beam radiotherapy and brachytherapy

Is the combination of brachytherapy with external beam radiotherapy more effective than either method alone for localised or locally advanced non metastatic prostate cancer?

Rationale

Radiotherapy can be delivered to the prostate in two ways; either using external x-ray beams from a linear accelerator, typically three or four beams using conventional methods and 5 to 7 beams using IMRT. Alternatively radiation sources can be placed directly into the prostate gland; this is brachytherapy. There are two different radiation sources used in prostate cancer; low dose rate I125 seeds which are implanted and remain in the prostate lifelong (permanent implants) or high dose rate Ir192 delivered using an after loading machine directed into the prostate along implanted plastic tubes which are subsequently removed (temporary implant). Theoretically brachytherapy can deliver a higher dose than external beam radiotherapy as it does not traverse normal tissues to reach the prostate, however it may itself deliver higher doses to the urethra. High dose rate brachytherapy by using large fraction sizes may be biologically more effective than low dose per fraction external beam delivery.

Brachytherapy has become accepted as a standard of care for localised prostate cancer, but its role in locally advanced disease is less clear. Recently published randomised trials have clearly established that external beam radiotherapy (in combination with hormone therapy) for patients with locally advanced prostate cancer is now standard treatment, and it has postulated that brachytherapy may also have a role to play in this group. However brachytherapy does not deliver significant radiation dose outside the prostate capsule which may be important particularly in high risk and locally advanced disease when extracapsular extension is more prevalent, hence a combination of the two approaches may be optimal.

PICO question

Population	Intervention	Comparison	Outcomes
Men with localised or locally advanced non-metastatic prostate cancer Subgroups: Low Intermediate High (D'Amico classification)	High dose rate brachytherapy (HDR-BT) plus external beam radiotherapy (EB-RT) Low dose rate brachytherapy (LDR-BT) plus external beam radiotherapy (EB-RT)	HDR-BT alone EB-RT alone LDR-BT alone	• Overall survival • Disease-free survival • Biochemical disease-free survival • Treatment-related morbidity • Treatment-related mortality • Health-related quality of life

How the information will be searched

Sources to be searched	
Can we apply date limits to the search	No date limits.
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	A randomised trials filter will be used
List useful search terms.	

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results?	We will use the evidence table for randomised trials (NICE guidelines manual appendix J).
Which quality checklist will we use for appraisal?	The RCT checklist will be used (NICE guidelines manual appendix C).
List subgroups here and planned statistical analyses	Given the numerous interventions and comparators a mixed treatment comparison may be appropriate (if both high and low dose rate brachytherapy are appropriate in the same population). Time to events meta-analysis will be done for survival outcomes. Dichotomous outcomes will be meta-analysed using risks ratios or odds ratios. Patient subgroups are noted in the PICO.

Evidence statements

External beam radiotherapy plus high dose rate brachytherapy (EBRT+HDR-BT) versus EBRT alone

Biochemical failure

Moderate quality evidence suggests better biochemical failure free survival when men are treated with EBRT+HDR-BT than when treated with EBRT alone (HR = 0.57, 95% C.I. 0.41 to 0.79). However this evidence comes from randomised trials (Sathya et al 2005; Hoskin et al 2012) that used lower doses in their EBRT-only arms (66 Gy and 50 Gy respectively) than the minimum of 74 Gy recommended in the 2008 NICE prostate cancer guideline.

Very low quality evidence from a meta-analysis of non randomised studies (Pieters et al, 2009) suggests better biochemical failure free survival combined EBRT and HDR-BT when compared to EBRT alone (HR 0.71; 95% C.I. 0.66 to 0.76).

All cause mortality

Moderate quality evidence suggests uncertainty about whether overall survival is equivalent or worse in men treated with EBRT+ HDR-BT when compared to men treated with EBRT alone. The pooled hazard ratio from two randomised trials trials (Sathya et al 2005; Hoskin et al 2012) for all cause mortality (combined versus EBRT) was 1.44 (95% C.I. 0.87 to 2.40).

Very low quality evidence from a meta-analysis of non randomised studies (Pieters et al, 2009) suggests a survival benefit for combined EBRT and HDR-BT compared to EBRT alone (HR 0.67; 95% C.I. 0.58 to 0.78).

Adverse events

There is low quality evidence of uncertainty about the relative rates of gastrointestinal complications in EBRT+ HDR-BT and EBRT (OR=1.48, 95% C.I. 0.55 to 4.01). Gastrointestinal complications occurred in 6% and 4% of men treated with EBRT+HDR-BT and EBRT respectively (Sathya et al 2005; Hoskin et al 2012).

There is low quality evidence of uncertainty about the relative rates of genitourinary in EBRT+ HDR-BT and EBRT (OR=1.24, 95% C.I. 0.71 to 2.17). Genitourinary complications occurred in 22% and 19% of men treated with EBRT+HDR-BT and EBRT respectively (Sathya et al 2005; Hoskin et al 2012).

Health related quality of life

Moderate quality evidence suggests equivalent health related quality of life following combined EBRT+HDR-BT and EBRT alone. Hoskin et al (2007) found average FACT-P scores returned to pre-treatment levels with 6 months of treatment in both EBRT+HDR-BT and EBRT groups. No significant differences in mean FACT scores were found for any of the three domains: general, prostate and Trial Outcome Index (TOI), or in erectile function scores over a 10.5 year follow-up period (Hoskin et al. 2013).

EBRT + HDR-BT versus EBRT alone

There was no evidence from randomised trials or observational studies comparing EBRT+HDR-BT to EBRT alone.

EBRT + Low dose rate brachytherapy (LDR-BT) versus EBRT alone

There was no evidence from randomised trials comparing EBRT+LDR-BT to EBRT alone. Very low quality evidence from an observational study indicates uncertainty about the relative effectiveness of the two options.

Biochemical failure

A systematic review (Bannuru et al, 2011) identified a small observational study (Wong et al, 2009), which found no significant difference between five year biochemical failure free survival of the two treatment arms: 94% versus 87% for EBRT+LDR-BT and EBRT respectively.

Adverse events

In Wong et al (2009) late grade 3 GI and GU toxicity were more likely with EBRT+LDR-BT than with EBRT alone.

EBRT + LDR-BT versus LDR-BT alone

There was no evidence from randomised trials comparing EBRT+LDR-BT to EBRT alone. Very low quality evidence from observational studies suggests uncertainty about the relative effectiveness of the two options.

Biochemical failure

A systematic review (Bannuru et al, 2011) identified two small observational studies (da Silva Franca et al, 2010; Wong et al, 2009) with conflicting results. Da Silva Franca et al (2010) reported better five year biochemical failure free survival with combined therapy than with LDR-BT alone whereas Wong et al (2009) found no significant difference.

Adverse events

Bannuru et al (2011) identified two relevant observational studies (Wong et al, 2009 and Zelefsky et al, 2008). There was uncertainty about the relative rates of late GI complications because only four cases were observed: for EBRT+LDR-BT vs LDR-BT, OR = 5.31 (95% C.I. 0.73 to 38.74). For late GU complications there was similar uncertainty: EBRT+LDR-BT vs LDR-BT, OR = 1.08 (95% C.I. 0.49 to 2.4).

EBRT (40 Gy) plus LDR-BT versus EBRT (20 Gy) plus LDR-BT

Biochemical failure

Low quality evidence suggests uncertainty about whether biochemical failure differs between higher and lower doses of supplemental EBRT. The evidence comes from a single randomised trial (Merrick et al, 2012) in which only 15 men experienced biochemical failure. The resulting confidence intervals (EBRT 40 Gy + LDR-BT versus EBRT 20 Gy + LDR-BT; HR = 1.0, 95% C.I. 0.36 to 2.76) are wide enough to include the possibility that either treatment option could be superior to the other in terms of biochemical failure.

All cause mortality, Adverse events and Health related quality of life

There was no evidence about these outcomes in studies comparing higher to lower dose EBRT with LDR-BT.

Table 102 Study Characteristics

Study and country	Treatment period	Design	Treatment 1	Treatment 2	Entry criteria
Hoskin (2012), UK	1997 to 2005	RCT	EBRT (34Gy) +HDR-BT	EBRT (50Gy)	Stage T1-T3, M0, PSA<50 ng/ml
Sathya (2005), Canada	1992 to 1997	RCT	EBRT (30Gy)+ HDR-BT	EBRT (66Gy)	Stage T2-T3, N0, M0
Merrick (2012), USA	1999 to 2004	RCT	EBRT (20Gy)+LDR-BT	EBRT (40Gy)+LDR-BT	Stage T1-T2, Gleason 7-10, PSA 10 -20 ng/ml
Pieters (2009)	Studies published 1980 to 2007	Systematic review of observational studies and RCTs	EBRT+LDR-BT, EBRT+ HDR-BT	EBRT (≥75Gy)	Any patient suitable for EBRT or BT
Bannaru (2011)	Studies published 2005 to 2011	Systematic review of comparative observational studies and RCTs	EBRT+LDR-BT, EBRT+ HDR-BT	EBRT(66 to 77Gy where reported), LDR-BT, HDR-BT	Clinically localised disease

Abbreviations: BT, brachytherapy; EBRT, external beam radiotherapy; HDR-BT, high dose rate brachytherapy; LDR-BT, low dose rate brachytherapy; RCT, randomised controlled trial

Evidence tables

Study	Hoskin (2012)
Methods	Study design: RCT Country: UK Study period: 1997 to 2005 Inclusion criteria: Histological diagnosis of prostate cancer, T1-T3 M0 (following pelvic CT or MR, isotope bone scan chest X-ray), PSA < 50 ng/ml Exclusion criteria: Recent TURP, unfitness for anaesthetic unable to give informed consent Length of follow up: median 7.1 years
Participants	**EBRT + HDR-BT arm** No. in trial arm: 109 Age (years): mean 68.4 (range 47 to 79) T category: T1 27%, T2 40%, T3 29% Gleason score: ≤5 11%, 6 21%, 7 36%, >7 14% **EBRT arm** No. in trial arm:111 Age (years): mean 69.4 (range 47 to 79) T category: T1 23%, T2 50%, T3 23% Gleason score: ≤5 13%, 6 24%, 7 32%, >7 13%
Interventions	**Combined EBRT + HDR-BT**, EBRT was 33.75Gy in 13 fractions. HDR-BT boost was 17Gy given in 2 doses over 24 hours. **EBRT alone,** total dose of 50Gy in 20 fractions.
Outcomes	Biochemical recurrence, defined as a PSA rise of 2 ng/ml or more above the nadir value Overall survival Morbidity: symptoms measured using Dische scorring method (translated to RTOG and CTC equivalents) acute morbidity up to 12 weeks from treatment and late morbidity thereafter. Quality of life measured with FACT-P.
Adjuvant therapy	EBRT + HDR-BT arm 76% had neoadjuvant hormone therapy. EBRT arm 76% had neoadjuvant hormone therapy.
Risk of bias	Blinding not mentioned but survival outcomes are unlikely to be affected by this. Allocation concealment unclear, method of randomisation not reported.

Notes	

Study	Sathya (2005)
Methods	Study design: RCT Country: Canada Study period: 1992 to 1997 Inclusion criteria: T2-T3 N0 M0 histologically confirmed prostate cancer Exclusion criteria: Prior history of pelvic radiotherapy, prostatectomy, TURP or androgen deprivation. Length of follow up : median 8.2 years
Participants	138 patients enrolled – but 34 excluded from analysis due to positive lymph nodes. **Combined HDR-BT+EBRT** No. in trial arm: 51 Age (years): mean 65 years (range 49 to 74) T category: T2 61%, T3 39% Risk status: intermediate 41%, high risk 59% **EBRT alone** No. in trial arm: 53 Age (years): mean 66 years (range 57 to 74) T category: T2 60%, T3 40% Risk status: intermediate 40%, high risk 60%
Interventions	**Combined HDR-BT+EBRT** 30Gy HDRT-BT plus 40 Gy EBRT in 20 fractions over 4 weeks. **EBRT alone** 66 Gy in 2Gy fractions over 6.5 weeks.
Adjuvant therapy	Androgen deprivation therapy was only started if PSA exceeded 20 µg/ml or if there was obvious clinical failure.
Outcomes	Biochemical recurrence, defined as PSA failure (ASTRO 1997) clinical failure or death from prostate cancer. Overall survival Toxicity – graded using NCI-Canada expanded common toxicity criteria.
Risk of bias	Adequate allocation concealment and randomisation. No blinding mentioned – probably not an issue for survival outcomes. Study stopped prematurely in 1997 when 66 Gy EBRT alone became considered suboptimal treatment.

Notes	

Study	Merrick (2012)
Methods	Study design: RCT Country: USA Study period: 1999 to 2004 Inclusion criteria: Clinically organ confined (T1-T2), Gleason score 7 to 10 and/or pretreatment PSA 10 to 20 ng/ml. Exclusion criteria: Length of follow up: Median follow up 9 years (range 0.2 to 11.6)
Participants	566 patients entered. Results from 319 treated at Puget Sound Veterans Affairs Hospital are embargoed leaving 247 for the 2012 publication. **EBRT (44Gy) + LDR-BT** No. in trial arm: 125 Age (years): median 68 years T category: T1b-T2b 96%, T2c-T3a 4% Gleason score: : ≤6 6%, 7 76%, 8-9 18% **EBRT (20Gy) + LDR-BT** No. in trial arm: 122 Age (years): median 65 years T category: T1b-T2b 98%, T2c-T3a 2% Gleason score: ≤6 3%, 7 83%, 8-9 14%
Interventions	EBRT (44Gy) + LDR-BT (Pd-103, 90Gy) EBRT (20Gy) + LDR-BT (Pd-103, 115Gy)
Outcomes	Biochemical failure, defined as PSA ≥ 0.40 ng/ml following nadir. Patients who did not achieve nadir of <0.40 ng/ml were categorised as having biochemical failure. Overall survival, cause specific survival. Morbidity (rectal, urinary.
Adjuvant therapy	80 patients (32%) received androgen deprivation therapy
Risk of bias	Adequate allocation concealment and randomisation. There was no blinding. Large number of missing results (56%) due to embargo on Puget

	Sound patients.
Notes	

Study	Bannuru (2011)
Methods	Study design: Systematic review of RCTs and non randomised comparative studies. Country: International Study period: studies published up to march 2011 were considered for inclusion Inclusion criteria: Studies comparing radiation treatments for clinically localised prostate cancer indexed in MEDLINE or Cochrane Central databases. Exclusion criteria: Studies in which more than 20% had locally advanced (T3 or T4) cancer; adjuvant, salvage or post-prostatectomy studies; studies specifically addressing ADT in conjunction with radiation therapy
Participants	Men with clinically localised prostate cancer (T1-T2, N0-NX, M0-MX).
Interventions	Combined radiotherapy (RT) versus single modality RT or other combined RT
Outcomes	Biochemical failure, GU toxicity, GI toxicity
Risk of bias	Includes mainly non-randomised studies: high risk of bias
Notes	Review was done to update the AHRQ report on treatment options for localised prostate cancer. The authors concluded that there was insufficient evidence to judge the relative benefits and harms of combined versus EBRT+BT versus BT alone, because results were inconsistent across the studies.

Study	Pieters (2009)
Methods	Study design: Systematic review and meta-analysis of randomised and non-randomised studies Country: International Study period: Studies published between 1980 and 2007 Inclusion criteria: Exclusion criteria: Length of follow up (range of medians for the treatment groups):
Participants	No patient selection criteria were used – any studies that had used the interventions below for treatment of prostate cancer were considered for inclusion. For EBRT-only studies dose had to be at least 75Gy. For LDR-BT studies

	only studies using the transperineal implantation technique. Analysis was adjusted (at study level) for initial PSA value, clinical T-stage, Gleason score, median age, hormonal therapy and year of publication.
Interventions	Prescription radiotherapy dose was expressed as biologically effective dose (BED_3), calculated for an αβ-ratio of 3 Gy. EBRT 10 studies (N=2410), BED_3 121 to 130 Gy EBRT plus LDR-BT, 13 studies (N=2460), BED_3 142 to 234 Gy EBRT plus HDR-BT, 17 studies (N=2450), BED_3 105 to 170 Gy
Outcomes	Biochemical recurrence free survival (typically using ASTRO 1997 consensus panel definition) , overall survival
Risk of bias	Includes mainly non-randomised studies: high risk of bias.
Notes	Authors note that initial PSA value, clinical T-stage and hormonal therapy were not well balanced between the three treatment groups.

References

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Hoskin PJ, Rojas AM, Ostler PJ, et al. (2013). Quality of life after radical radiotherapy for prostate cancer: longitudinal study from a randomised trial of external beam radiotherapy alone or in combination with high dose rate brachytherapy. *Clinical Oncology* 25: 321-327.

Earlier paper from this trial

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Other publications from this trial

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3.7 HIFU and cryotherapy

Cryotherapy versus watchful waiting or other radical therapies

Short Summary

Evidence comes from three systematic reviews of case series (Hummel *et al.* 2003; National Institute for Health and Clinical Excellence 2005; Shelley *et al.* 2007) and two Canadian randomised trials (Donnelly *et al.* 2007; Chin *et al.* 2007) comparing cryotherapy to external beam radiotherapy. The systematic reviews concluded that evidence was of poor quality: the length of follow-up was very limited so there was no good evidence about disease specific or overall survival. The intermediate end-points of biochemical recurrence and prostate biopsy, however, show that cryotherapy ablates prostate tissue. Treatment toxicity was also reported: most commonly sexual dysfunction and stress incontinence.

Both the randomised trials failed to enrol the planned number of patients, and their results should be viewed with caution. The results of one trial (Chin *et al.* 2007) suggested a greater risk of biochemical failure with cryotherapy than with external beam radiotherapy. The other trial (Donnelly *et al.* 2007), published as an abstract only, did not find a statistically significant difference in the rate of treatment failure in the first three years after treatment. Neither trial reported a difference in the overall survival of the cryotherapy and radiotherapy groups.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOMES
Men with localised or locally advanced prostate cancer with no prior treatment.	Cryotherapy	• Watchful waiting also • Radical prostatectomy • EBRT • Brachytherapy • Conformal Radiotherapy • Conventional radiotherapy • HIFU	• overall survival • disease-specific survival • biochemical disease-free survival • time until next intervention • 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)

Evidence summary

The literature search identified three systematic reviews (NICE 2005; Hummel, 2003; Shelley et al. 2007). The reviews included one non-randomised comparative study, three non-randomised uncontrolled studies and 15 case series investigating the use of cryotherapy as treatment in men with localised prostate cancer.

All study populations included men with prostate cancer. Most were clinical tumour stage T1-T3; but T4 patients were included in some studies. Some of the studies also included men who had cryotherapy for recurrent prostate cancer. Follow up was too short to report survival outcomes. Instead, studies used intermediate measures of clinical effectiveness: rates of PSA recurrence and positive prostate biopsy. The lack of an accepted definition of biochemical recurrence after cryosurgery means that there was variability in the reporting of recurrence free sur-

vival between series. Follow-up, however, was sufficient to provide information about treatment side effects at least within the first few years after cryotherapy.

A number of different cryotherapy protocols were used (TRUS-guided, urethral warming, ultrasound guidance, temperature monitoring etc). Some of the earlier studies used first generation machines: their results may not be applicable to current cryotherapy techniques. Biochemical disease-free survival and positive/negative biopsy rates, however, were comparable between studies.

Two Canadian randomised studies were identified (Donnelly *et al.* 2007; Chin *et al.* 2007), which compared cryotherapy with external beam radiotherapy. Both trials closed early after recruitment difficulty, and were probably underpowered. Both radiotherapy dosage and cryotherapy technique were suboptimal in the Chin and co-workers trial. Donnelly and co-workers (published as an abstract only) did not use a consistent radiotherapy protocol in their study.

Positive biopsy and biochemical recurrence

Shelley and co-workers reported results from eight cryotherapy case series (1483 patients) in their Cochrane review. The studies were too heterogeneous for the reviewers to combine their results. Between 72% and 99% of men in these series had post-treatment biopsy negative for cancer. Biochemical progression free survival ranged from 39% to 89% in the series.

NICE 2005 examined the effect of cryotherapy on biopsy results and biochemical disease-free survival. One non-randomised comparative study and six case series evaluated 2199 men with stage T1-T4 prostate cancer with follow-up duration between 6 months and 7 years. No pooled analysis was undertaken due to the heterogeneous groups of patients in the studies; however, it found that biochemical disease-free survival at 5 years was 52% (0.5ng/ml cut-off PSA) or 63% (1.0ng/ml cut-off PSA) (n = 975) and at 7 years was between 62% (0.5ng/ml cut-off PSA) and 89.5% (1.0ng/ml cut-off PSA)(n = 590). Negative biopsy rate at mean follow-up of 5 years was 87% (514/590).

Hummel 2003 examined the effect of cryotherapy on biopsy results and biochemical disease-free survival. Three prospective non-randomised uncontrolled studies and 9 retrospective case series evaluated a total of 2486 men with stage T1-T4 prostate cancer with follow-up duration between 3 months and 3 years. No pooled analyses was undertaken due to the heterogeneous groups of patients in the studies; however, it found that biochemical disease-free survival at 5 years ranged from 45% in high-risk groups (based on Gleason score, TNM stage and PSA level) to 80% in low-risk groups (n=1939 in 4 studies). Positive biopsy rate was between 16 and 21% at mean follow-up 21 to 34 months in 3 separate studies evaluating 1224 men with prostate cancer.

In the Chin and co-workers trial (Chin et al. 2007), positive biopsy rate was higher in the cryotherapy group than in the radiotherapy group, 20% and 12% respectively, but the difference was not statistically significant. Cryotherapy was associated with an increased risk of biochemical recurrence. Four year biochemical recurrence free survival was 47% in the radiotherapy group compared with 13% in the cryotherapy group (p=0.028).

Donnelley and co-workers (Donnelly et al.2007) did not biopsy all patients after therapy, so it is difficult to interpret their finding of greater positive post-treatment biopsy rates with EBRT than with cryotherapy. Donnelley and co-workers did not find a statistically significant difference in the rate of treatment failure (defined as biochemical failure, radiographic evidence of metastases or the initiation of salvage therapy) in the first three years after treatment.

Overall and disease specific survival

Chin and co-workers did not find any statistically significant differences in overall or disease specific survival in their trial. It is unclear whether the trial follow-up was sufficient to detect such differences.

Adverse events

The systematic reviews reported adverse events associated with cryotherapy, most commonly impotence, incontinence, fistula, urethral stricture, scrotal swelling and urinary tract infection. Chin and co-workers found no difference between the rates of genitourinary adverse events in the two treatment arms of their trial. Radiotherapy was, however, associated with more gastrointestinal adverse events.

Evidence Tables

National Institute for Health and Clinical Excellence. Cryotherapy as a primary treatment for prostate cancer 2005
Design: Systematic review of one non-randomised comparative study and six case series (see Appendix 1 for details of studies) Country: UK Setting: Secondary care Search date: 1996 to Sep 2004 **Inclusion criteria** Publication type: Clinical studies included. Emphasis placed on quality of studies. Population: Patients with prostate cancer Intervention: Cryotherapy as primary treatment Outcomes: Articles were retrieved if abstract contained information relevant to safety or efficacy References included: Gould 1999; Long 2001; Bahn 2002; Han 2003; Donnelly 2002; Aus 2002; Badalament 1999 **Exclusion criteria** Publication types: Abstracts excluded where no clinical outcomes reported, or where paper was review, editorial, laboratory or animal study **Population** Studies: one non-randomised comparative study and six case series Number of patients = 2199 Cancer stage: Long 2001 T1 – T4; Bahn 2002 T1-T3; Han 2003 T1-T3; Donnelly 2002 T1-T3; Aus 2002 T1 – T3; Badalament 1999 not stated; Gould 1999 not stated **Interventions** Cryotherapy: no details provided **Outcomes** Biopsy results Survival rates Biochemical-free survival (NB different PSA values were used to define this outcome) **Follow up** 6 months to 7 years **Results**

OUTCOME OF INTEREST	GROUP EFFICACY	OVERALL RESULT	
Overall survival	5 year overall survival 89%	N = 76 (1 study)	
Disease specific survival	5 year disease specific survival 98.6%	N = 76 (1 study)	
Negative biopsy rate	87% at mean follow-up of 5 years 72% at median follow-up 58.5 months	N = 590 (1 study) N = 54 (1 study)	
Biochemical disease-free survival	3 months biochemical disease free survival 81% 12 months biochemical disease-free survival 75% Median follow up 58.5 months actuarial biochemical disease-free survival 38.9% (1.0ng/ml cut-off) 5 year actuarial biochemical disease-free survival 52% (0.5ng/ml cut-off) or 63% (1.0ng/ml cut-off) depending on PSA cut-off value (n = 975) 7 year actuarial biochemical disease-free survival between 62% and 89.5%, depending on criteria used	N = 118 (1 study) N = 106 (1 study) N = 54 (1 study) N = 975 (1 study) N = 590 (1 study)	
Time until next intervention	Not reported		
Quality of life	Not reported		
Side effects:			
Impotence	Between 72% and 100% of patients	Total N = 1771 (5 studies)	
Incontinence	Between 1% and 18%	Total N = 1972 (6 studies)	
Transurethral resection required	Between 4% and 15%	Total N = 1891 (5 studies)	
Fistula	Between 0.3% and 1.8%	Total N = 1842 (4 studies)	

Urinary Tract Infection	33.3%	Total N = 54 (1 study)
Scrotal swelling	Between 5% and 18%	Total N = 324 (2 studies)
Pelvic pain	Between 6% and 12%	Total N = 323 (2 studies)
Penile tingling and numbness	Between 2% and 15%	Total N – 323 (2 studies)
Stricture	16.7%	Total N – 54 (1 study)
Stone formation in prostatic urethra	9.3%	Total n = 54 (1 study)
Bladder perforation	1.8%	Total N = 54 (1 study)
Paraphimosis	1.8%	Total N = 54 (1 study)
Paraesthesia in the legs	1.8%	Total N = 54 (1 study)

General comments

Treatment protocols varied within and between studies. Some patients received more than one cryotherapy session

Previous treatment: some studies reported that a proportion of patients were treated with neoadjuvant hormonal therapy prior to cryosurgery; this may have an effect on PSA levels. One study stated that 6% (3/54) patients had received previous radiation therapy.

Different definitions were used to describe outcomes (cut-off points for PSA 0.2 – 1.0 ng/ml) as biochemical failure.

Specialist advisors specified that the key-efficacy outcomes are 5 year + biochemical-free survival and PSA levels

11 other studies were included in an appendix but results were not reported in overview. References in appendix but not included in review: Anastasiadis 2003; Cohen 1996; De La Taille 2000; Ellis 2002; Derakhshani 1998; Koppie 1999; Long 1998; Robinson 1999; Saliken 1999; Wong 1997; Zisman 200. No reason specified (NB A number of these trials are included in Hummel et al., 2003).

Authors concluded that “current evidence on the safety and efficacy of cryotherapy, measured by reduction of PSA levels and biopsy findings, appears adequate to support the use of this procedure as primary treatment in patients with prostate cancer”. In addition, “the effects of cryotherapy as a primary treatment for prostate cancer on quality of life and long-term survival remain uncertain. Clinicians should therefore ensure that patients understand the uncertainties and the alternative treatment options.”

Hummel S, Paisley S, Morgan A, Currie E, Brewer N. Clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer: a systematic review. Health Technology Assessment 2003; Vol 7: No 33

Design: Systematic review of three prospective non-randomised uncontrolled studies and 9 retrospective case series.

Country: UK

Setting: Secondary care

Search date: 1992 to "present" (taken to be around 2003 AS)

Inclusion criteria

Publication type: Titles, abstracts and full papers, sample size ≥30 and median follow-up ≥1 year

Population: Patients with early, localised (T1 and T2) prostate cancer

Intervention: Cryotherapy

Outcomes: Survival, disease-free survival (DFS), Quality of life (including complications and adverse consequences such as incontinence) and acceptability

References included: Bahn 2000 (some of population may be in NICE SR); Cohen 1996; Coogan 1995; Derakhshani 1998; Koppie 1999; Long 1998 (included in NICE SR); Long 2001; Mack 1997; Robinson 1999; Saliken 1999; Wake 1996; Wong 1997

Exclusion criteria

Population: Papers where T1 and T2 constituted less than 50% of the study population or where subgroup analysis was not undertaken were excluded.

Population

Studies: three prospective non-randomised uncontrolled studies and 9 retrospective case series

Number of patients = Sample size 48 to 643

Cancer stage: Most studies included patients with TNM stages T1 to T3. Four studies included patients with T1-T4.

Median age: 65.4 to 69 years

Interventions

Cryotherapy (no details)

Outcomes

Survival rates

Biochemical disease-free survival (NB different PSA values were used to define this outcome)

Positive biopsy rates

Adverse events

Follow up

3 months to 36 months

Results

OUTCOME OF INTEREST	GROUP EFFICACY	OVERALL RESULT
Overall survival	5 year overall survival 90% Mean survival T1c-T2b – 7.11 years Mean survival T2c-T3c – 7.29 years	N = 66 (1 study - Mack)
Biochemical disease-free survival	Biochemical disease free survival 95% at 3 months Biochemical failure (PSA <1ng/ml) at 6 months T1 –14.3%; T2 – 33.3%; T3 – 40% Median PSA at 12 months 0.55ng/ml Median PSA at 12 months in those with no prior treatment 0.8ng/ml At 1 year 76% had undetectable PSA level Median PSA at 21 months was 1.2ng/ml for group with no prior treatment 5 year biochemical disease specific survival 45% high risk to 80% low-risk (based on PSA levels, Gleason grade and TNM stage)	N = 104 (Wake 1996) N = 48 (Derakhshani 1998) N = 87 (Coogan 1995) N = 71 (Saliken 1999) N = 383 (Cohen 1996) N = 1939 (4 studies – Long 1998; Koppie 1999; Long 2001; Bahn 2000)

Positive biopsy rate	Positive biopsy at 3 months 17% Positive biopsy at 3 months in those with no prior treatment 5% Positive biopsy at 6 months T1 – 14%; T2 - 16%; T3 – 33% Positive biopsy at 21 months in those with no prior treatment – 21% Positive biopsy at 24 months – 18% Positive biopsy at 34 months – 16% Positive biopsy at follow up (duration not known) – 25%	N = 87 (Coogan 1995) N = 48 (Derakhshani 1998) N =383 (Cohen 1996) N = 975 (Long 2001) N = 145 (Long 1998) N = 104 (Wake 1996)	
Time until next intervention	Not reported		
Quality of life:	Not reported		
	At 12 months after the operation, most of the FACT-P subscales had returned to pre-treatment levels. Sexual function was most affected by cryo-surgery and the score was still significantly below baseline at 12 months	N = 70 (Robinson 1999) Comment: At 36 months, 13% (5/38) patients had regained erectile functioning, and an additional 34% (13/38) were sexually active with the help of aids (from subsequent publication Robinson 2002)	
Side effects:			
Impotence	Between 47% and 93% of patients	Total N = 1400 (4 studies)	
Outlet obstruction	Between 9% and 15% of patients	Total N = 539 (3 studies)	
Incontinence	Between 3% and 10.4%%	Total N = 1783 (4 studies)	
Fistula	Between 0.4% and 0.5%	Total N = 1265 (2 studies)	
Urinary Tract Infection	4%	Total N = 87 (1 study)	

General comments

Quality of evidence relating to cryosurgery deemed to be “not good”.

Treatment protocols varied significantly between trials.

Previous treatment; many patients had received androgen deprivation before cryosurgery and

some had failed radiation therapy (Bahn 2000 68 patients had failed radiotherapy and 20 had failed initial cryotherapy; Cohen 1996 included patients who had previous treatment; Derakhshani 1998 30/48 patients received androgen deprivation therapy (ADT) before cryosurgery; Long 1998 45 patients had neoadjuvant hormonal therapy (NHT) if gland volume >50ml at study entry; Long 2001 ADT used for 3-8 months in 30% of patients; Mack 1997 3-4 months after cryosurgery all patients underwent extensive transurethral resection of prostate and/or perineal biopsy. No randomised trials

Authors concluded that "owing to the paucity and poor quality of evidence identified for cryosurgery, conclusions regarding its clinical effectiveness cannot be drawn". Furthermore, additional economic analysis found that cryotherapy appeared "not to be potentially cost-effective compared with traditional treatments, owing to the associated high incidence of impotence".

(Shelley *et al.* 2007)

Design: Systematic review of observational studies (therapy), evidence level: 2++

Inclusion criteria Randomised trials published between 1996 and 2006 comparing the effectiveness of cryotherapy with other radical therapies for the treatment of clinically localised prostate cancer.

Since no randomised trials were found, modified criteria were used: at least 50 patients, minimum follow-up of 1 year.

Interventions Cryotherapy (cryoablation of the prostate) using TRUS guidance and urethral warming. Half the included studies used temperature monitoring and half did not. Details of the cryotherapy procedure varied between studies. Some men received neoadjuvant hormonal therapy.

Outcomes PSA nadir, post-treatment biopsy status, overall survival, progression free survival and complications.

Follow up Minimum follow-up was 1 year.

Results Eight case series (1483 patients) met the inclusion criteria. The authors concluded that although cryotherapy offers a potential alternative to standard therapies for localised prostate cancer, the poor quality of the available evidence makes the relative benefits of cryotherapy uncertain.

COMPARISON IN MEN WITH CLINICALLY LOCALISED PCA	CRYOTHERAPY
Post-treatment biopsy	Between 72% and 99% of men had post-treatment biopsy negative for cancer.
Progression free survival	Range was 39% to 89%
Impotence	The range was 47% to 100%, although

	some recovery was reported.
Incontinence	Range was 1.3% to 19%
Fistula	Range was <0.1% to 2%
Sloughing	Range was 3.9% to 37%
5 year disease specific survival	Range was 94% to 99% from 2 studies
5 year overall survival	Range was 89% to 92% from 2 studies

(Chin *et al.* 2007)

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

Country: Canada, setting: Tertiary care

Inclusion criteria Men with histologically proven, clinical staged T2C, T3A or T3B prostate cancer.

Exclusion criteria -

Population number of patients = 64.

Interventions Men were randomised to receive either cryotherapy (2nd generation Cryocare system) or external beam radiotherapy (66 Gy in 33 fractions). All men had 6 months of neoadjuvant - adjuvant combined androgen blockade, starting from 3 months before radical therapy.

Outcomes Biochemical recurrence rate, biochemical recurrence free survival, disease specific survival, overall survival and complications

Follow up Mean follow-up was 37 months. Follow-up included 3 monthly PSA tests. Prostate biopsy at 6 months for the Cryotherapy group and at 18 and 24 months for the EBRT group.

Results -

COMPARISON IN MEN WITH LOCALLY ADVANCED PROSTATE CANCER	CRYOTHERAPY	EBRT	OVERALL RESULT
Biochemical failure	21/33 (64%)	14/31 (45%)	
4 year biochemical recurrence free survival	13%	47%	Favours EBRT, p=0.028
Positive biopsy rate	20%	12%	no statistically significant

			difference
Overall survival	87%	87%	no statistically significant difference
Disease specific survival	95%	97%	no statistically significant difference
Genitourinary toxicity	not reported	not reported	Authors report no difference
Gastrointestinal toxicity	45%	100%	Favours cryotherapy

General comments Study was under powered, only 64 out of the planned 150 patients were accrued. EBRT dose lower than optimal, Cryotherapy procedure 2nd generation.

(Donnelly *et al.* 2007)

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

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

Inclusion criteria Men with histologically proven prostate adenocarcinoma ; biopsy staged T1-3; no evidence of nodal or distant metastases; pretreatment PSA 20 or less; gland volume 60 cc or less.

Exclusion criteria Clinically bulky T3 tumour prior pelvic radiation; previous androgen deprivation therapy; TURP less than 3 months previously.

Population number of patients = 244, age range 53 to 81 years, median age = 69 years.

Interventions All men received neoadjuvant hormonal therapy. Initially 3 months of LHRH was given, this was changed to 6 months. Men were randomised to receive either EBRT or cryotherapy. Men in the EBRT arm were treated with a standard 4 field box technique (fractions of 2 Gy given daily for 5 days per week). Dose was initially 68 Gy, rising to 70 Gy in 2000 and finally to 73.5 Gy in late 2002 in response to the changing standards of practice.

Men in the cryotherapy arm were treated under TRUS guidance with Argon-Helium 3rd generation equipment. Thermo sensor monitoring, urethral warming, and saline injections to separate anterior rectal wall from posterior prostate were used in all cases. Two freeze-thaw cycles were used. Post treatment biopsies were done in some patients.

Outcomes Primary outcome was treatment failure within 3 years of the end of treatment. Treatment failure was defined as any of biochemical failure, radiological evidence of metastases or the initiation of adjuvant therapy. Biochemical failure was defined as PSA nadir + 2 ng/mL. Secondary outcomes were overall survival and positive biopsy rate.

Follow up Median follow-up for surviving patients was 82 months (range 47 to 110 months). 6 patients were lost to follow-up.

Results –

Biopsies were performed on some of the men at between 2 and 4 years after treatment (75% in the cryotherapy group and 62% in the EBRT group). Positive biopsy rate was significantly greater in the EBRT group than the cryotherapy group 22/76 versus 6/91 respectively.

COMPARISON IN MEN WITH LOCALISED OR LOCALLY ADVANCED PROSTATE CANCER, WITH NO METASTASES	EBRT	CRYOTHERAPY	OVERALL RESULT
Treatment Failure	32/122 (21 BCR, 1 radiological and 10 adjuvant therapy)	25/122 (24 BCR, 1 radiological)	No significant difference. Kaplan-Meier estimates of failure at 36 months: 15.3% EBRT vs. 18.5% cryotherapy Difference 3.2% (95% CI -6.6% to 13%).
5 year overall survival	Estimate from survival analysis 88.3%	Estimate from survival analysis 89.7%	No significant difference. Difference 1.4%, 95% CI: -6.7% to 9.5%

General comments Abstract only. Trial closed early due to accrual problems, the intended sample size is not reported. The treatment protocol changed considerably during the trial, both neoadjuvant therapy and radiotherapy dose was changed. Some men in the EBRT group had baseline PSA exceeding the 20 ng/mL exclusion criteria.

Health Economics

The health economics analysis relating to this topic can be found at the end of section 4.2.

Reference List

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Ref Type: Conference Proceeding

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National Institute for Health and Clinical Excellence Cryotherapy as a primary treatment for prostate cancer. *2005 ;Interventional Procedure.Guidance.145():* Interventional Procedure Guidance 145: .

Shelley, M., Wilt, T., Coles, B. & Mason, M. (2007) Cyrotherapy for localised prostate cancer. *Cochrane Database Syst Rev.,* CD005010.

HIFU versus watchful waiting or other radical therapies

Short Summary

All the included studies were case series (Beerlage et al. 1999; Chaussy & Thuroff 2003; Gelet et al. 1999; Gelet et al. 2000; Poissonnier et al. 2003; Thuroff et al. 2003; Uchida et al. 2002; Uchida et al. 2005; Ficarra et al. 2006; Ganzer et al. 2007; Lee et al. 2006; Poissonnier et al. 2007; Uchida et al. 2006). Follow-up in these series was short, most had a median follow-up of less than two years. This means there are limited disease specific or overall survival data for HIFU. The intermediate outcomes of biochemical recurrence and prostate biopsy suggest that HIFU ablates prostate tissue. Treatment toxicities associated with HIFU included: sexual dysfunction, stress incontinence, urethral strictures, and urinary tract infection.

Technical developments in both cryotherapy and HIFU procedures, mean that results from the earlier series may not be applicable to current practice.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOMES
Men with localised or locally advanced prostate cancer with no prior treatment.	HIFU	• Watchful waiting also • Radical prostatectomy • EBRT • Brachytherapy • Conformal Radiotherapy • Conventional radiotherapy • Cryotherapy	• overall survival • disease-specific survival • biochemical disease-free survival • time until next intervention • 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)

Evidence Summary

Thirteen case series (and one additional case series identified in a review) investigating the use of HIFU as first-line treatment in men with localised prostate cancer were identified NB Case series were included if <10% of population had previous treatment

Ganzer et al (2007) reported the series with longest follow up: results were available for 103 men at a median follow up of 4.9 years. Unfortunately, outcomes were not reported for the group as a whole, but were stratified by post HIFU PSA nadir (showing better biochemical failure free survival for men with lower PSA nadir). From the survival graphs, the overall biochemical failure rate would appear to be around 20%.

Thuroff 2003 examined the effect of HIFU (2.25MHz-3MHz for 4.5-5 second shots) on negative biopsy rate and biochemical disease-free survival (normally defined as PSA <4.0ng/ml) in 402 men with stage $T_{1-2}N_{0-x}M_0$ prostate cancer in a study with mean follow-up of 407.3 days. 87.2% of patients had a negative biopsy. No effect of pre-HIFU risk or prostate volume was seen on negative biopsy rate; however, those patients with prostate volume $\leq$40ml had significantly lower median nadir PSA values compared with those patients with prostate volume >40ml (median nadir PSA 0.4 vs. 2.0 respectively, p=0.0001). HIFU was associated with UTI and grade 1 stress incontinence in more than 10% of patients (Evidence level 3).

Chaussy 2003 compared the effect of HIFU alone (3MHz and 5 second shot) with TURP followed by HIFU on negative biopsy rate and biochemical disease-free survival in 271 men with

stage $T_{1-2}N_{0-x}M_0$ prostate cancer. It found that there was no significant difference between the groups in negative biopsy rate after first HIFU (66.3% with HIFU alone vs. 70.6% with TURP + HIFU; p = NS) and at last follow-up (87.7% with HIFU alone vs. 81.6% with TURP + HIFU). 25% in the HIFU alone group needed re-treatment compared with 4% in TURP + HIFU group. No significant difference between groups in mean PSA nadir at 15 weeks follow-up or PSA-antigen stability rate up to 180 weeks follow-up. Significantly more patients in the HIFU alone group had UTI compared with HIFU + TURP (47.9% HIFU alone vs. 11.40% TURP + HIFU; p<0.001). Significantly fewer patients had grade 1 incontinence in the TURP+ HIFU group (p<0.05) and suprapubic catheter time was significantly less (p<0.01 in favour of TURP + HIFU). No significant difference in quality of life was seen (Evidence level 3).

Uchida 2005 examined the effect of HIFU using the Sonablate 500 (4MHz in 3 second shots) on biochemical disease-free survival in 75 men with stage $T1_c$-$2N_0M_0$ prostate cancer. It found that biochemical disease-free survival by ASTRO definition was 78% at 1 year and 76% at 2 years. No effect of pre-treatment stage, Gleason score or serum PSA was seen. Side effects seen in more than 10% of patients included urethral stricture (grade 3) and post-operative erectile dysfunction. Quality of life measured on FACT scale did not change significantly up to 1 year post-treatment. (Evidence level 3)

Uchida 2002 examined the effect of HIFU using the Sonablate 200 on biochemical disease-free survival in 20 men with stage $T_{1b-2}N_{0-x}M_0$ prostate cancer. It found that in 100% of patients, post-operative biopsies were negative and there was no elevation on three successive PSA determinations. PSA nadir was <0.5ng/ml in 65% of patients. HIFU was associated with urethral stricture (2/20) and impotence (3/10) in more than 10% of patients. Frequency, urgency and difficulty urinating were all common in the 2 months after HIFU. (Evidence level 3)

Uchida et al (2006) reported results from 181 men treated using the Sonablate system. With median follow-up of 18 months, biochemical failure free survival was estimated at 84%, 80% and 70% at 1, 3 and 5 years respectively.

Gelet 1999 examined the effect of HIFU (2.25Hz two prototypes, the latter with additional safety features) on negative biopsy rate and biochemical disease-free survival in 50 men with stage T1 and T2 prostate cancer who were unsuitable candidates for radical prostatectomy (NB 2 patients had local recurrence after definitive external RT). The study had mean follow up of 24 months. 62% of patients had negative biopsy, 56% had negative biopsy AND PSA<4ng/ml. Biochemical disease-free survival (PSA <4.0ng/ml) was achieved by 74% of patients. (Evidence level 3)

Gelet 2000 examined the effect of HIFU (Ablatherm 3Mz in 5 second shots) on negative biopsy rate and biochemical disease-free survival in 82 men with T1 and T2 prostate cancer who were unsuitable candidates for radical prostatectomy (NB 4 patients had local recurrence after definitive RT). It found that at mean follow-up of 17.6 months 64% of patients had negative biopsy; of these 92% also had PSA <4.0ng/ml. Biochemical disease-free survival was 62% at 60 months in all patients (In those with moderate risk it was 68% and in those with low risk it was 83%). HIFU was associated with the following side effects: impotence (77% of those who were previously potent), urethral stenosis (17%) and stress incontinence (13%). Other side effects had less than 10% prevalence in this population. (Evidence level 3)

Beerlage 1999 examined the effect of HIFU (Ablatherm 2.25-3MHz in 4.5 second shots) administered 'selectively' (unilateral or bilateral) or globally (whole prostate) on negative biopsy rate and biochemical disease-free survival in 111 patients with stage $T1\text{-}3N_xM_0$ prostate cancer who were not suitable candidate for radical prostatectomy or unwilling to undergo the operation. Negative biopsies were found in 28% of the patients treated 'selectively' compared with 68% of those treated 'globally'. Biochemical disease-free survival at mean follow-up 12 months was 62% in those treated 'selectively' vs. 86% in those treated 'globally'. 100% of those treated 'globally' suffered from loss of erectile function. (Evidence level 3)

Poissonnier 2003 examined the effect of HIFU (no further details provided) on disease-free survival in 120 men with stage $T1\text{-}2N_0M_0$ prostate cancer who were not candidates for radical

prostatectomy. It found that 76.9% patients had a negative biopsy with no PSA elevation at 5 years. Significantly more patients with Gleason scores of 2 to 6 had negative biopsies compared with those with Gleason scores 7 to 10 (85.4% vs. 61.3% respectively; p = 0.024) (Evidence level 3).

Poissonnier 2007 reported outcomes after HIFU using successive generations of Ablatherm devices in 227 men with clinically localised prostate cancer. Mean follow-up was 27 months. They estimated five year disease free survival as 66%. Comparison of successive generations of HIFU devices showed a reduction in the rates of incontinence and stenosis with the newer HIFU machines.

Ficarra et al (2006) both reported treatment toxicity within one year of HIFU with adjuvant hormonal therapy in a series of 30 men with locally advanced or high risk prostate cancer. Lee et al (2006) reported short term outcomes after HIFU in another series of 58 men with clinically localised prostate cancer.

Evidence tables

Case series

Thuroff, S; Chaussy, C; Vallancien, G; Wieland, W; Kiel, HJ; Le Duc, A et al.; High Intensity Focused Ultrasound and Localized Prostate Cancer: Efficacy Results from the European Multicentric Study. Journal of Endourology 17 (8) 2003 673-77
Design: Phase I/II Prospective, multicentre, open-label, uncontrolled trial (therapy), evidence level 3 (case series) Country: Germany; France; The Netherlands (6 centres) Setting: Secondary care **Inclusion criteria** No formal inclusion criteria. All patients had biopsy-proven localized prostate cancer ($T_{1-2}N_{0-x}M_0$); not suitable candidates for radical prostatectomy. **Exclusion criteria** No formal exclusion criteria; however, the following patients were excluded from the analysis 8 who had undergone previous radical prostatectomy, 35 patients with previous external-beam radiation therapy, 104 patients with a previous orchiectomy or hormone deprivation, and 10 patients with locally advanced disease or distant metastases (T_{3-4} and/or N^+ and/or M^+) **Population** Number of patients = 402 treated between Nov 1995 and Nov 1999 Cancer stage: $T_{1-2}N_{0-x}M_0$ 114 (28.4%) low-risk patients= Stage T_{1-2a} AND PSA $\leq$10ng/ml AND Gleason score $\leq$6 193 (48.0%) intermediate-risk patients = Stage T_{2b} or 10< PSA $\leq$ 20ng/ml OR Gleason score = 7 95 (23.6%) high-risk patients = T_{2c} OR PSA >20ng/ml OR Gleason score $\geq$8 Mean PSA: 10.9 Gleason score: 2 to 4 (13.2%), 5 to 7 (77.5%), 8 to 10 (9.3%) Prostate volume: 28ml $\pm$ 12.7 **Interventions** Device: Ablatherm HIFU device (EDAP Technomed). NB several prototypes were used during course of study. Number of sessions: Two sessions (one session/lobe) under spinal anaesthesia (Mean 1.47 sessions/patients); 62.4% of patients treated with single session and 27.9% treated with two sessions. Frequency and short duration (see below): Progressive increase in frequency from 2.25 to 3 MHz and progressive increase in shot duration from 4 to 5 second. Group A 2.25MHz frequency and shot duration $\leq$4.5second (no cooling system) n= 49 (12.2%) Group B <3MHz frequency and a 4.5 second shot duration n = 59 (14.7%)

Group C 3MHz frequency and a 4.5 second short duration n = 184 (45.8%)

Group D 3MHz frequency and a 5 second shot duration n = 110 (27.4%)

Outcomes

Negative or positive biopsy (positive biopsy = presence of any positive core, whatever the cancer size

Median PSA (ng/ml)

Nadir PSA

Adverse events

Follow up

Biopsy performed 6 weeks or more after last treatment

Nadir PSA values (lowest concentration measured after last HIFU session)

Mean follow-up 407.3 days, median follow up 13 months

Results

OUTCOME OF INTEREST	**GROUP** **ALL**	**Group A**	**Group B**	**Group C**	**Group D**	**OVERALL RESULT**
Overall survival	Not reported					
Disease-specific survival	Not reported					
Negative biopsy rate	87.2% of 288 negative biopsy at follow-up	44.4% negative biopsy 66.7% negative biopsy at 1 year	82.1% negative biopsy 76.5% negative biopsy at 1 year	91.2% negative biopsy 91.2% negative biopsy at 1 year	94.8% negative biopsy 100% negative biopsy at 1 year	P<0.0001 in favour of each successive group
Negative biopsy rate according to previous risk group						
- low risk - intermediate risk - high risk	- 92.1% - 86.4% - 82.1%					
Negative biopsy rate according to prostate volume						

- prostate volume < 40ml - prostate volume >40ml	- 88.4% - 85%					
Biochemical disease-free survival	Nadir PSA (ng/ml) at follow-up median 0.6 and mean 1.8 (range 0-27ng/ml)	Nadir PSA Median 1.2 Mean 5.1	Nadir PSA Median 2.0 Mean 3.3	Nadir PSA Median 0.5 Mean 1.3	Nadir PSA Median 0.3 Mean 0.9	P=0.0001 in favour of successive groups
Biochemical-disease free survival according to prostate volume						
- prostate volume ≤ 40ml - prostate volume >40ml	Nadir PSA Median 0.4 Mean 1.8 Median 2.0 Mean 2.9					P = 0.0001 in favour of those with prostate volume ≤40ml
Time until next intervention	Not reported					
Quality of life	Not reported					
Side effects: Uretherorectal fistula Stress incontinence grade I Stress incontinence grade II Stress incontinence grade III Urinary tract infection Prolonged retention Urethral stenosis	 5 patients 10.6% patients 2.5% patients 6 patients 13.8% 8.6% 3.6%					

General comments

Previous treatment: All patients who had received prior treatment were excluded from analysis

Chaussy C and Thuroff S. The status of high-intensity focused ultrasound in the treatment of localized prostate cancer and the impact of a combined resection. Current Urology Reported 2003, 4:248-252
Design: Prospective controlled trial (therapy), evidence level Country: Germany Setting: Secondary care **Inclusion criteria** No specific inclusion criteria. All received HIFU as primary treatment for prostate cancer; organ-confined cancer with an initial PSA level at diagnosis of ≤15ng/ml. High Gleason score was acceptable **Exclusion criteria** Patients who had received hormones for more than 6 months before HIFU **Population** Number of patients = 271 Cancer stage prognosis subgroups: - low risk (clinical stage T1-T2a, PSA <10ng/ml and Gleason score <7) HIFU n = 37; TURP + HIFU n = 71 - intermediate risk (clinical stage T2b, PSA <20ng/ml, or Gleason score of 7) HIFU n = 55; TURP + HIFU n = 95 - high risk (clinical stage T2c or PSA >20ng/ml, or Gleason score >7) HIFU n = 4; TURP + HIFU n = 9 Mean PSA: HIFU 8.6 ± 3.2; TURP + HIFU 8.0 ± 3.4 Mean prostate volume: HIFU 21.7 ± 6.8; TURP + HIFU 20.5 ± 9.8 **Interventions** Device: 96 patients underwent HIFU only and 175 patients underwent TURP and HIFU TURP procedure was performed first and was controlled by ultrasound (TRUS). Number of sessions: 271 patients received total of 303 sessions (11.4% retreatment rate – 25% in HIFU group and 4% in TURP and HIFU group) Frequency: 3MHz Shot duration: 5 seconds **Outcomes** Urinary symptoms PSA (considered to be stable according to ASTRO – see glossary) Biopsy Adverse effects **Follow up** Urinary symptoms assessed using International Prostate Symptom Score (IPSS) questionnaire before and 3 months after treatment PSA measured every 3 months for first year and every 6 months thereafter Biopsies performed 6 and 12 months after treatment and in case of rising PSA

Results

OUTCOME OF INTEREST	Group A HIFU (n = 96)	Group B TURP and HIFU (n = 175)	OVERALL RESULT
Overall survival	Not reported		
Disease specific survival	Not reported		
Negative biopsy rate	Negative biopsy rate after first HIFU 66.3% Negative biopsy rate at last follow-up 87.7% patients	Negative biopsy rate after first HIFU 70.6% Negative biopsy rate at last follow-up 81.6% patients	P = NS between groups
Biochemical disease-free survival	Mean PSA nadir at 15 weeks (average) was 0.48ng/ml (±1.10)	Mean PSA nadir at 15 weeks average was 0.26 ng/ml (±0.90)	P = NS between groups
PSA-antigen stability rate (%) at 60 weeks follow-up	Approx 94% (ASTRO)	Approx 96% (ASTRO)	P=NS between groups
At 100 weeks follow-up	Approx 80%	Approx 92%	
At 140 weeks follow-up	Not reported	Approx 86%	
At 180 weeks follow-up	Not reported	Approx 84%	
Time until next intervention	25% retreatment	4% retreatment	P = NS
Side effects:			
Suprapubic catheter time			
Mean	45.1 days	13.7 days	P<0.01 in favour of TURP and HIFU
Median	40 days	7 days	
Incontinence			
Grade 1	9.10%	4.60%	P<0.05 in favour of TURP and HIFU
Grade 2	6.30%	2.30%	
Grade 3	0%	0%	
Urinary Tract Infections	47.90%	11.40%	P<0.001 in favour of TURP and HIFU
Quality of life (IPSS)			
Before	1.30 (±1.18)	2.05 ((±0.90)	P = NS
After	2.36 (±1.30)	1.86 (±0.68)	

General comments –

Previous treatment: No previous treatment

PSA-antigen stability rate read by AS from survival curve. Authors conclude that the addition of TURP to the HIFU treatment in a single surgical session has a positive impact on the treatment related morbidity with affecting its efficacy.

Uchida T; Baba S; Irie A; Soh S; Masumori N; Tsukamoto T et al. Transrectal high-intensity focused ultrasound in the treatment of localized prostate cancer: a multicentre study. Acta Urol Jpn 51: 651-658, 2005
Design: Prospective multicentre uncontrolled trial preliminary report (therapy), evidence level 3 (case series?) Country: Japan Setting: Secondary care **Inclusion criteria** Patients with biopsy proven and untreated stage T1c-2N0M0 localized prostate cancer, aged <80 years, serum PSA <20ng/ml, prostatic volume <50ml and treatable with a 4.0 focal length probe, WHO performance status 0-1 **Exclusion criteria** Patients with urethral stricture, anal stricture, bleeding tendency renal dys-function with serum Cr more than 2.0mg/dl, hydronephrosis, larger than 5mm calcifications in the prostate, uncontrolled diabetes mellitus, hypertension, angina, history of cardiac infarction or other malignant diseases. **Population** Number of patients = 75 (3 were excluded see comments below) Cancer stage: $T1_c$-$2N_0M_0$ (TNM stage was T1c in 40 patients, T2a in 18 patients and T2b in 14 patients). Gleason score: 2 to 4 (n = 9), 5 to 7 (n=55), 8 to 10 (n = 6) and unknown (n = 2) Median PSA: 8.1ng/ml Median prostate volume: 22.1 (range 8.5 to 52.8) Median age: 72 (range 45-79) **Interventions** Device: HIFU using the Sonablate 500 (focus Surgery, Indianapolis) Number of sessions: Frequency: 4MHz Shot duration:3 seconds **Outcomes** Urinary continence and erectile function (Functional Assessment of Cancer Therapy (FACT) questionnaire Urinary symptoms (International Prostate Symptom Score IPSS) Urinary flow analysis using uroflowmetry

Serum PSA

Biopsy (post-operative needle biopsy under TRUS)

Biochemical failure was defined by ASTRO (see summary)

Time to biochemical failure was defined as midway between post treatment PSA nadir and first of three consecutive PSA increases.

Distribution of biochemical disease-free survival times were calculated according to Kaplan-Meier curves.

Follow up

Serum PSA every 1 to 6 months during follow-up

Biopsy at 6 months

Median follow-up 14 months (range 2-24)

Results

OUTCOME OF INTEREST	**Group A HIFU (n = 72)**	**OVERALL RESULT**	
Overall survival **Disease-specific survival**	Not reported Not reported		
Biochemical disease-free survival (%) all			
1 year 2 year	78% 76%		
Biochemical disease-free survival (%) according to stage			
Stage T1c at 2 years Stage T2a at 2 years Stage T2b at 2 years	89% 67% 40%	P = NS between groups	
Biochemical disease-free survival (%) according to Gleason score			
Gleason 2-4 at 2 years Gleason 5-7 at 2 years Gleason 8-10 at 2 years	88% 72% 80%	P = NS between groups	
Biochemical disease-free survival (%) according to serum PSA level			
Serum PSA <10ng/ml Serum PSA 10-20ng/ml	75% 78%	P = NS between groups	
Time until next intervention	Not reported		
Side effects: Urethral stricture	 13/72 (all grade 3)		

Epididymitis	6/72		
Prostatitis	4/72		
Post-operative erectile dysfunction	12/31 (all grade 3)		
Nephrotic syndrome	1		
Transient urinary incontinence	1		
Transient stool incontinence	1		
Balanoposthitis	1		
Retrograde ejaculation	1		
Quality of life (FACT general)			
Before	48.9	P = NS	
3 months	46.9		
1 year	46.2		
Quality of life (FACT prostate)			
Before	14.4	P = NS	
3 months	14.1		
1 year	13.1		
Quality of life (FACT total)			
Before	63.3	P = NS	
3 months	31.0		
1 year	59.3		

General comments –

Previous treatment: no previous treatment

Patients had 1.2 HIFU sessions per patients

3 patients were excluded; 1 with stage T1b, 1 with a serum PSA of 20.6ng/ml and 1 in whom treatment was stopped during procedure because of appearance of large micro bubbles in prostate.

Biochemical disease-free survival rates were analysed in 60 patients (twelve were excluded from analysis for unsatisfactory follow-up)

Quality of life was analysed in 29 patients

Authors conclude HIFU therapy appears to be minimally invasive, efficacious and safe for patients with localized prostate cancer with pre-treatment PSA levels less than 20 ng/ml

Uchida T; Sanghvi NT; Gardner TA ; Koch MO ; Ishii D; Minei S et al. Transrectal high-intensity focused ultrasound for treatment of patients with stage T1b-2NM0 localized prostate Cancer: a preliminary report. Urology 59: 394-399, 2002

Design: Prospective uncontrolled trial (therapy), evidence level 1- (case series?)

Country: Japan

Setting: Secondary care

Inclusion criteria Patients with stage $T1_b$-$2N_0M_0$ localized prostate cancer, serum PSA <20ng/ml, prostatic volume <50ml. All patients showed evidence of adenocarcinoma by prostate biopsy

Exclusion criteria Patients with anal stricture

Population Number of patients = 20

Cancer stage: $T1_b$-$2N_0M_0$ (TNM stage was T1b in 1 patient, 7 patients with clinical stage T1c, T2a in 9 patients and T2b in 3 patients).

Gleason score: 2 to 4 (n = 4), 5 to 7 (n=16)

Mean PSA concentration 9.65 $\pm$ 4.43ng/ml (range 3.75 to 19.80)

Prostate volume 25.2 $\pm$ 10.5ml (range 13.2 to 50.6)

Mean age: 72.2 $\pm$ 7.4 years

Interventions

Patients were assigned to receive transrectal HIFU using the Sonablate 200 (focus Surgery, Indianapolis) HIFU machine

Outcomes

Serum PSA

Biopsy

Side effects

Follow up

Serum PSA at day 1, 14, 30, 90 and every 1 to 3 months during follow-up

Biopsy at 3 months or at time of any evidence of biochemical failure

Median follow-up 13.5 $\pm$ 6.8 months (range 6-31)

Results

OUTCOME OF INTEREST	Group A HIFU (n = 72)	OVERALL RESULT	
Overall survival	Not reported		
Disease-free survival	Not reported		

Negative biopsy rate	100% - no evidence of viable tumour cells by postoperative prostate biopsy		
Biochemical disease-free survival (%) all			
Follow-up not specified PSA nadir <0.50ng/ml	100% 13 (65%)		
PSA nadir 0.50 to 1.00 ng/ml	5 (25%)		
PSA nadir 1.01 to 2.00 ng/ml	2 (10%)		
Time until next intervention	Not reported		
Side effects: Frequency Urgency Difficulty urinating Rectourethral fistula Urethral stricture Persistent urinary retention Incontinence Impotence	 "Common in first 2 months after HIFU" "Common in first 2 months after HIFU" "Common in first 2 months after HIFU" 1/20 2/20 1/20 0/20 3/10		
Quality of life	Not reported		

General comments –

Previous treatment: Neoadjuvant hormonal therapy using antiandrogen and luteinising hormone-releasing hormone agonist in 4 patients was introduced for 4 months before visit to study centre.

Patients had 1.4 HIFU sessions per patients.

Retreatment reasons: 1 patient's pre-operative biopsy showed unilateral disease only, 4 patients because remaining tumour foci by postoperative prostate biopsy and/or PSA elevation. 2 patients because of larger prostate size and 1 because of technical difficulty with device.

Authors conclude HIFU may be a potentially useful treatment option for patients with localized prostate cancer and that it has an acceptable side effect profile to warrant further investigation.

Gelet A, Chapelon JY, Bouvier R, Pangaud C, Lasne Y. Local control of prostate cancer by transrectal high intensity focused ultrasound therapy: preliminary results. Journal of Urology

1999, 161 (1) 156-162

Design: Case series (therapy), evidence level 3

Country: US

Setting: Secondary care

Inclusion criteria No formal inclusion criteria. 48 patients were unsuitable candidates for radical prostatectomy and 2 patients had local recurrence after definitive external radiotherapy.

Exclusion criteria No formal exclusion criteria

Population Number of patients = 50

Cancer stage: T1 (n = 21) T2 (n = 27)

Gleason score 4 (n = 2), 5 (n = 4), 6 (n = 22), 7 (n = 15), 8 (n = 7)

Mean PSA 9.61 ± 7.42 ng/ml

Mean prostate volume 37.3 ± 19.1 ml

Mean age 70.7 ± 4.54 years range 61 to 86

Interventions

First 20 patients were treated with HIFU 2.25MHz

All other treatments treated with HIFU with a number of safety improvements to improve morbidity

All done under spinal anaesthesia

Outcomes

PSA levels

Biopsy

Biochemical disease-free rate (PSA less than 4 ng/ml)

Follow up

PSA and biopsy 1 to 3,3 to 12, 12 to 24, 24 to 36 and 36 to 49 months.

Median post-operative follow-up was 24 months (range 3 to 46)

Results

OUTCOME OF INTEREST	Group A HIFU (n = 50)	RESULTS ACCORDI GLEASON SCORE
Overall survival	Not reported	
Disease specific survival	Not reported	

Negative biopsy rate	"Success" - Negative biopsy and PSA less than 4ng/ml (n=28 (56%))	Gleason score 4-5 (58%) Gleason score 6-7 (64%) Gleason score 8 (14%)	
	"Biochemical failure" Negative biopsy and PSA greater than 4ng/ml (mean 6.22) (n = 3 (6%))	Gleason score 4-5 (0%) Gleason score 6-7 (8%) Gleason score 8 (0%)	
Biochemical disease-free survival	Between 35 and 55% after 10 years		
	Negative biopsy and PSA less than 4ng/ml (n = 28 (56%))	(as above)	
	"Biochemical control" Positive biopsy and PSA less than 4 ng/ml (n = 9 (18%)	Gleason score 4-5 (14%) Gleason score 6-7 (14%) Gleason score 8 (43%)	
	"Complete failure" Positive biopsy and PSA greater than 4 ng/ml (n = 10 (20%)	Gleason score 4-5 (28%) Gleason score 6-7 (14%) Gleason score 8 (43%)	
		Hormonal therapy required (n= 3) Radiotherapy required (n = 5)	
Time until next intervention	Not reported		
Side effects:			
Prototype 1.0 1993-1995 (n = 20)			
Rectourethral fistula	2		
Asymptomatic rectal burns	2		
Stable urinary retention	2		
Total incontinence	1		
Bladder neck sclerosis			
Febrile urinary infection			
Prototype 1.1 1996-1997 (n = 30)			
Stable urinary retention	1		

Febrile urinary infection	1		
Bladder neck sclerosis	1		
Stress incontinence	2		
Quality of life	Not reported		

General comments –

Previous treatment: 2 patients had prior treatment with radiotherapy

Mean shot number was 248 per session

Prostate was treated in 1 (9 patients), 2 (24 patients), 3 (12 patients) or 4 (5 patients) sessions.

PSA nadir was achieved within 4 to 5 months

Authors conclude transrectal high intensity focused ultrasound is a new treatment for localized prostate cancer which is relatively non-invasive.

Gelet A, Chapelon JY, Bouvier R, Rouviere O, Lasne Y, Lyonnet D et al. Transrectal high-intensity focused ultrasound: Minimally invasive therapy of localized prostate cancer. Journal of Endourology 2000, 14 (6) 519-528

Design: Case series (therapy), evidence level 3

Country: France

Setting: Secondary care

Inclusion criteria Patients with stages T1 or T2 cancer of any Gleason score having a pre-treatment PSA <20ng/ml. Negative preoperative bone scans and biopsy evidence of adenocarcinoma of the prostate. Not suitable candidates for radical prostatectomy.

Exclusion criteria None specified

Population 82 patients

Cancer stage: T1 (n = 38), T2 (n = 40), Local recurrence after definitive external radiotherapy (n = 4)

Gleason score: 2 to 4 (8%), 5 and 6 (40%), 7 (21%), 8 to 10 (13%)

Mean PSA 8.11 $\pm$ 4.64 ng/ml

Mean prostate volume 34.9 $\pm$ 17.4 cm3

Mean age 71 $\pm$ 5.7 years (range 60-86 years)

Interventions

HIFU (Ablatherm) 3MHz 5 sec treatment shot and 5 sec interval under spinal anaesthesia

Prostate was treated in 1 (n = 34), 2 (n = 32), 3 (n=9), 4 (n = 6) or 5 (n=1) sessions for a total of 154 treatments (1.8 per patient)

Mean shot number was 335 per session and 613 per patients

Outcomes

Serum PSA

Biopsy

Follow up

Serum PSA at 6 weeks and 3 months post operatively and every 3 months during follow-up

Biopsies at 3 months and 12 months or when evidence of biochemical failure

Mean follow-up was 17.6 months (range 3 to 68.5 months)

Results

OUTCOME OF INTEREST	Group A HIFU (n = 184)	OVERALL RESULT
Overall survival	Not reported	
Disease-specific survival **Negative biopsy rate**	Not reported Negative biopsy (64%) Of those with negative biopsy - PSA< 1.0ng/ml (66%) - PSA 1.0-4.0 (26%) - PSA >4.0 (8%) Of those with positive biopsy - PSA< 1.0ng/ml (22%) - PSA 1.0-4.0 (28%) - PSA >4.0 (50%)	
Biochemical disease-free survival	Disease free survival in all patients at 60 months – 62% Disease free survival in moderate risk patients (PSA<15ng/ml, Gleason sum <8, prostate volume <40cm3, and number of core biopsies <5 n = 50) – 68% Disease free survival in low risk patients (PSA <10ng/ml and Gleason sum <7 n = 32) – 83%	

Time until next intervention	Not reported		
Side effects:			
Stress incontinence	11 (13%)		
Total incontinence	2 (4%)		
Impotence	22 (77%)		
Retention >3 weeks	5 (6%)		
Febrile urinary infection	5 (6%)		
Urethral stenosis	14 (17%)		
Rectourethral fistula	1 (1%)		
Transient perineal pain	1 (1%)		
Quality of life	Not reported		

General comments –

Previous treatment: Four patients had local recurrence after definitive treatment with radiotherapy and neoadjuvant hormonal therapy was used in seven patient before HIFU. One patients received hormonal therapy after HIFU

Authors conclude HIFU is a new minimally invasive treatment for localized prostate cancer. The observed benefits largely outweigh the potential risks.

Beerlage H, Thuroff S, Debruyne, C Chaussy, De la Rosette J.. Transrectal high-intensity focused ultrasound using the Alblatherm device in the treatment of localized prostate carcinoma. Urology 1999, 54 (2) 273-277

Design: Case series (therapy), evidence level 3

Country: Germany

Setting: Secondary care

Inclusion criteria No formal inclusion criteria. Biopsy proven prostate carcinoma, clinical stage T1-3N_xM_0, PSA< 25ng/ml. All patients unfit for radical prostatectomy or unwilling to undergo operation, life expectancy exceeding 5 years.

Exclusion criteria None specified

Population

111 patients

Cancer stage: T1-3N_xM_0

Gleason score: not reported

Mean PSA: not reported

Mean prostate volume: not reported

Mean age: not reported

Interventions

HIFU (Ablatherm) 2.25MHz to 3MHz for 4.5 sec bursts

First 65 treatments (n = 49) were unilateral or bilateral in one or two sessions – "selective"

Second 78 treatments (n = 62) whole prostate was treated – "global"

Outcomes

PSA (unknown)

Biopsy 1 and 3 months after HIFU

Side effects

Follow up

Mean follow-up 12 months (range6 to 27)

Results

OUTCOME OF INTEREST	Group A "selective" HIFU (n = 49)	Group B "Global" HIFU (n=62)	OVERALL RESULT
Overall survival	Not reported		
Disease specific survival	Not reported		

Negative biopsy rate	Negative biopsy 28% - Negative biopsy, PSA <4ng/ml 25% - Negative biopsy, PSA >4ng/ml 3%	Negative biopsy 68% - Negative biopsy, PSA <4ng/ml 60% - Negative biopsy, PSA >4ng/ml 8%		
Biochemical disease-free survival	PSA <4ng/ml 62% - PSA <4ng/ml, negative biopsy 25% - PSA <4ng/ml, biopsy positive 37%	PSA <4ng/ml 86% - PSA <4ng/ml, negative biopsy 60% - PSA <4ng/ml, biopsy positive 26%		
PSA nadir - 0.5ng/ml - 0.5 to 4 ng/ml - >4 ng/ml	 19% 50% 30%	 55% 36% 9%		
Time until next intervention	Not reported			
Side effects: Stress incontinence Loss of erectile function Urethral stenosis Recto urethral fistula	 9 0% 1 3	 100%		
Quality of life	Not reported			

General comments –

Previous treatment: No previous treatment reported

Authors conclude that HIFU is a promising treatment for prostatic carcinoma that needs more evaluation in clinical trials and under controlled circumstances

Poissonnier L, Gelet A, Chapelon JY, Bouvier R, Rouviere O, Pangaud C et al. Results of transrectal focused ultrasound for the treatment of localized prostate cancer (120 patients with PSA < or + 10ng/ml). Prog Urol 2003; 13: 60-72

Design: Prospective open-label, uncontrolled trial (therapy), evidence level 3 (case series)

Country: not specified in review

Setting: Secondary care

Inclusion criteria Not specified in review. Localised prostate cancer ($T1\text{-}2N_0M_0$) with preoperative PSA concentration of <10ng/ml, not candidates for radical prostatectomy, life expectancy >10 years

Exclusion criteria Nor specified in review

Population Number of patients = 120

Cancer stage: $T1\text{-}2N_0M_0$

Gleason score 2 to 6 (64%), 7 to 10 (36%)

Mean age 71 years (range 56-86 years).

Mean PSA 5.67

Interventions HIFU but details not specified in review

Outcomes

Not specified in review

Follow up

Not specified in review

Median follow-up 27 months (from external source)

Results

OUTCOME OF INTEREST	**GROUP**	**OVERALL RESULT**	
	ALL		
Overall survival	Not reported		
Disease specific survival	Not reported		
Negative biopsy rate	Negative biopsy, no PSA elevation 76.9% @ 5 years (ASTRO)		
Biochemical disease-free survival	Negative biopsy, no PSA elevation 76.9%		
Biochemical disease-free survival according to baseline PSA			
- baseline PSA <4ng/ml	88%		
- baseline PSA >4ng/ml	73.1%		
Biochemical disease-free survival according to Gleason score			

- Gleason score 2 to 6 - Gleason score 7 to 10	85.4% 61.3%	P=0.024 in favour of those with Gleason score 2 to 6	
Biochemical disease-free survival according to prostate volume			
- prostate volume <40ml - prostate volume >40ml	71.5% 72.3%		
Biochemical disease-free survival according to PSA nadir			
PSA nadir <0.5ng/ml	91% negative-biopsy rate 86% progression free survival rate		
Time until next intervention	Not reported in review		
Quality of life	Not reported in review		
Side effects:	Not reported in review		

General comments

Previous treatment: none reported

Unclear whether these patients are included in other publications

(Ficarra *et al.* 2006)

Design: Retrospective case series (therapy), evidence level: 3

Country: Austria, setting: Tertiary care

Inclusion criteria Men with locally advanced or high risk prostate cancer, treated using HIFU and adjuvant hormonal therapy at a single institution between 2003 and 2004. Men had pre-operative PSA of at least 20 ng/mL or biopsy Gleason score of at least 7.

Exclusion criteria Evidence of nodal or distant metastases. Life expectancy of less than 5 years. High anaesthesiological risk. ECOG performance status >2. History of colorectal cancer or inflammatory bowel disease, previous rectal surgery, fistula or prostate brachytherapy. Prosthesis for treatment of erectile dysfunction or urinary incontinence. Radiotherapy or neoadjuvant hormonal therapy.

Population number of patients = 30.

Interventions All men were treated with HIFU, using the Ablatherm device and always combined with TURP. All men had adjuvant hormonal therapy: LHRHa for a period of 3 years.

All men had a prostate biopsy 6 months after HIFU

Outcomes Treatment toxicity, post operative prostate biopsy result.

Follow up Outcomes were reported at one year of follow-up.

Results Rates of treatment toxicity within 1 year of treatment

Urinary tract infection 5%, urethral stenosis 10%, infravesical urinary tract obstruction 13%.

The rate of urinary incontinence was 50%, 17%, 10% and 7% at 3, 6, 9 and 12 months after HIFU respectively.

The positive biopsy rate was 7/30 (23%).

General comments Small study, short follow-up, no reported toxicity scale.

(Ganzer *et al.* 2007)

Design: Retrospective case series (therapy), evidence level: 3

Country: Germany, setting: Tertiary care

Inclusion criteria Men with clinically localised prostate cancer, treated using HIFU as either primary curative therapy or salvage therapy. PSA 20 ng/mL or less, Gleason score 7 or less. Men were treated between 1997 and 2003

Exclusion criteria Previous hormonal therapy.

Population number of patients = 103.

Interventions All men were treated with the second generation Ablatherm prototype.

Outcomes Biochemical failure (defined using the revised ASTRO definition), positive biopsy rate after HIFU.

Follow up Median follow-up was 4.9 year (range 3 to 8.6 years) Authors report that some men were lost to follow-up and excluded.

Results 86/103 men (81%) had a prostate biopsy after HIFU. The positive biopsy rate was 5/86 (6%).

The overall biochemical failure rate was not reported. From the survival graph, the overall rate of biochemical failure could range from 17% to 20%.

A subgroup analysis by treatment response was done, showing higher post treatment PSA nadir was an predictive factor for biochemical failure. Men with larger prostates were more likely to have higher post treatment nadir, suggesting this group were poor candidates for this treatment.

General comments Overall rates of biochemical failure not reported. The proportion of primary versus salvage therapies not reported. Figures and tables do not match-up. There ap-

pear to be fewer patients in the survival plot than in the tables.

(Lee *et al.* 2006)

Design: Retrospective case series (therapy), evidence level: 3

Country: Korea (South), setting: Tertiary care

Inclusion criteria Men with clinically localised prostate cancer treated with HIFU between 2004 and 2005 at a single institution. All men were unsuitable (or unwilling) candidates for radical prostatectomy.

Exclusion criteria Men with less than 6 months of follow-up data.

Population number of patients = 58.

Interventions Men were treated using HIFU (Ablatherm commercial device). 17/58 men (29%) had neoadjuvant hormonal therapy. 53/58 (91%) had a combined TURP and HIFU procedure.

Outcomes Treatment failure, defined as a positive post operative biopsy or three consecutive increases in PSA of 1 ng/mL or more. Treatment related complications.

Follow up Mean follow-up was 14 months (range 6 to 21 months)

Results Failure free survival

Treatment failure occurred in 18/58 men (31%). The estimated 18 month treatment failure free survival (from Kaplan-Meier analysis) was 81% and 51% for men with clinical T1 and T2 stage disease respectively.

Multivariate analysis did not identify any statistically significant preoperative variables that could predict treatment success (although the small sample size is likely to limit the validity of this analysis).

Treatment toxicity

Grade 1 stress urinary incontinence was reported by 16% of men, but resolved with time or pelvic floor muscle exercise. Sloughing was observed in 8/58 (14%), stricture in 7% and acute urinary retention in 3%.

(Poissonnier *et al.* 2007)

Design: Retrospective case series (therapy), evidence level: 3

Country: France, setting: Tertiary care

Inclusion criteria Men treated with HIFU for clinically localised prostate cancer. PSA 15 ng/mL or less, prostate volume 40 cc or less, and no previous radical treatment. Men were treated between 1994 and 2003.

Exclusion criteria -

Population number of patients = 227.

Interventions All men were treated using the Ablatherm HIFU system. Between 1994 and 1999 men were treated using a prototype device and from 2000 onwards using a commercially available device. The machines differed in their transducer frequency, shot duration and safety features. Clinical procedures also changed over time, with combined TURP and HIFU becoming standard. Some later procedures were nerve-sparing.

All men were biopsied before and 3 months after HIFU. Men with rising PSA after HIFU had additional prostate biopsies. Hormonal therapy or external beam radiotherapy was used when indicated (such as after PSA failure).

Outcomes Disease free survival (treatment failure was defined as positive biopsy or PSA > 1ng/mL), treatment related toxicity.

Follow up All men were assessed at baseline, immediately after treatment then at 1, 3, 6 and 12 months after treatment. Mean follow-up was 27 months (range 12 to 121 months).

Results The actuarial 5 year disease-free survival rate was estimated as 66%.

The rates of treatment toxicity were: incontinence 13%, stenosis 12%, sloughing 9%, urgency 5%, perineal pain 3%, acute UTI 2% and haematuria 0.5%. A loss of sexual potency was reported in 16/41 (39%) of previously potent men treated without a nerve sparing procedure, compared with 8/26 (31%) treated with a nerve sparing procedure.

Comparison of the time periods 1993-1999 with 2000-2003 suggested that rates of incontinence and stenosis had declined (27% vs. 9% and 31% vs. 6% respectively).

General comments -

(Uchida *et al.* 2006)

Design: Retrospective case series (therapy), evidence level: 3

Country: Japan, setting: Tertiary care

Inclusion criteria Men with clinically localised prostate cancer treated using HIFU at a single institution. Prostate volume less than 40 mL.

Exclusion criteria Men with anal stricture or large calcifications.

Population number of patients = 181, age range 45 to 88 years, median age = 70 years.

Interventions All men were treated using the Sonablate HIFU device (Focus Surgery USA). Treatment was one HIFU session for 156/181 men, 2 sessions for 22/181 men and 3 sessions for 1 man . 95/181 (52%) had neoadjuvant hormonal therapy, on average for 6 months.

Outcomes Biochemical failure free survival. Biochemical failure was defined using the ASTRO-1997 definition. Treatment toxicity, measured using patient completed questionnaires.

Follow up Median follow-up was 18 months, range 4 to 68 months. Serum PSA was measured every 1 to 6 months during follow-up.

Results Biochemical failure free survival

Estimated biochemical disease free survival was 84%, 80% and 70% at 1,3 and 5 years respectively (from Kaplan-Meier analysis).

Rates of treatment toxicity

Urethral stricture 22%, urinary tract infection 6%, recto-urethral fistula 1%, grade 1 incontinence 1%, urinary retention 1%.

9/45 men (20%), who were potent before HIFU and did not receive neoadjuvant hormonal therapy, reported erectile dysfunction.

General comments -

Health Economics

The health economics analysis relating to this topic can be found at the end of section 4.2.

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3.8 Managing adverse effects of treatment

3.8.1 Rectal problems after radiotherapy

What is the most effective intervention for bowel toxicity following radical radiotherapy for prostate cancer?

Rationale

Acute and late toxicity in the rectum and bowel is an important complication of radiotherapy for prostate cancer. Many men develop acute rectal symptoms during and shortly after radiotherapy. These are usually self-limiting but very occasionally can be severe and prolonged. In addition many men develop functional changes to the bowel, often without underlying anatomical disturbance, which often do not require any treatment, but a small proportion may have radiation-induced injury, with or without anatomical disturbance, which may lead to significant long term symptoms. The actual incidence of GI toxicity following radiotherapy is not well reported. Although there is a 30 – 45 % range in reported incidences of grade 1 toxicity, the incidence of grade 3 toxicity is reported to be between 0.6 and 3%, and of grade 4, 0 – 1%.

Many interventions have been tried to prevent or treat bowel complications of radiotherapy- for acute side-effects, changes in diet, anti-diarrhoeal agents (loperamide, lomotil) and rectal steroids are commonly used, and have the advantages of being relatively cheap and readily available, but interventions such as aminosalicylates (sulphasalazine), sucralfate and somatisation analogues (octreotide) have also been investigated. For late effects, rectal sucralfate, rectal steroids, dietary changes and interventions such as thermal coagulation have been examined, but no treatment has been shown to confer clear benefit.

A previous review, performed as part of a position paper which is an appendix to NICE guideline 58, failed to identify any clear evidence of interventions being effective for treatment, but did propose possible interventions which might diagnose 'clear functional abnormalities within the gastrointestinal tract which may respond to specific treatments'.

Irrespective of the recommendations made in GDG 58, it is clear that the approach to prevention and management of radiation induced bowel toxicity in patients with prostate cancer is extremely varied throughout the UK. It is uncertain whether more evidence is now available, but it clear that the recommendations made in GD 58 have not been accepted by the radiotherapy community, and so may need to be revisited.

PICO question

Population	Intervention	Comparison	Outcomes
Men who develop bowel toxicity following radical radiotherapy for prostate cancer	Interventions for bowel toxicity: • Diet • Exercise • Hyperbaric oxygen therapy • Steroid enemas • Formalin • YAG laser • Sucralfate	Each other No intervention	• Bowel toxicity • Treatment related morbidity • Colostomy rate • Health-related quality of life

How the information will be searched

Sources to be searched	
Can we apply date limits to the search	This topic is an update of one in the original 2008 guideline so we will search for studies published since.
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	A randomised trials filter will be used
List useful search terms.	

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results?	We will use the evidence table for randomised trials (NICE guidelines manual appendix J).
Which quality checklist will we use for appraisal?	The RCT checklist will be used (NICE guidelines manual appendix C).
List subgroups here and planned statistical analyses	

Methods

Search strategy

The full strategy will be available in the full guideline. The search was restricted to randomized controlled trials published since the search for the previous guideline.

Selection of studies

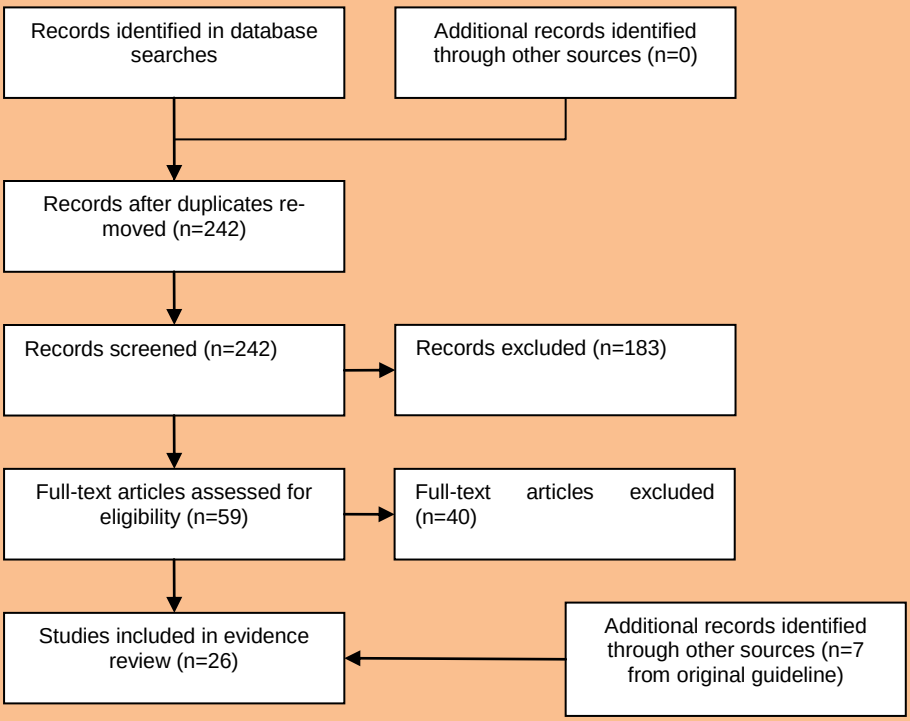
The information specialist (EH) did the first screen of the literature search results. Two reviewers (KC and NB) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO question. The full articles were then obtained for possibly eligible studies and checked against the inclusion criteria.

Analysis

Where possible, dichotomous data were pooled into a meta-analysis and risk ratios calculated.

Results

Results of the literature searches



The literature searches identified 242 possibly relevant studies of which 59 were ordered as full text articles and 19 were included plus 7 studies from the previous guideline.

One meta-analysis of 8 trials (Hovdenak 2005), 1 systematic review of 4 trials (Fuccio 2009), and 24 RCTs (including the 4 trials reported in Fuccio 2009).

Characteristics of included studies

Types of patients

Four studies included only men with prostate cancer (Fuccio 2011, Kapur 2010, Pettersson 2012, Botten 2011). The other studies included patients undergoing pelvic radiotherapy for the treatment of other cancers, such as cervical or rectal cancer.

Prophylactic or treatment

Most studies assessed the efficacy of preventative treatment for acute radiation-induced toxicity symptoms such as diarrhoea or rectal bleeding. Nine studies assessed the efficacy of treatments for patients who developed bowel toxicity after undergoing radiotherapy.

Evidence statements

Prophylactic treatments

Bowel toxicity

Diet: Bowel toxicity was a primary outcome in all included studies. Seven low quality studies were indentified with interventions including a low or modified fat diet (Wedlake et al. 2010), a reduced insoluble fibre and lactose diet (Pettersson et al., 2012), a low-fat, low-lactose diet (Bye et al., 1992), enzyme supplement (Martin et al., 2002), one study of elemental diet supplement (Capirci et al., 2000), and one study of elemental diet replacement (McGough et al., 2008). In Bye et al., (1992) 23% (14/71) of the intervention group and 48% (32/72) of the control group reported diarrhoea ($p<0.01$). The intervention group also took half the amount of anti-diarrhoeal medication (mean 0.6 tablets per day versus 1.1, $p<0.01$). At 12 months there were no differences between groups. However, the control group also had a relatively low fat intake and it is unclear whether the low-fat or low-lactose intervention had a beneficial effect. One unpublished study by Capirci et al. (2000) of elemental diet supplement in 677 patients reported a beneficial effect on toxicity in the intervention arm. 16.5% versus 25.1% Grade 1 diarrhoea; 11.9% versus 27.2% Grade 2 diarrhoea. Details of the intervention are not reported. In McGough et al.'s study, patients achieved only 65% compliance with elemental diet replacement. One study provided evidence of a significantly lower risk of, and increase in grade of, acute diarrhea at the end of treatment following a steady diet compared to no diet ($p=0.04$) (Arregui Lopez 2012). No details of the diet were given as only an abstract was available. None of the other studies reported a beneficial effect of dietary interventions on gastrointestinal symptoms following pelvic radiotherapy. These studies had relatively small sample sizes and patients were non-blinded to their treatment allocation. Pooling of data was not applicable due to the different methods of reporting toxicity between studies and heterogeneity in the interventions.

Probiotics: Four studies of very low quality compared probiotic supplements with a placebo control in the prevention of radiation-induced diarrhoea (Giralt et al., 2008; Delia et al., 2007; Chitapanarux et al., 2010; Salminen et al., 1998). Although all studies reported being double-blind, the methods of allocation concealment were not reported and none of the studies utilised an intent-to-treat analysis. The pooled analysis yielded an RR of 0.73 [CI 0.35 to 1.53] for any grade of diarrhoea during radiotherapy (see Figure 41). As reported in the meta-analysis by Fuccio (2009) for diarrhoea of Grade 3 or above, three of these studies do not provide definitive conclusions that probiotic supplementation may be effective for the prevention of radiation-induced diarrhoea [RR= 0.37, CI 0.04 to 3.27] (see Figure 42). Two studies reported on the number of patients requiring anti-diarrhoeal medication during the study period, with 25% (19/76) and 30.6% (22/72) of patients in the intervention group and control group respectively [RR in favour of probiotics 0.66, CI 0.16 to 2.77] (see Figure 43).

Germain et al. (2011) reported that survival at 60 days without grade $\geq$ 2 diarrhoea was 17% for patients with placebo, 35% for patients with standard dose probiotics, and 27% for high dose probiotics. They report a HR of 0.69 ($p=0.04$) for standard dose compared to placebo. No significant difference was found between standard dose and placebo for the incidence of grade $\geq$ 3 diarrhoea. Only the abstract was available for this study and there was insufficient data to be included in the pooled analysis.

One very low quality study reported that patients receiving the probiotic '5' strain dophilus were more likely to have $\geq$4 daily bowel movements but were less likely to need anti-diarrhoeal medication than patients taking the probiotic Hylak Tropfen (Timko, 2010).

Exercise: One study of moderate quality (Kapur et al., 2010) evaluated the rectal toxicity data of men being treated for localised prostate cancer who took part in a trial of aerobic exercise. There were no differences in mean rectal toxicity scores at the 4-week post-treatment review [MD 0.19 lower (0.57 lower to 0.19 higher)].

Steroid enema: One moderate quality study compared a glucocorticosteroid beclomethasone dipropionate (BDP) enema with a placebo (Fuccio et al, 2010). There was no significantly beneficial effect of BDP on bowel toxicity based on the RTOG/EORTC toxicity scales, or for the bowel frequency and urgency of defecation items of the SCCAI. 22% (12/55) of patients in the BDP group and 42% (25/59) of patients in the placebo group presented blood in the stool at

least once a week as measured by the SCCAI [RR in favour of BDP 0.51, CI 0.29 to 0.92]. Placebo patients were more likely than intervention patients to develop grade 2 or higher toxicity as assessed by endoscopy and the Vienna Rectoscopy Score (VRS) [RR 0.59, CI 0.41 to 0.85].

Sucralfate: One meta-analysis of 6 randomised controlled trials (Hovdenak et al., 2005) did not show a benefit of sucralfate for the prevention of acute diarrhoea after pelvic EBRT [RR 0.96, CI 0.81 to 1.14]. Some of the trials noted increased bowel toxicity in the patients treated with sucralfate.

Colostomy rate

This outcome was not reported in any of the studies.

Treatment-related morbidity

This outcome was not reported in any of the studies.

Health-related quality of life

Diet: Two studies reported the effects of dietary interventions on quality of life with no significant differences between intervention and control groups. One study found there was less decrease in the quality of life of patients (measured using the FACIT-D) in the diet group compared to the control at 3 weeks, but not after completion of the radiotherapy (Arregui Lopez 2012).

Probiotics: One study (Giralt 2008) showed a similar improvement in mean quality of life scores between those receiving probiotic supplements and control group patients [MD 3.70 higher (1.21 lower to 8.61 higher)].

Steroid enema: The mean quality of life score was higher at 12 month follow-up for patients receiving BDP than patients in the placebo group (Fuccio et al, 2010). Both groups IBDQ scores decreased over time although the reduction was more pronounced in the placebo group (p=0.034). This difference may be due to the higher rates of rectal bleeding in the placebo group.

Treatment of radiation-induced toxicity

Bowel toxicity

Probiotics: One RCT (Urbancsek et al., 2001) investigated the efficacy of 1-week probiotic supplementation as a treatment for patients with radiation-induced diarrhoea. Patients in the probiotics group less frequently needed anti-diarrhoeal medication than placebo patients. However, this difference was non-significant. There was a significant reduction in symptoms over time in both groups. There were no significant differences in number of bowel movements and rating of diarrhoea between the two groups at follow-up.

HBOT: Two studies reported the use of hyperbaric oxygen therapy (HBOT) for the treatment of radiation-induced toxicity (Clarke et al., 2008; Sidik et al., 2007). The study by Sidik et al. (2007) was of very low quality and poorly reported outcomes. Participants were not blinded to treatment allocation, and there is a lack of information about the intervention procedure or other treatments received by participants. Both studies used the LENT-SOMA scoring system for the assessment of radiation proctitis. Due to the reporting of this outcome the data was not suitable for pooling. Clarke et al. (2008) also reported on the complete resolution or significant improvement of proctitis. 45% (29/64) of the HBOT group achieved this outcome versus 27% (15/56) of the control group [RR for improvement in HBOT 1.69, CI 1.02 to 1.82] (see Figure

44). However, this is sensitive to the allocation of drop-outs and missing cases [best case: RR 2.73, CI 1.66 to 4.49] [worst case: RR 0.66, CI 0.47 to 0.93] (see Figure 45 and Figure 46).

Sulcrafate: One study of moderate quality reported the effects of Pentosanpolysulfate (PPS – a substance similar to sulfracate) compared to a placebo for the treatment of radiation-induced toxicity (Pilepich et al., 2006). There was no beneficial effect of PPS on the improvement of bowel toxicity [RR for improvement in control group 0.90. CI 0.62 to 1.32]. In Kochhar et al. (1991) as reported in the Denton (2009) systematic review, sulfracate showed greater improvement compared to anti-inflammatories for clinical features [RR 1.76, CI 1.08 to 2.87]. For endoscopic features no discernable difference was detected between groups [RR 1.51, CI 0.81 to 2.82]. Two patients in the anti-inflammatory group did not tolerate the drug and had to be excluded due to myalgia, nausea, and headaches. Chruscielewska-Kiliszek et al. (2012) found low quality evidence that the improvement in chronic radiation proctitis or endoscopy scores (overall severity, diarrhea, bleeding, or tenesmus) at 8, 16 and 52 weeks did not significantly differ between patients receiving sucralfate or placebo after APC.

Formalin: Two studies reported the use of topical formalin for the treatment of bowel toxicity following radiotherapy (Botten 2011; Sahakitrungruang 2012). One unpublished study provided low quality evidence of the effects of Argon Plasma Coagulation (APC) versus Topical Formalin for treating rectal bleeding after radiation therapy for carcinoma of the bladder (Botten et al., 2011). Rectal bleeding was improved in all 29 patients after a median of 2 (range 1-4) sessions of Formalin, or 1.5 (range 1-4) sessions of APC treatment. Other GI symptoms did not change. However, rectal compliance (5.8$\pm$ 1.2 to 3.7 $\pm$ 0.4 ml/mmHg, $p<0.05$), and threshold for first perception of rectal sensation (18$\pm$ 2 to 14$\pm$ 1 mls, $p<0.01$) both reduced after treatment. No differences in the efficacy of the two treatments were observed. Only the abstract was available for this study. A second low quality study found a significant improvement in rectal bleeding and bowel frequency at 8 weeks following formalin application. However, there was also significant improvement in rectal bleeding, bowel frequency, urgency, diarrhea, and tenesmus in the comparator group at 8 weeks following colonic irrigation and antibiotics. This resulted in a significantly greater improvement in rectal bleeding, urgency, and diarrhea in the colonic irrigation group.

Sucralfate + steroids vs formalin: One study provided low quality evidence of the effectiveness of a sucralfate-steroid enema versus topical formalin in the treatment of radiotherapy induced bowel toxicity (Nelamangala 2012). Patients experiencing rectal bleeding in both groups experienced a significant decrease in symptom (measured using the Radiation Proctopathy System Assessment Scale (RPSAS)) and sigmoidoscopic scores at 4 weeks ($p<0.001$). There was no significant difference between the groups in the number of patients reaching and maintaining an improvement in symptom score and sigmoidoscopy grade.

Colostomy rate

This outcome was not reported in any of the studies.

Treatment-related morbidity

HBOT: Clarke et al. (2008) reported that 19 patients (15.8%) complained of ear pain and discomfort after HBOT. Of these, 7 had tympanic membrane changes consistent with barotraumas, and 1 had both tympanic membrane injury and middle ear effusion. 7 underwent ventilation tube replacement. Two patients (1.7%) complained of confinement anxiety. One was treated with reassurance alone, the other required mild sedation.

Sucralfate: Chruscielewska-Kiliszek et al. (2012) found low quality evidence of severe constipation (7%) and urticaria (2%) in patients receiving sucralfate following APC compared to no complications in the placebo group.

Formalin: The low quality study comparing formalin application to colonic irrigation and antibiotics also reported that 20 (80%) patients in the formalin group experienced anorectal discomfort during application and six (24%) patients in the colonic irrigation group experienced nausea due to antibiotic use (Sahakitrungruang 2012).

Sucralfate + steroids vs formalin: The study providing low quality evidence of the effectiveness of a sucralfate-steroid enema versus topical formalin reported mild pain in 33.3% of patients during formalin application and no complications following the sucralfate-steroid enema (Nelamangala 2012).

Health-related quality of life

HBOT: Two studies reported an improvement of health related quality of life in both HBOT and control groups, with a greater improvement in the HBOT group. In Clarke et al (2008) the mean Bowel Bother quality of life score after treatment was 59.96 for the HBOT group and 59.74 for the control group. The mean Bowel Function quality of life score was 69.82 for the HBOT group and 68.30 for the control group after treatment. In Sidik et al (2007) the percentage mean difference in quality of life scores before and after the intervention was 19.67 for the HBOT group and 4.53 for the control group ($p<0.001$).

Sulcrafate: One moderate quality study found no beneficial effect of PPS compared to placebo on quality of life [RR for improvement in control group 0.80, CI 0.46 to 1.39].

Figure 41 Forest plot of comparison: Probiotics vs placebo, outcome: Diarrhoea (any grade)

Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Chitapanarux 2010	32	32	31	31	27.8%	1.00 [0.94, 1.06]
Delia 2007	77	243	124	239	27.2%	0.61 [0.49, 0.76]
Giralt 2088	30	44	24	41	26.4%	1.16 [0.84, 1.62]
Salminen 1998	3	11	9	10	18.6%	0.30 [0.11, 0.81]
Total (95% CI)		**330**		**321**	**100.0%**	**0.73 [0.35, 1.53]**
Total events	142		188			

Heterogeneity: Tau² = 0.51; Chi² = 113.97, df = 3 (P < 0.00001); I² = 97%

Test for overall effect: Z = 0.84 (P = 0.40)

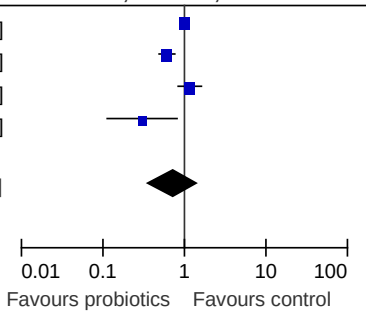


Figure 42 Forest plot of comparison: Probiotics vs placebo, outcome: Diarrhoea (Grade 3 or higher)

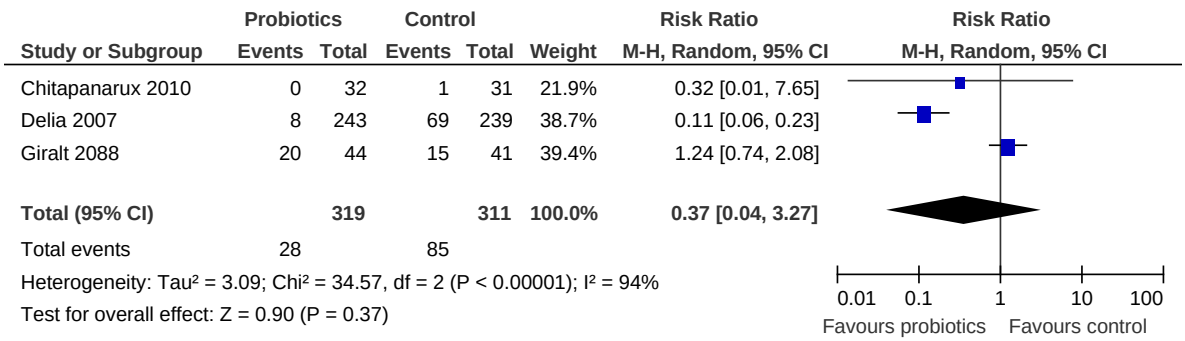


Figure 43 Forest plot of comparison: Probiotics vs placebo, outcome: Anti-diarrhoea drug used

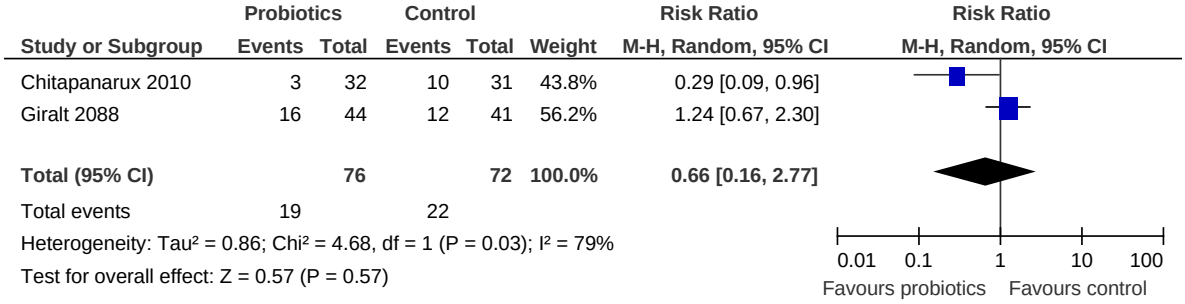


Figure 44 Forest plot of comparison: HBOT vs control, outcome: Complete resolution or significant improvement of proctitis

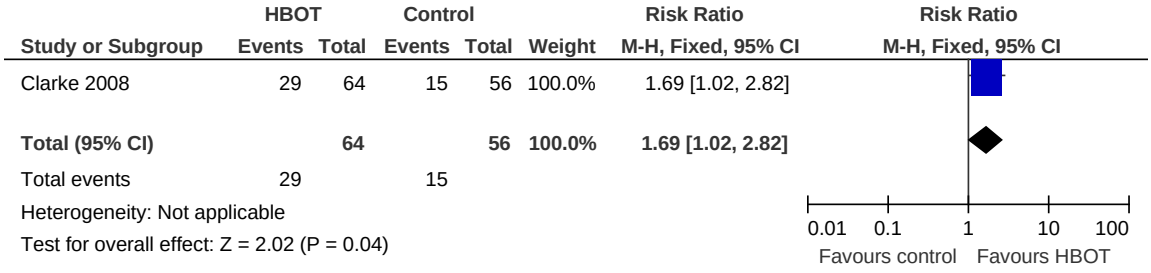


Figure 45 Forest plot of comparison: HBOT vs control, outcome: Complete resolution or significant improvement of proctitis. Sensitivity analysis (best case)

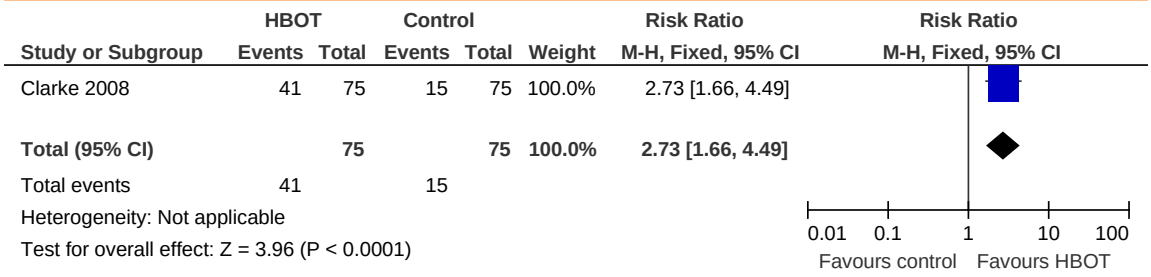


Figure 46 Forest plot of comparison: HBOT vs control, outcome: Complete resolution or significant improvement of proctitis. Sensitivity analysis (worst case)

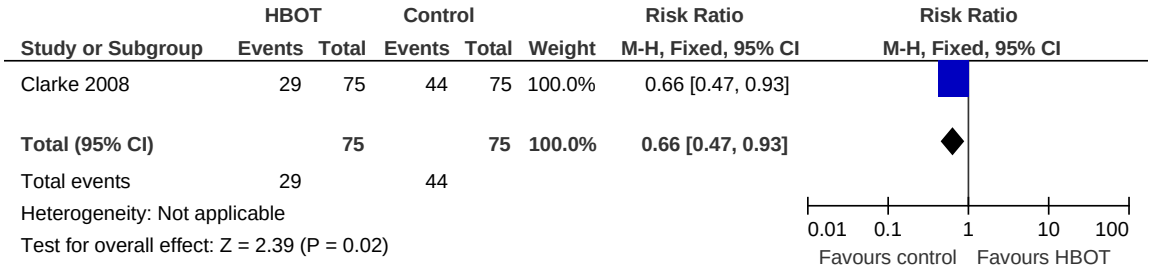


Table 103 Summary of study characteristics

Abbreviations: RCT = randomised controlled trial; RT = radiotherapy; EBRT = external beam radiotherapy; BT = brachytherapy; NR = none reported; HBOT = hyperbaric oxygen therapy; CT = chemotherapy

Study	Study type	Study period	Number of patients	Median age (range)	Patient characteristics	Intervention	Comparison	Additional treatments reported	Additional comments
Botten et al (2011)	RCT Treatment	NR	Randomised: 29 Intervention: 16 Comparison: 13	74 years (58-87)	Prostate carcinoma with chronic radiation proctitis	1-4 sessions of Argon Plasma Coagulation (APC) Therapy	1-4 sessions of Topical Formalin	NR	Abstract only
Capirci et al (2000)	RCT Prophylactic	1994-1998	Randomised: 677 Intervention: 332 Control:345	NR	Patients with cancer of the cervix, prostate and rectum undergoing post-operative RT	Elemental diet supplement – no further details	Standard diet	NR	Abstract only
Martin et al (2002)	RCT Prophylactic	1994-1997	Randomised: 56 Intervention: 28 Control:28	Mean = 55.5 years	Patients undergoing pelvic EBRT including rectal, uterine and cervical cancers	3x4 enzyme WOBE-MUGOS capsules. Starting 3 days before RT and finishing on the last day of RT.	Identical placebo	All patients irradiated using 4-field box technique. EBRT was given using fractionation of 5x1.8 Gy weekly to a dose of 50.4 Gy, specified at the isocentre.	
Bye et al (1992)	RCT Prophylactic	NR	Randomised: 143 Intervention: 71 Control:72	Mean = 53.5 (29-74)	Women with cancer of the cervix, uterus, ovaries, stage 1-2 receiving EBRT	Diet of 40g fat per day and 5g lactose per meal.	Hospitals regular diet, with an average fat content of 80g	NR	
Hovdenak et al (2005)	RCT and meta-analysis	1999-2000	Randomised: 52 Intervention: 24 Control:27	NR	Patients with localised pelvic tumour scheduled for EBRT	Sucralfate 2 tablets 3xday (1g per tablet) taken throughout RT	Identical placebo	Studies included in the meta-analysis varied in the additional treatments received by partici-pants and sucralfate schedules provided	
Kochhar et al (1991)	RCT	NR	Randomised: 37 Intervention: 18 Control:19	NR	36 females treated for cervi-cal cancer, 1 man for prostate cancer with RT-induced proctitis	Anti-imflammatories group: rectal prednisole 20mg bd and oral sulfasalzine 500mg tds. 4 wks treatment	Sucralfate: 2g rectal sucralfate suspension with oral placebo for sulfasalzine. 4 wks treatment	No details	As reported in systematic review by Denton 2009
Chitapanarux et al (2010)	RCT Prophylactic	2007-2009	Randomised: 62 Intervention: 32 Comparison:31	50 years (no range)	Locally advanced cervical cancer (Stage IIB-IIIB) + planning to receive whole pelvis EBRT and BT with weekly cisplatin	2x109 lactobacillus acidophilus plus bifidobacterium bifidum (2 capsules), twice a day, beginning 7 days before RT and every day during RT	Identical placebo schedule	Fermented dairy products forbid-den. No group differences in RT technique. All received external pelvic RT 200 cGy per fraction, 5 fractions/week. 4 insertions of BT with 700 cGy per fraction. 40mg/m2 Cisplatin, weekly, for 6 weeks during RT.	

Study	Study type	Study period	Number of patients	Median age (range)	Patient characteristics	Intervention	Comparison	Additional treatments reported	Additional comments
Clarke et al (2008)	RCT Treatment	NR	Randomised: 150 Intervention: 75 Comparison:75	NR	Radiation proctitis nonresponsive to other treatments. Various tumour sites/cancer stages, inc.gynaecological and prostate cancer	HBOT: 100% oxygen at 2.0 ATA for 90mins, 30 or 40 sessions over 6 to 8 weeks	Control: Air breathing at 1.1 ATA for 90mins, 30 times over 6 weeks. Sham brief compression for patient blinding purposes.	All patients had pelvic RT. A majority of patients had previous tissue damage treatment including antibiotics, anti-inflammatory agents, colostomy, intestinal resection.	No summary of patient characteristics
Delia et al (2007)	RCT Prophylactic	1999-2005	Randomised: 490 Intervention: 245 Comparison:245	NR	Receiving adjuvant RT for sigmoid, rectal or cervical cancer	One sachet VSL#3 probiotics from first day RT until last day, containing 450 billions/g of viable bacteria.	Identical placebo	Groups were balanced in terms of tumour grade, size and post-operative complications and local invasion at operation. Total radiation dose between 60 and 70 Gy.	Included in Fuccio 2009 met-analysis
Fuccio et al (2011)	RCT Prophylactic	2007-2010	Randomised: 120 Intervention: 60 Comparison:60	Mean: 70 years	Prostate cancer patients without distant metastases undergoing EBRT.	3mg beclomethasone diproprionate (BDP) enema the evening before each RT session. After RT patients received 2 daily 3mg BDP suppositories for 4 weeks.	Identical placebo	No between group differences were found in RT technique, dose, and no. of sessions. EBRT range = 66 -74 Gy, given in 33-37 fractions over 6-7 weeks. Daily fraction of 2 Gy, 5 days/week. 17 intervention and 19 control patients received hormone therapy (n.s.).	
Giralt et al (2008)	RCT Prophylactic	2002-2005	Randomised: 118 Intervention: 56 Comparison:62	Mean: 60 years	Females with endometrial adenocarcinoma or cervical carcinoma treated with pelvic RT	96ml, 3x/day fermented liquid yoghurt containing 108 CFU/g of L.casei DN-114 001, and Streptococcus and Lactobacillus. Taken 1 week before RT and throughout treatment.	Palcebo drink – active product sterilized	4-field technique RT. 1.8-2 Gy/d, 5x/ weekly for 5-6 weeks. Total dose = 45-50.4 Gy. Cervical cancer patients received a weekly intravenous dose of 40mg/m2 cisplatin. BT given 2-3 weeks later, according to local investigator criteria. 11 intervention and 14 control patients received RT plus CT.	Study sample below planned size. Included in Fuccio 2009 met-analysis
Germain et al (2011)	RCT Prophylactic	2006-2010	Randomised: 246 Intervention: NR Comparison:NR	NR	Patients with rectal, cervical, endometrial or prostatic cancer, due to undergo pelvic radiotherapy	Standard dose (bifilact 2 caps of 1.3 milliards of Lactobacillus acidophilus and Bifidobacterium) or High dose (3 caps of 10 milliards) during - radiotherapy	Placebo	No details – patients had surgery or chemotherapy prior to radiotherapy	Abstract only
Kapur et al (2010)	RCT Prophylactic	2001-2002	Randomised: 66 Intervention: 33 Comparison: 33	Mean: 67 years	Men with localized prostate carcinoma on the waiting list for radical conformal RT	Moderate-intensity, continuous walking for 30 mins at least 3 days/week during RT. Target heart rate of 60–	Perform normal activities but advised to rest when fatigued.	3-field, beam-directed RT technique. No differences in rectum or bladder dose between groups. Mean rectal dose in intervention = 45.01 Gy and 45.71 Gy in the	Retrospective analysis of toxicity data of Windsor, 2004.

Study	Study type	Study period	Number of patients	Median age (range)	Patient characteristics	Intervention	Comparison	Additional treatments reported	Additional comments
						70% max heart rate.		control.	
McGough et al (2008)	RCT Prophylactic	Jan 2005 - Jul 2005	Randomised: 50 Intervention: 25 Comparison: 25	61.5 (29-82)	Gynaecological (n=21), urological (n=13) or lower gastrointestinal (n=13) malignancy, due for RT	Replace one meal a day, equivalent to 33% of total calorific intake, with an elemental diet drink (E028 Extra), during the first 3 weeks of pelvic RT.	Continue with normal diet during RT	Patients were treated with a 3-field technique, fraction size between 1.8 -2 Gy. Total RT dose similar between groups: Intervention mean = 50.4 Gy; Control mean = 54 Gy. 44% intervention and 28% control group received concomitant CT.	
Pettersson et al (2012)	RCT Prophylactic	2006-2008	Randomised: 130 Intervention: 64 Comparison 66	66 years (50-77)	Prostate cancer patients (T1-T3) referred to EBRT in combination with either high dose BT or proton therapy	Avoid foods high in insoluble dietary fibre and lactose and instead consume foods with a higher proportion of soluble fibres and low in lactose, from prior to RT until 24 months post-RT.	Continue with normal diet during RT	All patients received EBRT, in combination with BT or proton therapy.	
Pilepich et al. (2006)	RCT Treatment	1999-2001	Randomised: 180 Intervention: 57 Intervention: 53 Comparison: 59	69 years (35-96)	4 weeks since the completion of RT to abdomen/pelvis + proctitis. No details on cancer site/grade.	Group 1: 300mg Pentosanpolysulfate (PPS) – 100mg, 3 times per day Group 2: 600mg PPS – 200mg, 3 times per day..	Identical placebo	NR	
Sidik et al (2007)	RCT Treatment	2005-2006	Randomised: 75 Intervention: 35 Comparison:40	Mean: 46 years	Neck cervical cancer patients aged <55yrs, (stage I-IIIB) who had received pelvic radiation.	HBOT: Among 32 patients, most received HBOT more than 18 times. No other details about intervention reported.	No HBOT	NR	Poorly reported outcomes
Wedlake et al (2010)	RCT Prophylactic	2006-2009	Randomised: 117 Intervention: 40 Intervention: 38 Comparison:39	Mean: 65 years	Patients with proven gynaecological (20%), urological (48%) or lower gastrointestinal (32%) malignancy due to receive radical EBRT	Group 1: low fat diet during first 4 weeks of treatment. Group 2: diet with fats to comprise 40% of total energy intake. 50% of this as MCT -based fat emulsion 'Liquigen'	Group 3: Normal fat diet with LCT dietary fats to comprise 40% of total energy.	45% of Group 1, 63% of Group 2, and 44% of Group 3 received concomitant chemotherapy. Median radiotherapy dose was 64, 54 and 54 Gy for Groups 1, 2, and 3 respectively, with comparable ranges of fractionation.	
Timko (2010)	RCT Prophylactic	2005-2006	Randomised: 42 Intervention: 20	65 years (34-83)	Patients undergoing adjuvant RT in the abdominal/pelvic region. 13 colorectal cancer,	L-Group given '5' strain dophilus, containing 5 probiotic cultures (6	H-Group given Hylak Tropfen i.e. cell-free fermentation products of	Radiation delivered using 4-field box technique. 2 Gy/day for 5-7 weeks. Total cumulative dose=50	

Study	Study type	Study period	Number of patients	Median age (range)	Patient characteristics	Intervention	Comparison	Additional treatments reported	Additional comments
			Comparison:22		4 uterine cancer, 8 prostate cancer, 4 urinary bladder cancer, 1 sigmoid colon cancer	billion active bacteria/capsule) 1 capsule 2x/day. Starting on first day of RT until end of RT.	lactobacillus, helveticus and gut symbionts. 40 drops 3x/day. Starting on first day of RT until end of RT.	Gy. High risk patients (e.g. patients with prostate cancer), received 65-67 Gy (2 Gy/day). Some patients received RT and CHT.	
Urbancsek et al (2001)	RCT Treatment	1996-1998	Randomised:205 Intervention:102 Comparison:103	Mean:60 years (25-86)	Cancer patients with diarrhoea 4 wks after abdominal RT. 75% female patients	One week treatment with probiotic 'Antibiophilus' 3x/day.	Identical placebo	RT daily dose =2 Gy. Median 25 RT sessions prior to study. Median cumulative radiation dose of 50 Gy per patient in both study arms	Included in Fuccio 2009 met-analysis
Salminen et al (2001)	RCT Prophylactic	NR	Randomised:24 Intervention:11 Comparison:10	NR	Patients undergoing RT – cervix or uterus carcinoma	1x daily dose of live Lactobacilus rhamnosus (1.5x109 CFU/sachet) during treatment period	Dietary restriction	Intra-cavity pre-operative caesium and post-operative external radiotherapy. 80 Gy for the tumour and 50 Gy for the pelvic area.	Included in Fuccio 2009 met-analysis
Sahakitrungruang et al. (2012)	RCT Treatment	2010-2012	Randomised: 50 Intervention: 25 Comparison: 25	Mean: 64 (27-85)	Cancer patients with chronic hemorrahagic radiation proctitis for ≥ 6 months without complications	Colonic irrigation daily & oral antibiotics (ciprofloxacin 500 mg daily + metronidazole 500 mg 3 x daily) for 1 week	4% formalin application (once)	NR	
Nelamangala et al. (2012)	RCT Treatment	2005-2007	Randomised:102 Intervention:51 Comparison:51	Mean: 51/52 years	Patients with rectal bleeding following RT for cervix carcinoma	Formalin (4%) application + 5 mg oral bisacodyl the night before	Sucralfate-steroid enema (100 mg prednisolone + 1 g sucralfate) twice daily for 7-10 days	Oral liquid paraffin and low residue diet.	
Chruscielewska-Kiliszek et al. (2012)	RCT Treatment	2003-2006	Randomised:122 Intervention:60 Comparison: 62	Mean: 66 years	Patients with chronic radiation proctitis or proctosigmoiditis following RT for a pelvic tumour ≥ 3 months previously; with rectal bleeding & telangiectasia	Sucralfate 6 mg twice daily.	Placebo.	Argon plasma coagulation prior to sucralfate or placebo.	
Arregui Lopez et al. (2012)	RCT Prophylactic	2010-2011	Randomised:29 Intervention:15 Comparison: 14	NR	Patients with adenocarcinoma of the rectum treated after pelvic RT	Steady diet.	No diet.	Median dose: 45 Gy RT + concomitant preoperative capecitabine.	Abstract only

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What is the diagnostic yield of screening sigmoidoscopy in the detection of radiation induced bowel cancer?

Rationale

There is no doubt that radiation can induce cancer as a late complication of radiotherapy, usually many years after treatment. Results of studies of second bowel malignancy after radiotherapy for prostate cancer have not been consistent, some showing that there was no increased risk, others that there is an increased risk after 5 years, whilst other studies suggest the risk is not apparent for 10 years. There have also been studies of second cancers after treatment for cervical cancer, which have shown an increase in rectal cancers but not colon cancers. Some authors have advocated surveillance for colorectal tumours after pelvic irradiation for gynaecological cancer, and based on this, recommendations were made in GDG 58 for a similar programme for patients after radiotherapeutic treatments of the prostate.

It is not clear that this practice has been adopted, and most centres appear to have a policy of only investigating symptomatic patients, and it is proposed that further evidence is sought on the benefit of sigmoidoscopy in detecting bowel cancers after radiotherapy to the prostate. It is not known whether new evidence is now available, or indeed whether there is more evidence on the role of sigmoidoscopy after treatment of other pelvic cancers with radiation. As there are concerns that this original recommendation is not being followed, it is suggested that there is now an opportunity to look at the evidence for the utility of sigmoidoscopy in high risk individuals, including its frequency of use, particularly in relation to post-radiotherapy prostate patients, so that the GDG 58 recommendation can be re-examined and reviewed.

PICO question

Population	Intervention	Outcomes
Asymptomatic men who have received radical radiotherapy for prostate cancer	Sigmoidoscopy	• Diagnostic yield for bowel cancer • Diagnostic yield for other non-malignant pathology • Overall survival • Bleeding • Sepsis • Perforation • Health-related quality of life

How the information will be searched

Sources to be searched	
Can we apply date limits to the search	No date limits
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	No study design filter
List useful search terms.	

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results?	We will use the evidence table for diagnostic or cochort studies (NICE guidelines manual appendix J).
Which quality checklist will we use for appraisal?	The diagnostic or cohort studies checklists will be used (NICE guidelines manual).
List subgroups here and planned statistical analyses	

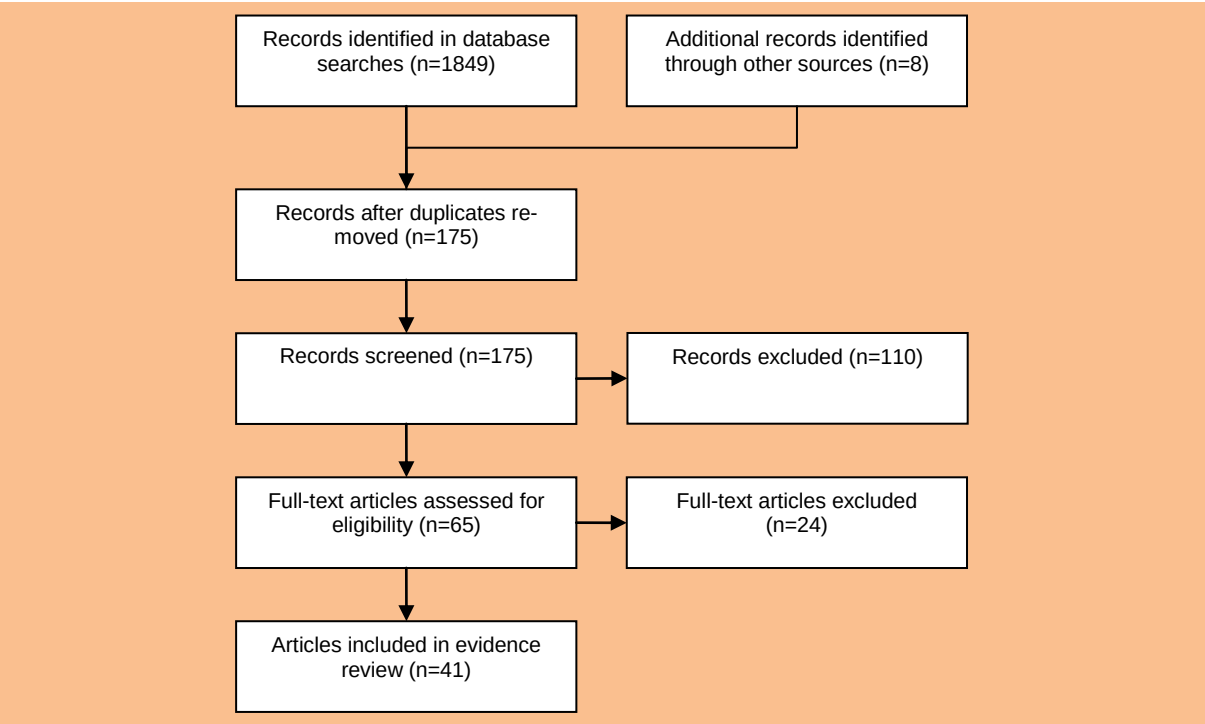
Methods

Selection of studies

The information specialist (EH) did the first screen of the literature search results. Two reviewers (NB and KC) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO question. The full articles were then obtained for possibly eligible studies and checked against the inclusion criteria.

Results

Results of the literature searches



The literature searches identified 175 possibly relevant articles (including eight identified from the reference lists of included articles and 19 from the update search) of which 65 were ordered in full text. Forty-one articles referring to 34 different studies were included.

Characteristics of included studies

The characteristics of included studies are summarised in Table 108. Seven of the studies were only available in abstract form. All studies were observational and of cohort design.

Sigmoidoscopic studies

In three of the studies patients underwent 3D conformal external beam radiotherapy for prostate cancer. In one study the patients underwent local-field non-conformal external beam radiotherapy and one study did not report details of the radiotherapy. Patients were screened with flexible sigmoi-

doscopy (where reported) performed at varying time intervals following radiotherapy for a maximum duration between 2 and 3 years.

Incidence of bowel cancer

Twenty-nine cohort studies reported information on the incidence of bowel cancer following radiotherapy for prostate cancer. Median length of follow-up for these studies was between 3.1 and 11.4 years (where reported) and the median age of radiotherapy patients studied varied between 63 and 72 years (where reported).

The majority (18) of the studies did not report restricting cases to those occurring over a minimum time after prostate cancer diagnosis or radiotherapy. However, one study (Pickles et al. 2002) only included colorectal cancers diagnosed more than 2 months after radiotherapy; three studies (Nieder et al. 2008; Margel et al. 2009; Neugut et al. 1997) only included those diagnosed more than 6 months after the prostate cancer diagnosis; two studies (Abdel-Wahab et al. 2008 and 2009) more than 1 year after diagnosis; one study (Ciezki et al. 2012) more than 3 years after diagnosis; and five studies (Rapiti et al. 2008; Moon et al. 2006; Baxter et al. 2005; Brenner et al. 2000; Liauw et al. 2006) only included those diagnosed more than 5 years after initial diagnosis or radiotherapy.

Only four studies report limiting included cases by age: Leung et al. 2010 excluded those aged < 16 years; Baxter et al. 2005 excluded those aged < 18 or > 80 years; Abdel-Wahab et al. 2008 excluded those aged < 20 years; and Nieder et al. 2008 excluded those aged < 40 years.

Evidence statements

Asymptomatic men who have received radical radiotherapy for prostate cancer and undergone sigmoidoscopy

Overall survival, sepsis and perforation

These outcomes were not reported in any of the studies.

Health-related quality of life

This outcome was not reported in any of the studies.

Malignancy

Very low quality evidence from a cohort study (Bolin *et al*. 2001), for which only an abstract was available, suggests malignancy may be found in around 3% of asymptomatic men screened using sigmoidoscopy following radiotherapy for prostate cancer. Screening was performed 16 months following radiotherapy.

Polyps

Very low quality evidence from two observational studies (Bolin *et al*. 2001; Wachter *et al*. 2000) suggest that polyps may occur in 21% (20% and 23% in each of the studies) of asymptomatic men screened using sigmoidoscopy following radiotherapy for prostate cancer.

Stricture

One cohort study (O'Brien *et al*. 2004) provided very low quality evidence on the absence of stricture in asymptomatic men screened using sigmoidoscopy following radiotherapy for prostate cancer, finding none in any of 20 men screened.

Hemorrhoidal nodes

One cohort study (Wachter *et al*. 2000) provided very low quality evidence on the presence of haemorrhoidal nodes in asymptomatic men screened using sigmoidoscopy following radiotherapy for prostate cancer. The study found a prevalence of 48% (21 cases in 44 men screened).

Ulceration

Very low quality evidence from two observational studies (Goldner *et al*. 2007; Wachter *et al*. 2000) suggests the presence of ulceration in asymptomatic men screened using sigmoidoscopy following radiotherapy for prostate cancer. Both studies found microulcerations in the distal anterior rectum wall. When combined, the studies estimate a prevalence of 2% (with rates of 1% and 5% individually).

A third observational study (O'Brien *et al*. 2004) found no evidence of ulceration in any of 20 asymptomatic men screened following radiotherapy for prostate cancer.

Telangiectasia

Four observational studies (Goldner *et al*. 2007; Karamanolis *et al*. 2009; O'Brien *et al*. 2004; Wachter *et al*. 2000) provided very low quality evidence on the presence of telangiectasia in asymptomatic men screened using sigmoidoscopy following radiotherapy for prostate cancer. Combined these studies suggest a prevalence of telangiectasia of 57% and multiple telangiectases of 39% (individual studies ranged from 43% to 80% and 25% to 60% respectively).

Congested mucosa

Very low quality evidence from two cohort studies (Goldner *et al*. 2007; Wachter *et al*. 2000) suggests a prevalence of congested mucosa of 43% (range of 39% to 57% in individual studies) in asymptomatic men screened using sigmoidoscopy following radiotherapy for prostate cancer.

Grade 1 congested mucosa (focal reddening of the mucosa with edematous mucosa) was found in 15% to 32% of men; grade 2 (diffuse, not confluent, reddening of the mucosa with edematous mucosa) in 16% to 30%; and grade 3 (diffuse, confluent, reddening of the mucosa with edematous mucosa) in 8% to 13% of men in these studies.

Rectal bleeding

Four observation studies (Goldner *et al*. 2007; Karamanolis *et al*. 2009; O'Brien *et al*. 2004; Wachter *et al*. 2000) provided very low quality evidence on the prevalence of rectal bleeding in men screened using sigmoidoscopy following radiotherapy for prostate cancer. The studies suggest an overall prevalence of 27% (ranging from 20% to 50% in individual studies).

Incidence of bowel cancer in men who have received radiotherapy for prostate cancer

Observational studies (see Table 105) suggest a geometric mean raw incidence of 1.3% (range 0.1% to 6.6%) for the development of any secondary bowel cancer in men who have received radiotherapy for prostate cancer. Observational studies which report rates of secondary colon or rectal cancer in men who have received radiotherapy for prostate cancer suggest geometric mean[1] raw incidences of 1.1% (range 0.4% to 3.4%) and 0.5% (range 0.0% to 8.3%) respectively. Median follow-up (where reported) in the above studies ranged from 3.2 to 11.4 years.

The meta-analysis included six studies and found a significantly higher risk of developing colorectal cancer following radiotherapy compared with no radiotherapy in men previously diagnosed with prostate cancer (RR 1.27 95% CI 1.23-1.31) (see Figure 47). The risk was also significantly higher for colon and rectal cancers individually (RR 1.09 95% CI 1.05-1.13 and RR 1.15 95% CI 1.10-1.21 respectively). However, there was wide variability between studies.

Six of the studies specifically looked at the increased risk of bowel cancer in those who had received EBRT alone for prostate cancer. There was no significant difference in the risk of any colorectal cancer or specifically colon cancer in those treated with EBRT compared to no radiotherapy (p ≥

0.1). However, there was still a significantly increased risk of rectal cancer following EBRT when compared with no radiotherapy (RR 1.21 95% CI 1.11-1.32).

In many of the studies a latency period was used to exclude the possibility of synchronous colorectal cancers, which varied considerably in length between studies. The exclusion of any studies which included secondary bowel cancers occurring within 5 years of diagnosis or treatment resulted in no significant increase in risk of any colorectal or colon cancer following radiotherapy ($p \geq 0.1$), but a significant increase in risk of rectal cancer for those treated with radiotherapy (RR 1.18 95% CI 1.07-1.31) (see Figure 48).

Only one observational study (Rapiti *et al*. 2008) allowed calculation of the incidence rate per person-year for any secondary bowel cancer in men who have received radiotherapy for prostate cancer; this was found to be 1,169 cases/100,000 person-years. The geometric mean incidence rates for colon (Huo *et al*. 2009; Brenner *et al*. 2000; Hinnen *et al*. 2011) and rectal cancer (Huo *et al*. 2009; Margel *et al*. 2009; Nieder *et al*. 2008; Brenner *et al*. 2000; Hinnen *et al*. 2011; Rapiti *et al*. 2008) were found to be 220 cases/100,000 person-years (range 188 and 248 cases/100,000 person-years) and 102 cases/100,000 person-years (range 52 and 220 cases/100,000 person-years) respectively. This compares to 190 and 105 cases/100,000 person-years in the no-radiotherapy control groups respectively. From these figures, if 1,000 men were screened for 10 years we might expect to detect around 32 colorectal cancers in those undergoing radiotherapy, compared to around 30 colorectal cancers in those not undergoing radiotherapy.

The standardised incidence ratio (SIR) for any secondary bowel cancer following radiotherapy for prostate cancer was between 1.2 and 3.4 where reported (Pickles *et al*. 2002; Rapiti *et al*. 2008). The SIR^2 for colon cancer alone was between 0.9 and 4.0 where reported (Hinnen *et al*. 2011; Huo *et al*. 2009; Rapiti *et al*. 2008) and the SIR for rectal cancer alone was between 0.7 and 2.0 where reported (Hinnen *et al*. 2011; Huo *et al*. 2009; Margel *et al*. 2009; Nieder *et al*. 2008; Pawlish *et al*. 1997; Rapiti *et al*. 2008). However, varying degrees of standardisation for the number of expected cases in the population were used between studies, for example, whether expected incidence rates were age-, gender-, year- or ethnicity-specific.

Table 104 Asymptomatic* men who have received radical radiotherapy for prostate cancer and undergone sigmoidoscopy

Study	Radiotherapy method	Sigmoidoscopy method	Median follow-up (months)	Patients screened	Clinical symptoms – number of patients									Retroscopy scoring system	Number of patients			
					Malignancy	Polyps	Stricture	Hemorrhoidal nodes	Ulceration	Telangiectasia	Multiple telangiectases	Congested mucosa	Rectal bleeding		Grade 0	Grade 1	Grade 2	Grade 3
Bolin et al. (2001)	NR	NR	NR	277	7	56	-	-	-	-	-	-	-	NR	16	106	20	4
Goldner et al. (2007)	External beam	Recto-sigmoid area	40	166	-	-	-	-	2	58-57%[1]	43-31%[1]	39-40%[1]	45	VRS	53	36	54	23
														EORTC/ RTOG	95	19	47	5
Karamanolis et al. (2009)	3-D planned conformal	Flexible	NR	28	-	-	-	-	-	-	16	-	6	-	-	-	-	-
O'Brien et al. (2004)	Local field non-conformal	Flexible	27	20	-	-	0	-	0	16	12	-	10	Wachter et al. (2000)	NR	NR	NR	NR
Wachter et al. (2000)	3-D planned conformal	Flexible	29	44	-	10	-	21	2	19	11	25	9	New	20	10	7	7
														EORTC/ RTOG	15	20	9	0

*Patients not reported to have any symptoms by articles

[1]12 and 24 months follow-up screen respectively

Table 105 Incidence of colorectal cancer in men who have received radical radiotherapy for prostate cancer

Abbreviations: SIR = standardized incidence ratio; CI = confidence interval; p-y = person years; BT = brachytherapy; EBRT = external beam radiotherapy; NR = not reported

Study	Overall follow-up (median / person-years)	Radiotherapy group							No radiotherapy group							Difference between groups		
		Treat-ment	Median follow-up	Number of pa-tients	Cases seen	Incid-ence (calcula-ted)	SIR	SIR 95% CIs	Treat-ment	Median follow-up	Number of pa-tients	Cases seen	Incid-ence (calcula-ted)	SIR	SIR 95% CIs	p-value	Rela-tive risk	Relative risk 95% CIs
Bartkowiak et al. (2011)	-	NR	-	1,155	9	0.8%	-	-	-	-	-	-	-	-	-	-	-	-
Baxter et al. (2005)[1]	-	EBRT (with or without surgery)	7.9 years	30,552	533	1.7%	-	-	Surgery alone	8.3 years	55,263	904	1.6%	-	-	<0.01	1.7	(1.4 – 2.2)
Gutman et al. (2006)	4.6 years	BT + EBRT	-	699	17	2.4%	-	-	-	-	-	-	-	-	-	-	-	-
		BT alone	-	652	8	1.2%	-	-	-	-	-	-	-	-	-	-	-	-
Henry et al. (2012)	-	BT alone	Range: 6-17 years	1,805	30	1.7%	-	-	-	-	-	-	-	-	-	-	-	-
Huo et al. (2009)	3,420,432 p-y	Mixed	-	211,882	3,543	1.7%	-	-	NR	-	424,028	6,636	1.6%	-	-	-	-	-
Johnstone et al. (1998)	10.9 years	Definitive	-	164	4	2.4%	-	-	-	-	-	-	-	-	-	-	-	-
Leung et al. (2010)	-	NR	-	752	32	4.3%	-	-	NR	-	2,729	27	1.0%	-	-	<0.01	4.30	-
Liauw et al. (2006)[1]	10.5 years	BT + EBRT	10.2 years	223	2	0.9%	-	-	-	-	-	-	-	-	-	-	-	-
		BT alone	11.4 years	125	1	0.1%	-	-	-	-	-	-	-	-	-	-	-	-
Movsas et al. (1998)	-	Definitive EBRT	-	543	2	0.4%	-	-	NR	3.9 years	18,135	NR	-	-	-	-	-	-
Pickles et al. (2002)[4]	-	EBRT	4.8 years	9,890	NR	-	121	NR	None	1.7 years	29,371	NR	-	99	NR	<0.01	-	-
Rapiti et al. (2008) & Weber et al. (2009)[1]	7.4 years / 3,798 p-y	EBRT	7.8 years	264	11	4.2%	3.4	(1.7 – 6.0)	Surgery	7.3 years	870	8	0.9%	0.7	(0.3 – 1.5)	-	-	-
Tobi et al. (2011)	-	NR	-	24,706	1,635	6.6%	-	-	NR	-	442,238	15,846	3.6%	-	-	<0.01	1.76	(1.68 – 1.85)
Sharp et al.	-	BT alone	6.1 years	183	3	1.6%	-	-	-	-	-	-	-	-	-	-	-	-

Study	Overall follow-up (median / person-years)	Radiotherapy group							No radiotherapy group							Difference between groups		
		Treat-ment	Median follow-up	Number of pa-tients	Cases seen	Incid-ence (calcula-ted)	SIR	SIR 95% CIs	Treat-ment	Median follow-up	Number of pa-tients	Cases seen	Incid-ence (calcula-ted)	SIR	SIR 95% CIs	p-value	Rela-tive risk	Relative risk 95% CIs
(2012)																		
Zelefsky et al. (2012)	-	EBRT	-	897	5	0.6%	-	-	Surgery alone	-	1,348	9	0.7%	-	-	-	-	-
		BT alone	-	413	2	0.5%	-	-										

[1]Cases of CRC diagnosed within 5 years of PCa diagnosis/radiotherapy for Pca not included; [2]Cases of CRC diagnosed within 1 year of Pca diagnosis/radiotherapy for Pca not included; [3]Cases of CRC diagnosed within 6 months of Pca diagnosis/radiotherapy for Pca not included; [4]Cases of CRC diagnosed within 2 months of Pca diagnosis/radiotherapy for Pca not included.

Table 106 Incidence of colon cancer in men who have received radical radiotherapy for prostate cancer

Abbreviations: SIR = standardized incidence ratio; CI = confidence interval; p-y = person years; BT = brachytherapy; EBRT = external beam radiotherapy; NR = not reported

Study	Overall follow-up (median / person-years)	Radiotherapy group							No radiotherapy group							Difference between groups		
		Treat-ment	Median follow-up	Number of pa-tients	Cas-es seen	Raw incid-ence (calcu-lated)	SIR	SIR 95% Cis	Treat-ment	Median follow-up	No. of patien-ts	Cases seen	Raw incid-ence (calcula-ted)	SIR	SIR 95% Cis	p-value	Rela-tive risk	Relative risk 95% Cis
Abdel-Wahab et al. (2008)[2]	-	EBRT, BT or both	4.7 years	67,719	816	1.2%	-	-	No RT or surgery	4.3 years	40,733	488	1.2%	-	-	-	-	-
Abdel-Wahab et al. (2009)[2]	-	Surgery & RT	-	5,044	46	0.9%	-	-	Surgery alone	-	80,157	767	1.0%	-	-	-	-	-
Baxter et al. (2005)[1]	-	EBRT (with or without surgery)	7.9 years	30,552	409	1.3%	-	-	Surgery alone	8.3 years	55,263	761	1.4%	-	-	-	-	-
Brenner et al. (2000)[1]	-	NR	218,341 p-y	51,584	541	1.0%	-	-	Surgery	312,499 p-y	70,539	823	1.7%	-	-	0.97	-	-
Henry et al. (2012)	-	BT alone	Range: 6-17 years	1,805	19	1.1%	-	-	-	-	-	-	-	-	-	-	-	-
Hinnen et al. (2011) & van Vulpen et al. (2011)	7.5 years / 14,380 p-y	BT	7.1 years / 8,491 p-y	1,187	16	1.3%	0.93	(0.53 – 1.52)	Surgery	8.7 years / 5,889 p-y	701	7	1.0%	0.73	(0.29 – 1.50)	-	-	-
Huang et al. (2011)	-	Mixed	6.9 years / 21,276 p-y	2,955	-	-	-	-	Surgery	9.2 years / 138,797 p-y	14,309	-	-	-	-	0.68	1.12	(0.64 – 1.97)
Huo et al. (2009)	3,420,432 p-y	Mixed	-	211,882	2,602	1.2%	1.08	(1.04 – 1.12)	NR	-	424,028	4,949	1.2%	1.04	(1.01 – 1.07)	0.13	-	-
Johnstone et al. (1998)	10.9 years	Definitive	-	164	3	1.8%	-	-	-	-	-	-	-	-	-	-	-	-
Liauw et al. (2006)[1]	10.5 years	BT + EBRT	10.2 years	223	1	0.4%	-	-	-	-	-	-	-	-	-	-	-	-
		BT alone	11.4 years	125	1	0.8%	-	-	-	-	-	-	-	-	-	-	-	-
Moon et al. (2006)[1]	10 years	Mixed	-	46,226	341	0.7%	-	-	NR	-	94,541	638	0.7%	-	-	-	-	-
Rapiti et al. (2008)[1]	7.4 years / 3,798 p-y	External	7.8 years	264	9	3.4%	4.0	(1.8 – 7.6)	Mixed	7.3 years	870	4	0.5%	0.5	(0.1 – 1.4)	-	-	-

[1]Cases of CRC diagnosed within 5 years of Pca diagnosis/radiotherapy for Pca not included; [2]Cases of CRC diagnosed within 1 year of Pca diagnosis/radiotherapy for Pca not included; [3]Cases of CRC diagnosed within 6 months of Pca diagnosis/radiotherapy for Pca not included; [4]Cases of CRC diagnosed within 2 months of Pca diagnosis/radiotherapy for Pca not included.

Table 107 Incidence of rectal cancer in men who have received radical radiotherapy for prostate cancer

Abbreviations: SIR = standardized incidence ratio; CI = confidence interval; p-y = person years; BT = brachytherapy; EBRT = external beam radiotherapy; NR = not reported

Study	Overall follow-up (median / person-years)	Radiotherapy group							No radiotherapy group							Difference between groups		
		Treat-ment	Median follow-up	Number of pa-tients	Case s seen	Raw inci-dence (cal-cula-ted)	SIR	SIR 95% Cis	Treat-ment	Median follow-up	Number of pa-tients	Cases seen	Raw inci-dence (calcu-late-ed)	SIR	SIR 95% Cis	p-value	Rela-tive risk	Relative risk 95% Cis
Abdel-Wahab et al. (2008)[2]	-	EBRT, BT or both	4.7 years	67,719	286	0.4%	-	-	No RT or surgery	4.3 years	40,733	164	0.2%	-	-	-	-	-
Abdel-Wahab et al. (2009)[2]	-	Surgery & RT	-	5,044	32	0.6%	-	-	Surgery alone	-	80,157	302	0.4%	-	-	-	-	-
Bae et al. (2011)	-	NR	-	24	2	8.3%	-	-	-	-	-	-	-	-	-	-	-	-
Baxter et al. (2005)[1]	-	EBRT (with or without surgery)	7.9 years	30,552	124	0.4%	-	-	Surgery alone	8.3 years	55,263	143	0.3%	-	-	<0.01	-	-
Brenner et al. (2000)[1]	-	NR	218,341 p-y	51,584	198	0.4%	-	-	Surgery	312,499 p-y	70,539	298	0.4%	-	-	0.87	-	-
Bhojani et al. (2010)	-	EBRT	-	9,390	29	0.3%	-	-	Surgery	-	8,455	37	0.4%	-	-	-	-	-
Ciezki et al. (2012)	-	EBRT & RP	**9.2** years	20,545	-	1.1%	-	-	Surgery	20 years	127,189	-	0.7%	-	-	-	-	-
Henry et al. (2012)	-	BT alone	Range: 6-17 years	1,805	11	0.6%	-	-	-	-	-	-	-	-	-	-	-	-
Hinnen et al. (2011) & van Vulpen et al. (2011)	7.5 years / 14,380 p-y	BT	7.1 years	1,187	9	0.8%	0.90	(0.41 – 1.72)	Surgery	8.7 years	701	9	1.3%	1.50	(0.68 – 2.85)	-	-	-
Huang et al. (2011)	-	Mixed	6.9 years / 21,276 p-y	2,955	-	-	-	-	Surgery	9.2 years / 138,797 p-y	14,309	-	-	-	-	0.83	0.91	(0.39 – 2.14)
Huo et al. (2009)	3,420,432 p-y	Mixed	-	211,882	941	0.4%	1.04	(0.97 – 1.11)	NR	-	424,028	1,687	0.4%	0.95	(0.91 – 1.00)	0.03	-	-
Kendal et al. (2006a & 2006b)	-	EBRT	5.1 years	63,831	251	0.4%	-	-	Surgery	-	167,583	635	0.4%	-	-	-	-	-
									None	-	89,923	298	0.3%	-	-	-	-	-

Study	Overall follow-up (median / person-years)	Radiotherapy group							No radiotherapy group							Difference between groups		
		Treat-ment	Median follow-up	Number of pa-tients	Case s seen	Raw inci-dence (cal-cula-ted)	SIR	SIR 95% Cis	Treat-ment	Median follow-up	Number of pa-tients	Cases seen	Raw inci-dence (calcu-late-ed)	SIR	SIR 95% Cis	p-value	Rela-tive risk	Relative risk 95% Cis
Johnstone et al. (1998)	10.9 years	Definitive	-	164	1	0.6%	-	-	-	-	-	-	-	-	-	-	-	-
Lesperance et al. (2008)	3.3 years (mean)	EBRT	3.2 years (mean)	183	1	0.5%	-	-	-	-	-	-	-	-	-	-	-	-
		BT	3.1 years (mean)	50	0	0.0%	-	-	-	-	-	-	-	-	-	-	-	-
Liauw et al. (2006)[1]	10.5 years	BT + EBRT	10.2 years	223	1	0.4%	-	-	-	-	-	-	-	-	-	-	-	-
		BT alone	11.4 years	125	0	0.0%	-	-	-	-	-	-	-	-	-	-	-	-
Margel et al. (2009 & 2011)[3]	11.2 years	NR	-	2,163	26	1.2%	1.81	(1.2 – 2.5)	Surgery	-	6,762	41	0.6%	1.22	(0.85 – 1.65)	-	-	-
Moon et al. (2006)[1]	10 years	Mixed	-	46,226	265	0.6%	-	-	NR	-	94,541	421	0.4%	-	-	-	-	-
Neugut et al. (1997)[3]	-	NR	-	34,889	101	0.3%	-	-	NR	-	106,872	310	0.3%	-	-	-	-	-
Nieder et al. (2008)[3]	4.1 years	EBRT	-	93,059	418	0.4%	0.99	(0.9 – 1.1)	Surgery	-	109,178	379	0.3%	0.91	(0.82 – 1.01)	-	1.26	(1.08 – 1.47)
		BT	-	22,889	38	0.2%	0.68	(0.49 – 0.93)								-	1.08	(0.77 – 1.54)
		BT + EBRT	-	17,956	48	0.3%	0.86	(0.65 – 1.14)								-	1.21	(0.89 – 1.65)
Pawlish et al. (1997)	60,000 p-y	NR	-	2,308	10	0.4%	0.95	(0.45 – 1.74)	NR	-	7,481	26	0.3%	0.86	(0.56 – 1.25)	-	-	-
Rapiti et al. (2008)[1]	7.4 years / 3,798 p-y	External	7.8 years	264	2	0.8%	2.0	(0.2 – 7.2)	Mixed	7.3 years	870	4	0.5%	1.2	(0.3 – 3.1)	-	-	-

[1]Cases of CRC diagnosed within 5 years of Pca diagnosis/radiotherapy for Pca not included; [2]Cases of CRC diagnosed within 1 year of Pca diagnosis/radiotherapy for Pca not included; [3]Cases of CRC diagnosed within 6 months of Pca diagnosis/radiotherapy for Pca not included; [4]Cases of CRC diagnosed within 2 months of Pca diagnosis/radiotherapy for Pca not included.

Figure 47 Forest plot of the relative risk of bowel cancer in male prostate cancer patients treated with radiotherapy compared to no radiotherapy

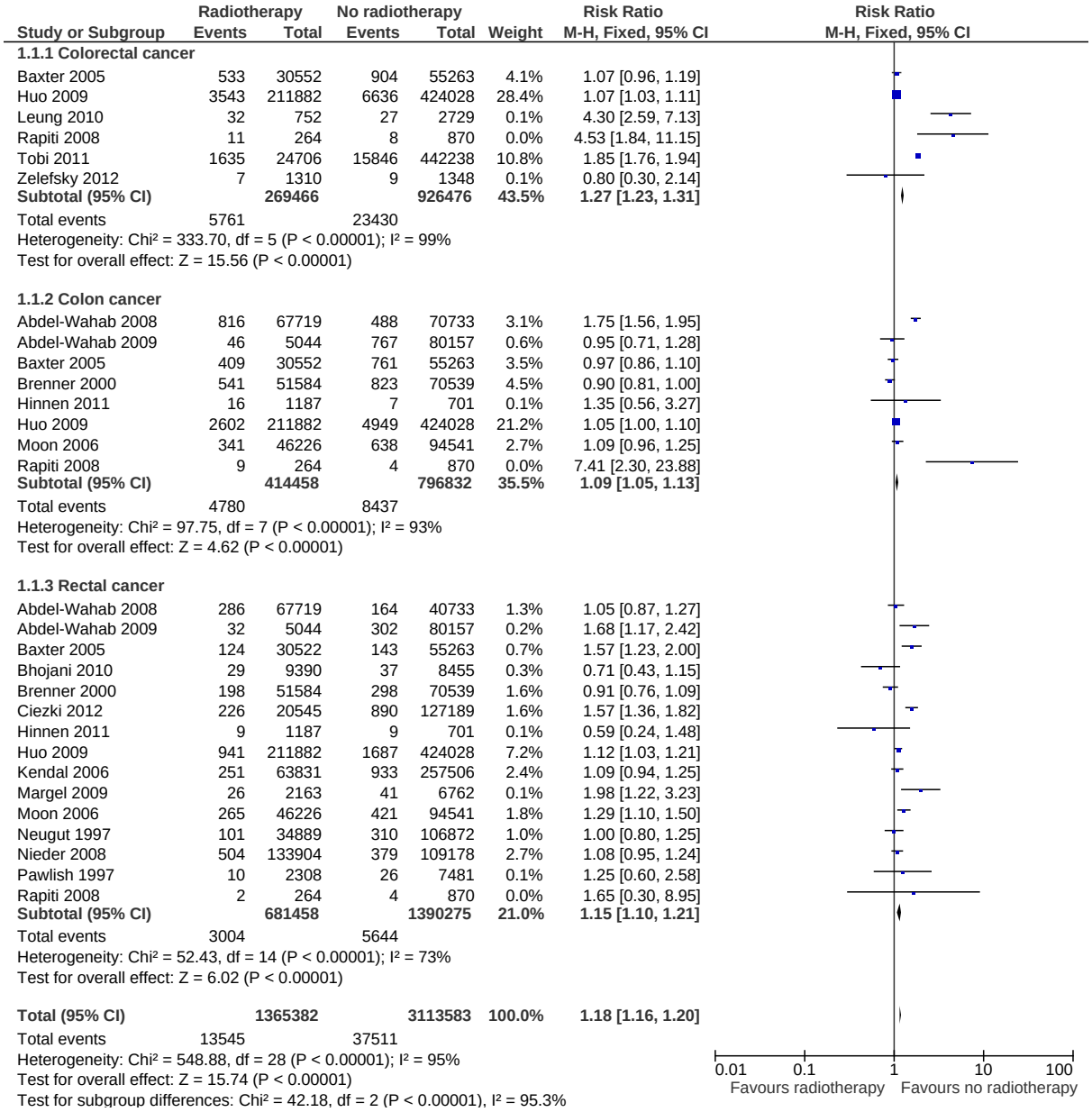


Figure 48 Forest plot of the relative risk of bowel cancer in male prostate cancer patients treated with radiotherapy compared to no radiotherapy, where cancers occurring within 5 years of diagnosis are excluded

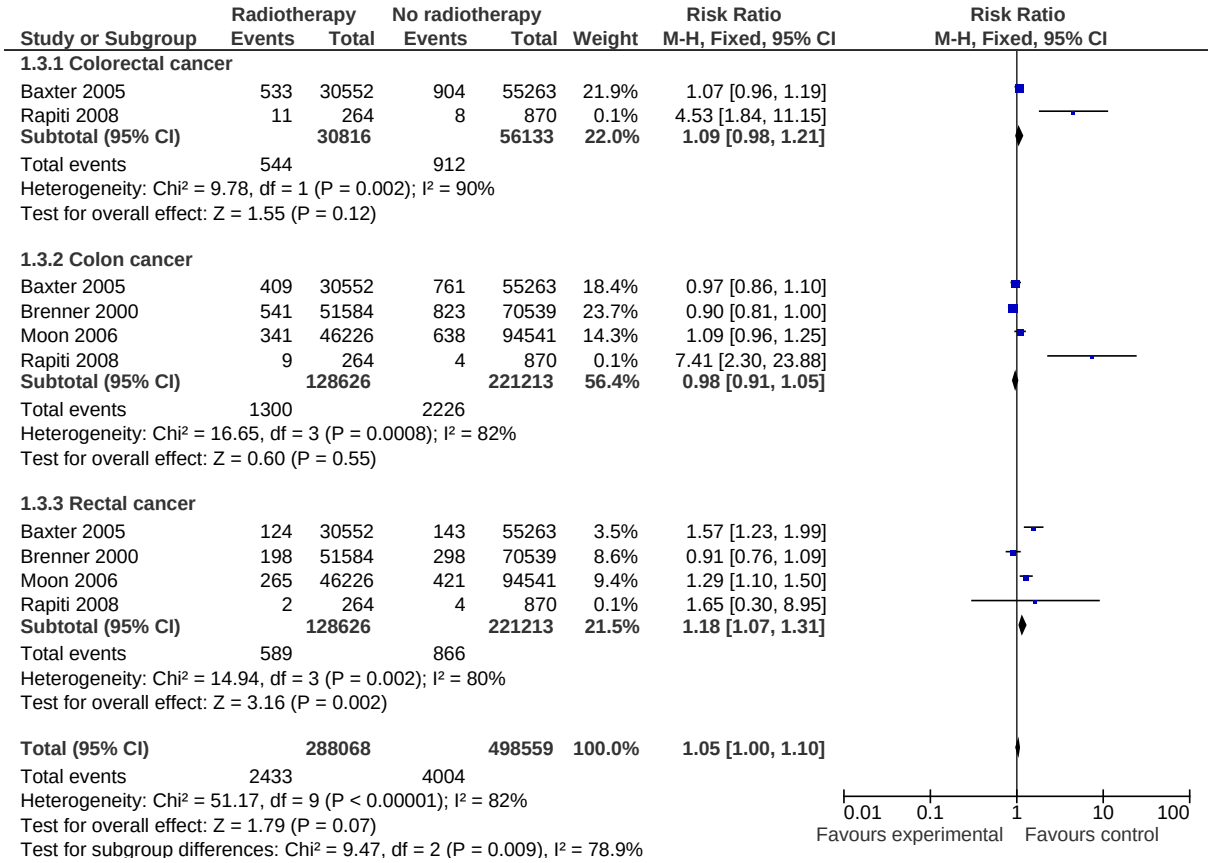


Table 108 Summary of study characteristics

Abbreviations: RCT = randomised controlled trial; RT = radiotherapy; EBRT = external beam radiotherapy; BT = brachytherapy; SIR = standardised incidence ratio reference; Pca = prostate cancer

Study	Study type	Country/ies	Study period	Number of RT patients	Median age (range)	Inclusion criteria	Exclusion criteria	Radiotherapy (RT)	Data source	Additional comments
Abdel-Wahab et al. (2008)	Retrospective cohort	US	1973-2002	67,719	70 years (34-99)	Men diagnosed with locoregional Pca as first malignancy	Patients with follow-up < 1 year, aged < 20 years, or who developed CRC within 1 year of Pca diagnosis	RT only (EBRT, BT or both)	Surveillance, Epidemiology, and End Results (SEER) registry	
Abdel-Wahab et al. (2009)	Retrospective cohort	US	1988-2002	5,044	63 years	Men diagnosed with locoregional Pca as first malignancy	Patients with follow-up < 1 year or who developed CRC within 1 year of Pca diagnosis	Surgery & RT	Surveillance, Epidemiology, and End Results (SEER) registry	
Bae et al. (2011)	Retrospective cohort	Australia	1998-2010	NR	NR	NR	None reported	NR	NR	Only abstract available
Bartkowiak et al. (2007)	Cohort	Germany	1981-2007	1,155	NR	Cancer patients undergoing RT	Follow-up ≥ 1 year	NR	Radiation Oncology Department, University Hospital Ulm	
Baxter et al. (2005)	Retrospective cohort	US	1973-1994	30,552	70 years	Men with invasive, non-metastatic, microscopically-confirmed Pca	Aged < 18 or > 80 years, follow-up < 5 years, previous CRC, or CRC within 5 years	EBRT	Surveillance, Epidemiology, and End Results (SEER) registry	
Bhojani et al. (2010)	Retrospective cohort	Canada	1983-2003	9,390	70 years (43-93)	Men in Pca treatment database	None reported	EBRT	Quebec Health Plan insurance company	
Brenner et al. (2000)	Retrospective cohort	US	1973-1993	51,584	70 years (mean)	Men with Pca as primary tumour	CRC within 2 months after Pca diagnosis	NR	Surveillance, Epidemiology, and End Results (SEER) registry	
Ciezki et al. (2012)	Retrospective cohort	US	1973-2008	147,734	67 years	Men with PCa treated with RP	Patients with < 3 years follow-up or cancer < 3 years after diagnosis	EBRT + RP	Surveillance, Epidemiology, and End Results (SEER) registry	Only abstract available
Gutman et al. (2006)	Cohort	NR	1995-2004	1,351	67 years	T1b-T3a Pca patients undergoing BT	None reported	BT; Pd-103 (125 Gy) or I-125 (110 Gy), prior to EBRT (n=699, 4-fold conformal) or alone (n=652)	American Joint Committee on Cancer	
Henry et al. (2012)	Retrospective cohort	UK	1995-2005	1,805	NR	Localised PCa	None reported	BT I^{125} monotherapy	UK cancer registry: NYCRIS	Only abstract available
Hinnen et al. (2011) & van Vulpen et al. (2011)	Retrospective cohort	The Netherlands	1989-2005	1,187	67 years	PCa patients undergoing brachytherapy or prostatectomy monotherapy	None reported	I-125 BT monotherapy, 145 Gy dose	University Medical Centre Utrecht & Netherlands Cancer Institute (RT) & Dutch Cancer Registry (control/SIR)	
Huang et al. (2011)	Cohort	US	1984-2005	2,955	71 years	Clinically localised PCa	Patients who received adjuvant or salvage RT after radical prostatectomy	Conventional EBRT/2-D RT; BT; combination of 2-D RT and BT; or 3-D	William Beaumont Hospital, Michigan (RT) & Metropolitan Detroit Cancer Surveillance	

								conformal and/or IMRT	System (control)	
Huo et al. (2009)	Retrospective cohort	US	1973-2005	211,882	NR	Men with first PCa	Those with no follow-up time or whose age, race, or RT therapy was unknown	EBRT or BT or other	Surveillance, Epidemiology, and End Results (SEER) registry	
Johnstone et al. (1998)	Retrospective cohort	US	1974-1987	164	67 years (mean)	Men with localised PCa	None reported	Definitive, mostly 4-field, median of 66.7 Gy	University of California (RT) & Connecticut Tumor Registry (control/SIR)	
Kendal et al. (2006a & 2006b)	Retrospective cohort	Canada	1973-2001	33,831	71 years (mean)	Pathologically-confirmed, invasive, only or first primary		EBRT	Surveillance, Epidemiology, and End Results (SEER) registry	
Lesperance et al. (2008)	Retrospective cohort	US	1999-2005	233	(47-98)	T1b-T3+ PCa patients undergoing EBRT or BT	In situ, other forms of cancer, or receiving palliative RT for metastatic PCa	EBRT (64-76 Gy) or BT (transperineal I-125 or Pd-103)	Department of Defense medical centre's tumor registry	
Leung et al. (2010)	Retrospective cohort	US	1993-2008	752	NR	NR	Aged < 16 years	NR	Virginia Commonwealth University hospital tumour registry	Only abstract available
Liauw et al. (2006)	Cohort	US	1987-1994	348	70 years (47-91)	Biopsy-proven PCa treated with BT	CRC within 5 years of RT	Supplemental EBRT (45 Gy, daily for 5 days/week) prior to I-125 or Pd-103 BT; or BT monotherapy	Seattle Prostate Institute (RT) & Surveillance, Epidemiology, and End Results (SEER) registry (control/SIR)	
Margel et al. (2009 & 2011)	Retrospective cohort	Israel	1980-2005	2,163	70 years	Localised PCa	Those who developed CRC < 6 months after diagnosis	NR	Israeli National Cancer Registry (INCR)	Only abstract available
Moon et al. (2006)	Retrospective cohort	US	1973-1999	46,226	NR	Men with histologically-confirmed incident PCa	Follow-up < 5 years after diagnosis or CRC within 5 years of PCa diagnosis	Mixed	Surveillance, Epidemiology, and End Results (SEER) registry	
Movsas et al. (1998)	Retrospective cohort	US	1973-1993	543	70 years (mean)	Localised PCa, stage T1-T3	None reported	Conformal or conventional EBRT	Fox Chase Centre (RT) & Connecticut Tumor Registry (control/SIR)	
Neugut et al. (1997)	Retrospective cohort	US	1973-1990	34,889	69 years (mean)	Diagnosis of PCa	CRC within 6 months of PCa diagnosis	NR	Surveillance, Epidemiology, and End Results (SEER) registry	
Nieder et al. (2008a & 2008b)	Retrospective cohort	US	1988-2003	133,904	NR	ICD-O-3 site code C619 PCa; stage T1-T4N+	Age < 40 years or who developed CRC < 6 months after diagnosis	EBRT or BT alone or in combination	Surveillance, Epidemiology, and End Results (SEER) registry	
Pawlish et al. (1997)	Retrospective cohort	US	1973-1993	2,308	NR	Firs t primary microscopically-confirmed invasive PCa diagnosis	In situ lesions, sarcoma of the prostate, or lost to follow-up < 2 months after diagnosis	NR	Surveillance, Epidemiology, and End Results (SEER) registry	
Pickles et al. (2002a & 2002b)	Retrospective cohort	Canada	1984-2000	9,890	72 years (38-89	Invasive first primary PCa	No follow-up or CRC within 2 months of RT	Radical EBRT ≥45 Gy	British Columbia Tumor Registry	
Rapiti et al. (2008) & We-	Retrospective cohort	Switzerland	1980-2003	264	68 years (mean)	Localised PCa & no prior invasive cancer	Invasive cancer prior to PCa or who developed	External, 65-66 Gy	Geneva Cancer Registry	

ber et al. (2009)							CRC within 5 years of RT			
Sharp et al. (2012)	Retrospective cohort	US	2000-2009	451	64 years (mean) (46-86)	Low-intermediate risk PCa	None reported	Permanent BT mono-therapy I^{125} to 145 Gy	Tertiary cancer care centre records	
Tobi et al. (2011)	Retrospective cohort	NR	1999-2006	NR	NR	Diagnosis of PCa	None reported	NR	VHA National Database	Only abstract available
Zelefsky et al. (2012)	Retrospective cohort	US	1998-2001	2,658	NR	Clinically localised PCa		IMRT EBRT (n=897) or BT (n=413) (mixed types)	Surveillance, Epidemiology, and End Results (SEER) registry	
Study	**Study type**	**Country /ies**	**Study period**	**Number of RT patients**	**Median age (range)**	**Prostate cancer characteristics**	**Exclusion criteria**	**Radiotherapy (RT)**	**Sigmoidoscopy**	**Additional comments**
Bolin et al. (2001)	Cohort	Australia	NR	277	NR	Patients receiving prostate RT	None reported	NR	16 & 36 months following RT	Only abstract available
Goldner et al. (2007)	Cohort	Germany & Austria	1999-2002	166	71 years (52-81)	Primary localised (T1-T3Nx-N0M0) PCa	None reported	3-D conformal EBRT ≤74 Gy (2 Gy/fraction)	Flexible endoscopy; performed prior to RT and at 12 and/or 24 months after RT	
Karamanolis et al. (2009)	Cohort	NR	NR	28	68 years (mean)	Asymptomatic patients treated with RT for PCa	None reported	3-D planned conformal 4-field; 72-74 Gy of total dose	Flexible endoscopy; performed every 6 months for up to 2 years following RT	Only abstract available
O'Brien et al. (2004)	Cohort	Australia	1995	20	NR	Patients undergoing RT for PCa	None reported	Local field non-conformal 65 Gy in 33 fractions	Flexible endoscopy; performed every 6 months for up to 3 years after RT	
Wachter et al. (2000)	Cohort	European	1994-1996	44	68 years (mean; 49-87)	Patients undergoing RT for localised PCa	None reported	3-D planned conformal, 66 Gy	Flexible rectosigmoidoscopy; performed every 3-6 months after RT	

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Excluded studies

Modeling study

Bezak, E et al. Risk of rectal second cancer following prostate radiotherapy. Radiotherapy and Oncology 2007; 84: S68-S69.

Editorial

Brenner, DJ. Induced second cancers after prostate-cancer radiotherapy: no cause for concern? International Journal of Radiation Oncology, Biology, Physics 2006; 65(3): 637-639.

Letter to the Editor

Jahraus, CD et al. Inflammation's role in rectal cancer following prostate radiotherapy, and emerging evidence for a protective role for balsalazide. Gastroenterology 2005; 129(2): 770-772.

Review article

Bostrom, PJ and Soloway, MS. Secondary cancer after radiotherapy for prostate cancer: should we be more aware of the risk?. [Review] [42 refs]. European Urology 2007; 52(4): 973-982.

Muller, AC et al. Risk of second malignancies after prostate irradiation?. [Review] [51 refs]. Strahlentherapie und Onkologie 2007; 183(11): 605-609.

Sountoulides, P et al. Secondary malignancies following radiotherapy for prostate cancer. Therapeutic Advances in Urology 2010; 2(3): 119-125.

Case series

Cho, KJ and Christie, D. Rectosigmoid cancer after radiotherapy for prostate cancer can be detected early and successfully treated. Australasian Radiology 2006; 50(3): 228-232.

Case-control study

Hollingdale, AE et al. Colorectal tumours in patients after radical radiotherapy for prostate cancer. Clinical Oncology 2007; 19(3): S31-S31.

No radiotherapy

McCredie, M et al. Second primary cancers following cancers of the kidney and prostate in New South Wales (Australia), 1972-91. Cancer Causes Control 1996; 00: 337-344.

Rogal, SS, Pinsky, PF, and Schoen, RE. Relationship Between Detection of Adenomas by Flexible Sigmoidoscopy and Interval Distal Colorectal Cancer. Clinical Gastroenterology and Hepatology 2013; 11(1): 73-78.

No prostate cancer

Dorr, W et al. Second primary tumours after radiotherapy for malignancies. Strahlentherapie und Onkologie 2002; 178(7):357-362.

No relevant outcomes reported

Bae S., A. Understanding second primary colorectal cancer in the modern era of prevalent screening and imaging. Asia-Pacific Journal of Clinical Oncology 2011; Conference(var.pagings): 122.

Brenner, DJ et al. Prostate radiotherapy is associated with second cancers in many organs, not just the colorectum. And Reply. Gastroenterology 2005; 129(2): 773-775.

De Gonzalez, AB. Proportion of second cancers attributable to radiotherapy treatment in adults: A cohort study in the US SEER cancer registries. The Lancet Oncology 2011; 12(4): 353-360.

De Gonzalez, AB. Proportion of second cancers attributable to radiotherapy treatment in adults: A cohort study in the US SEER cancer registries. The Lancet Oncology 2011; 12(4): 353-360.

Housman, DM. Incidence and predictors of secondary cancer development after high-dose IMRT and image-guided brachytherapy for the treatment of localized prostate cancer. International Journal of Radiation Oncology Biology Physics 2011; Conference(var.pagings): 2-S566.

Huang, J et al. Rates of Secondary Primary Cancers after Definitive Treatment for Prostate Cancer using Modern Radiation Therapy Techniques. International Journal of Radiation Oncology Biology Physics 2009; 75(3): S296-S296.

Jao, SW et al. Colon and anorectal cancer after pelvic irradiation. Diseases of the Colon & Rectum 1987; 30(12): 953-958.

Reddy, C et al. Colorectal cancer screening rates in a medicare cohort with preexisting malignancies. Gastroenterology 2010; Conference(var.pagings): 5-S194.

Reddy, C et al. Second malignancies after definitive radiotherapy for prostate cancer. Brachtherapy 2010; Conference(var.pagings): S78

Teslova, T. Comparison of the incidence of secondary cancers after IMRT, brachytherapy and surgery for the treatment of prostate cancer. Journal of Urology 2012; Conference(var.pagings): 4

Williams, HRT et al. The significance of rectal bleeding after pelvic radiotherapy. Alimentary Pharmacology & Therapeutics 2005; 21(9): 1085-1090.

Zelefsky, MJ. Comparison of long-term incidence of secondary cancer development and mortality for brachytherapy versus external beam radiotherapy for prostate cancer. Brachytherapy 2010; Conference(var.pagings): S30-S31.

No relevant outcomes reported in English language

Hausmann, R. Rectal cancer - Radiotherapy for prostate cancer moderately increases the sickness risk. Zeitschrift fur Gastroenterologie 2006; 44(2): 156-156.

3.8.2 Sexual dysfunction

In men with prostate cancer, what are the effective interventions for sexual dysfunction (either caused by radical treatment or the disease itself)?

Short summary

There is good evidence, from placebo controlled randomised trials, that PDE5 inhibitors can improve erectile function in men with erectile problems after radical treatment for prostate cancer. Sildenafil (Incrocci et al. 2001) and tadalafil (Incrocci et al. 2006) have shown effectiveness for the treatment of erectile dysfunction after external beam radiotherapy. Sildenafil (Carson et al. 2002), tadalafil (Montorsi et al. 2004) and vardenafil (Brock et al. 2003) have shown effectiveness for the treatment of erectile dysfunction after nerve sparing radical prostatectomy. The literature search did not find any trials directly comparing different PDE5 inhibitors in men with prostate cancer.

In a cohort study (Stephenson *et al.* 2005) and a large case series (Schover *et al.* 2002b) of men after therapy for localised prostate cancer about half had tried treatment for erectile dysfunction. Sildenafil was the most widely used treatment. Invasive treatments (penile prostheses, penile injection) tended to be more effective but were less widely used; psychosexual counselling was the least effective.

A meta-analysis of placebo controlled trials in patients with erectile dysfunction of mixed aetiology concluded prostaglandin E1 was beneficial (Urciuoli *et al.* 2004). Three RCTs examined psychosexual counselling in men with prostate cancer (Canada *et al.* 2005; Giesler *et al.* 2005; Lepore *et al.* 2003), but none showed an improvement in sexual function.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Men with prostate cancer	Any interventions for sexual dysfunction	No interventions	• Sexual function • Quality of life

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

Evidence Summary

In a systematic review of 14 observational studies (Dubbelman *et al.* 2006) between 64% and 100% of men were potent before radical prostatectomy (RP). The reported rates of postoperative potency were 18% to 76% for bilateral nerve-sparing RP, 13% to 56% for unilateral nerve-sparing RP and 0% to 34% for non-nerve sparing RP.

There is good evidence, from placebo controlled randomised trials, that PDE5 inhibitors can improve erectile function in men with erectile problems after radical treatment for prostate cancer.

Sildenafil (Incrocci *et al.* 2001) and tadalafil (Incrocci *et al.* 2006) have shown effectiveness for the treatment of erectile dysfunction after external beam radiotherapy. Sildenafil (Carson *et al.* 2002), tadalafil (Montorsi *et al.* 2004) and vardenafil (Brock *et al.* 2003) have shown effectiveness for the treatment of erectile dysfunction after nerve sparing radical prostatectomy. The literature search did not find any trials directly comparing different PDE5 inhibitors in men with prostate cancer.

In a cohort study (Stephenson *et al.* 2005) and large case series (Schover *et al.* 2002b) of men after therapy for localised prostate cancer about half had tried ED treatment. Treatment of ED met with limited success. Sildenafil was the most widely used treatment. Invasive treatments

(penile prostheses, penile injection) tended to be more effective but were less widely used; psychosexual counselling was the least effective.

A meta-analysis of placebo controlled trials in patients with ED of mixed aetiology concluded prostaglandin E1 was beneficial (Urciuoli *et al.* 2004). Three RCTs tested variations on psychosexual counselling in men with prostate cancer (Canada *et al.* 2005; Giesler *et al.* 2005; Lepore *et al.* 2003), but none showed an improvement in sexual function.

Perceived helpfulness

In the cohort study of Stephenson and co-workers (Stephenson *et al.* 2005), the perceived helpfulness of ED treatment was greatest for penile prostheses, penile injections and vacuum devices (around 70% of patients who tried them found them helpful). 47% of patients who tried sildenafil found it helpful, compared to 40% of patients who tried psychosexual counselling

A review of case series estimated that, despite apparent effectiveness, between 30% and 50% of patients after RP discontinue the use of sexually assistive aids within a year (Matthew *et al.* 2005). An Israeli study (Baniel *et al.* 2001), which followed a cohort of patients through their treatment of post RP erectile dysfunction, noted that while the vacuum device was often effective few patients continued to use it at home.

Quality of life

A review of case estimated that between 33% and 82% in patients with erectile dysfunction after RP are distressed (Matthew *et al.* 2005). A prospective study (Perez, 1997) compared QOL and satisfaction with sex life in men after RP who did and did not use treatment for ED. ED treatment was not associated with improved overall QOL, but was associated with improved the sexual items on the QOL scale.

Adverse effects

The most common adverse effects associated with PDE-5 inhibitors were headache, flushing, rhinitis and dyspepsia (Incrocci *et al.* 2001) (Montorsi *et al.* 2004; Brock *et al.* 2003).

The use of PGE1 was associated penile pain, minor urethral trauma (for intraurethral application) and dizziness (Urciuoli *et al.* 2004). At least four percent of couples enrolled in trial of psychosexual counselling (Canada *et al.* 2005) were not comfortable with the sexual explicit topics of the program and withdrew from the trial.

Estimate of the adverse effects associated with vacuum devices and penile prostheses rely on evidence from case series. In the series reported by Baniel and co workers (Baniel *et al.* 2001), 7% of patients discontinued vacuum therapy due to pain in the area of the constriction ring.

Evidence tables

Systematic reviews of RCTs

(Carson *et al.* 2002)

Design: Systematic review of RCTs, evidence level: 1+

Country: , setting: Other

Inclusion criteria 11 RCTs of sildenafil for ED in patients of broad spectrum aetiology. 109/2667 patients (4%) had ED due to radical prostatectomy.

Exclusion criteria -

Population number of patients = 109.

Interventions The studies included a 4 week baseline period during which ED was assessed, and then patients were randomised to either placebo or sildenafil for 12 weeks. Initial dose was 50 mg but dose could be adjusted up to 100 mg or down to 25 mg based on efficacy or tolerability. Patients were instructed to take their tablet 1 hour before sexual activity with a maximum of 1 dose per day.

Outcomes International Index of Erectile Function (IIEF), a global efficacy question (did treatment improve your erections?). In 6/11 trials patients maintained a log of their sexual activity and recorded the proportion of successful sexual attempts.

Follow up Length of follow up not reported. All patients had at least a baseline evaluation and one evaluation after the start of treatment.

Results IIEF results for the post-prostatectomy patients are reported in this appraisal. The IIEF global score ranges from 0 to 30, mean values are presented for each group. Scores on IIEF question 3 (ability to achieve erections) and question 4 (ability to maintain erections) are measured on a scale ranging from 1(never/almost never) to 5 (always or almost always). Mean scores are presented for each group.

COMPARISON in Men with erectile dysfunction after radical prostatectomy	Sildenafil	Placebo	
International index of erectile function	15.7	8.6	in favour of sildenafil (p<0.001, ANCOVA)
Ability to achieve erections	2.3	1.1	in favour of sildenafil (p<0.001, ANCOVA)
Ability to maintain erections	2.4	1.3	in favour of sildenafil (p<0.001, ANCOVA)

General comments No data about adverse events are presented.

(Urciuoli *et al.* 2004)

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

Country: International, setting: Tertiary care

Inclusion criteria Randomised controlled trials comparing prostaglandin E1 (PGE1) and placebo treatment in participants with erectile dysfunction (ED) of different aetiology were considered. 4 trials met the inclusion criteria, 2 of these were used for the meta-analysis. It was not clear what proportion of patients had ED because of prostate cancer. In the 2 trials included in the meta-analysis, approximately 30% of patients had ED due to major surgery or trauma.

Exclusion criteria -

Population -

Interventions Colli (1994) intracavernous injection of PGE1 (5 or 10 mcg) or placebo.

Hellstrom (1996) transurethral PGE1 (125 to 1000 mcg) or placebo.

Padma-Nathan (1997) transurethral PGE1 (125 to 1000 mcg) or placebo.

Williams (1998) transurethral PGE1 (125 to 1000 mcg) or placebo.

Outcomes At least one successful sexual intercourse attempt, adverse effects.

Results Priapism was reported in one patient treated with PGE1 and hypotension in one patient treated with placebo.

The authors concluded "PGE1 was beneficial for many participants with ED of different aetiology. Adverse effects were proportional to dosage, albeit never serious."

COMPARISON in Men with erectile dysfunction	Prostaglandin E1 (alprostadil)	Placebo	
One or more successful sexual intercourse attempts	345/528 (2 studies)	101/573 (2 studies)	favours PGE1, OR 7.22 [95% CI 5.68 to 9.18]
Penile pain	170/567 (2 studies)	18/589 (2 studies)	favours placebo, OR 7.39 [95% CI 5.40 to 10.12]
Minor urethral trauma	26/567 (2 studies)	6/589 (2 studies)	favours placebo, OR 3.79 [95% CI 1.88 to 7.65]
Dizziness	9/567 (2 studies)	1/567 (2 studies)	favours placebo, OR 5.57 [95% CI 1.79 to 17.37]

General comments The 2 studies used in the meta-analysis included only patients who showed response to PGE1 in an initial test. This biases the effectiveness results in favour of PGE1.

Randomized controlled trials

(Canada *et al.* 2005)

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

Country: United States, setting: Tertiary care

Inclusion criteria Men who had been treated with either surgery or EBRT for localised prostate cancer at a single centre. Treatment was between 3 months and 5 years before study entry. Men had to have been living with a partner who was willing to participate, for at least a year.

Exclusion criteria Men currently on hormonal therapy, men able to achieve an erection sufficient for intercourse without medical or mechanical assistance on more than 50% of attempts, men currently using a satisfactory treatment for ED.

Population number of patients = 168.

Interventions A four session psycho-sexual counselling program. Men were randomised to either attend the program with their partner or alone.

Outcomes International Index of Erectile Function (IIEF), women completed the Female Sexual Function Index (FSFI). Another questionnaire was used to evaluate use of treatment for ED. The Brief Symptom Inventory was used to measure psychological distress and the Dyadic Adjustment Scale was used to measure marital satisfaction. Male patients completed the urinary and bowel symptom scales of the UCLA prostate cancer index. Health related quality of life was measured using the SF-36 Short Form Health Survey.

Follow up Patients and their partners completed questionnaires at the end of the counselling program, and again at 3 months and 6 months later. 33 couples dropped out before the end of the counselling program (39%). In 19 of these couples, the reason for withdrawal was not known.

Results The authors report that there was no statistical difference in the outcomes of the men-only and couples group. Participants completing the intervention showed improvement in male overall distress ($P < 0.01$), male global sexual function ($P < 0.0001$), and female global sexual function ($P < 0.05$) at 3-month follow-up, but regression toward the baseline levels was noted at 6-month follow-up. The use of ED treatments increased from 31% at the time of study entry to 49% at the 6-month follow-up ($P = 0.003$).

COMPARISON in Men with erectile dysfunction after radical prostatectomy or EBRT	Psycho-sexual counselling (couple)	Psycho-sexual counselling (man only)	
International index of erectile function	not reported	not reported	authors report no significant difference
Female Sexual Function Index	At baseline : mean 12.37, SD 10.01; At 6 months : mean 14.80, SD 10.21	At baseline : mean 19.68, SD 9.97; At 6 months : mean 23.71, SD 8.34	statistically significant in favour of the men only group

Psychological distress	not reported	not reported	authors report no significant difference
Marital happiness	not reported	not reported	authors report no significant difference

General comments Poorly reported, figures not given for treatment outcomes in the 2 groups. Combined figures are used to assess the overall effectiveness of the counselling intervention, but the study is not well designed to answer this question.

(Giesler *et al.* 2005)

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

Country: United States, setting: Tertiary care

Inclusion criteria Patients were required to have a diagnosis of T1a-T2c prostate cancer, treated (or about to be treated) with surgery, EBRT or brachytherapy. Men had to have a partner who was willing to participate. Age over 18 and fluency in English.

Exclusion criteria -

Population number of patients = 198.

Interventions Participants were randomised to a psycho educational intervention or to standard care. Participants in the intervention arm met once each month for 6 months with an oncology nurse, who helped patients identify their quality-of-life needs using an interactive computer program. The nurse then provided education and support tailored to participants' needs.

Outcomes Disease-specific quality of life, including sexual, urinary, and bowel outcomes and cancer worry was measured using the Prostate Cancer Quality of Life Instrument (PCQoL).

Depression was measured using the Center for Epidemiologic Studies Depression Scale. Marital happiness was assessed using the Dyadic Adjustment Scale and general quality of life using the SF-36 questionnaire.

Follow up Outcomes data were collected prior to randomization and again at 4 months, 7 months, and 12 months post treatment. 14/99 couples (14%) dropped out of the study before completing the intervention.

Results -

COMPARISON in Prostate cancer	Psycho-sexual counselling (couple)	Standard care	
Prostate cancer related quality of life (PCQoL)	No overall score reported	No overall score reported	Authors claim in favour of the intervention for sexual function item (p =0.05 at 4 months) and cancer worry item (p= 0.03 at 12 months) (probably not signifi-

			cant given multiple comparisons)
Quality of life (SF-36)	No overall score reported	No overall score reported	Authors report no significant difference
Marital happiness	No overall score reported	No overall score reported	Authors report no significant difference
Depression	No overall score reported	No overall score reported	Authors report no significant difference

General comments Poorly reported. Multiple comparisons made on the individual items of the PCQoL and SF-13 scales (no correction for multiple comparisons). No overall scores for the individual scales are reported.

(Incrocci *et al.* 2001)

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

Country: Netherlands, the, setting: Tertiary care

Inclusion criteria Men with ED following EBRT for PCa were identified from the records of a single institution (1996 to 1999), and invited to participate. None of the patients had used treatment for their ED. All were in a stable relationship and consented to attempt sexual activity at least once a week.

Exclusion criteria Metastases, post EBRT rise in PSA, men on hormonal therapy, men using nitrates, history of myocardial infarction, stroke or radical prostatectomy.

Population number of patients = 60.

Interventions A 4 week (no treatment) run-in period was used to collect baseline data on sexual functioning. After this period, patients were randomised to receive either sildenafil citrate (50 mg) or placebo (50 mg), for 12 weeks. After 2 weeks, any patient claiming inadequate erectile function (in either treatment arm) was given 100 mg tablets. At week, 6 patients crossed over (from treatment to control or vice versa). The dosage could be decreased to 25 mg if adverse events were experienced.

Outcomes Patients filled out the International index of erectile function questionnaire (IIEF), at the end of the run-in period and after 2, 6, 8 and 12 weeks. 2 extra questions were added to the questionnaire - for a global efficacy assessment.

Side effects were recorded using a questionnaire.

Follow up Patients visited the clinic at weeks 2, 6, 8 and 12. All patients completed the study. No patients dropped out of the study

Results Ninety percent of the patients needed a dose adjustment to 100 mg sildenafil. Side effects were mild or moderate; the sildenafil group experienced significantly more headache, flushing and dyspepsia.

COMPARISON in Men after EBRT for PCa	Sildenafil	Placebo	
International index of erectile function	significant increase ($p<0.05$) from baseline for all IIEF items except 12	significant increase ($p<0.05$) from baseline for IIEF items 6,10 and 15	
One or more successful sexual intercourse attempts	33/60 (55%)	11/60 (18%)	in favour of sildenafil ($p<0.001$)
Headache	25/60	9/60	in favour of placebo ($p<0.001$)
Flushing	8/60	1/60	in favour of placebo ($p=0.04$)
Myalgia	9/60	8/60	$p=1.00$
Nasal congestion	13/60	7/60	$p=0.10$
Dyspepsia	19/60	5/60	in favour of placebo ($p<0.001$)
Vision disturbances	10/60	5/60	$p=0.18$
Dizziness	10/60	6/60	$p=0.29$

General comments No 'wash-out' period is reported after cross-over.

(Incrocci *et al.* 2006)

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

Country: Netherlands, the, setting: Tertiary care

Inclusion criteria Men treated with 3D conformal radiotherapy for prostate cancer betwen1998 and 2002 at a single institution.

Exclusion criteria Previous pelvic surgery, chemotherapy, antiandrogen therapy or metastatic disease. Any contraindications for PDE-5 therapy.

Population number of patients = 60, age range 53 to 84 years, mean age = 69 years.

Interventions Men had been treated with 3D conformal radiotherapy (mean dose 70 Gy in 2 Gy fractions). The trial therapy was started at least one year after radiotherapy (mean 3 years, range 1 to 8 years). Men were randomised to receive either tadalafil 20 mg orally (Cialis) or placebo for 6 weeks. The drug was taken on demand at the patient's discretion. After 6 weeks, the patient's crossed over to the other arm of the trial.

Outcomes Erectile function and sexual satisfaction (assessed using the erectile function questions of the IIEF questionnaire). Scores on each item ranged from 1 to 5 (1 being the worst and 5 the best)

Another 5 item questionnaire was used for self assessment of erectile function after each sexual encounter. Side effects were recorded after 6 weeks of treatment.

Follow up Patients were assessed before treatment, at the end of the first 6 week treatment period and again after the second 6 week treatment period. All men completed the study.

Results Only men who attempted sexual activity at least twice in each 6 week treatment period were included in the analysis.

Score was significantly improved from baseline after tadalafil in 11 of the 15 IIEF questions. Score was significantly better with tadalafil than with placebo in 12 of the 15 IIEF questions.

Side effects were mild or moderate and transient. The risk of headache, flushing and dyspepsia was significantly increased with tadalafil.

COMPARISON IN MEN AFTER EBRT FOR PCa	BASELINE	TADALAFIL	PLACEBO	OVERALL RESULT
Erection frequency	Mean 2.1 SD 1.3	Mean 3.3 SD 1.8	Mean 1.8 SD 1.4	Statistically significant improvement from baseline with tadalafil
Intercourse satisfaction	Mean 1.4 SD 0.9	Mean 2.9 SD 1.9	Mean 1.5 SD 1.0	"
Overall satisfaction	Mean 2.1 SD 1.1	Mean 3.2 SD 1.5	Mean 2.1 SD 1.2	"
Headache		16/60 (27%)	1/60 (2%)	favours placebo ($p<0.0001$)
Flushing		10/60 (10%)	1/60 (2%)	favours placebo ($p<0.012$)
Myalgia		7/60 (7%)	2/60 (3%)	favours placebo ($p=0.06$)
Dyspepsia		14/60 (14%)	1/60 (2%)	favours placebo ($p<0.0001$)

(Lepore *et al.* 2003)

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

Country: United States, setting: Tertiary care

Inclusion criteria Men with prostate cancer, living within 1 hour's driving distance of their institution. Of 362 eligible patients, 279 completed the baseline interview and agreed to randomisation.

Exclusion criteria History of other (non-prostate) cancer, metastases at the time of diagnosis.

Population number of patients = 279.

Interventions Patients were randomly assigned to a control group, a group education intervention (GE), or a group education-plus-discussion intervention (GED). Group education was a series of 6 weekly lectures about prostate cancer topics of relevance to patients. The GED group also had a 45 group discussion after each lecture, which was led by a clinical psychologist. The wives of the men in the GED arm also had separate discussion, led by a female oncology nurse.

Outcomes Prostate cancer knowledge assessed using a 13 item quiz. Ratings of the lectures. Health behaviour index - questions to measure whether patients engaged in the recommended positive health behaviours. Quality of life, measured using the SF-36 scale. Depression was measured using the Center for Epidemiological Studies Depression Scale. Disease specific quality of life was assessed using the UCLA Prostate Cancer Index.

Follow up 29/279 patients (10%) were lost to follow up. Patients were interviewed at baseline, and at 0.5, 6 and 12 months after the intervention.

Results -

COMPARISON in Prostate cancer	Group education	Group education with discussion	Standard care	
Quality of life (SF-36)	Overall score not reported	Overall score not reported	Overall score not reported	No significant difference between groups at any time point (baseline, 0.5, 6 and 12 months) on mental and physical functioning items
Depression	mean (SD) CES-D score 0.54 (0.45) at baseline, 0.43 (0.42) at one year	mean (SD) CES-D score 0.49 (0.48) at baseline, 0.35 (0.44) at one year	mean (SD) CES-D score 0.46 (0.52) at baseline, 0.40 (0.49) at one year	No significant difference between groups at any time point (baseline, 0.5, 6 and 12 months).
Prostate cancer related quality of life	Overall score not reported	Overall score not reported	Overall score not reported	No significant difference between groups at any time point (baseline, 0.5, 6

	and 12 months), statistically significant improvement with time for sexual and urinary functioning.

General comments

(Brock *et al.* 2003)

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

Country: North America, setting: Tertiary care

Inclusion criteria Men with erectile dysfunction (ED) after documented nerve sparing radical retropubic prostatectomy (NSRP) for localised prostate cancer. Age over 18 years. PSA levels consistent with absence of tumour. Patients were required to be involved in a stable heterosexual relationship for at least 6 months, and 50% of attempts to obtain, penetrate with or maintain erection during 4 separate attempts in the baseline period must have failed.

Exclusion criteria Low serum testosterone, Gleason score of 8 or more, men taking medications which could interact with vardenafil. Men with ED of non prostatectomy aetiology. Men with a history of retinitis pigmentosa, myocardial infarction, stroke, electro cardiac ischemia, life threatening arrhythmia or significant peptic ulcer.

Population number of patients = 440.

Interventions After a 4 week baseline period, during which ED was assessed, patients were randomised to receive either 10 or 20 mg vardenafil or placebo for 12 weeks. Patients were instructed to take the medication 1 hour before sexual intercourse with a maximum of 1 dose daily.

Outcomes International index of erectile function (IIEF), the per patient success rate for vaginal penetration and the per patient success rate for sexual intercourse. Adverse events were classified as serious or clinically significant.

Follow up 97/145 (67%) in the placebo arm completed the study compared to 114/146 (78%) in the vardenafil 10 mg arm and 119/149 (80%) in the vardenafil 20 mg arm.

Results Subgroup analysis by baseline ED (mild, moderate and severe) was also carried out, showing that improvement depends on the baseline ED, with best results in those with mild baseline ED. Subgroup analysis by bilateral or unilateral nerve sparing prostatectomy was also done.

COMPARISON in Men after nerve sparing prostatectomy	Placebo	Vardenafil 10 mg	Vardenafil 20 mg

International index of erectile function	baseline 9.1, at 12 weeks 9.2	baseline 9.3, at 12 weeks 15.3	baseline 9.2 at 12 weeks 15.3	Favours vardenafil over placebo (p<0.0001, ANCOVA) for both doses
Percentage of successful vaginal penetration attempts	baseline 14%, at 12 weeks 22%	baseline 21%, at 12 weeks 47%	baseline 18%, at 12 weeks 48%	Favours vardenafil over placebo (p<0.0001, ANCOVA) for both doses
Percentage of successful sexual intercourse attempts	baseline 6%, at 12 weeks 10%	baseline 7%, at 12 weeks 37%	baseline 7%, at 12 weeks 34%	Favours vardenafil over placebo (p<0.0001, ANCOVA) for both doses
Headache	4/140	16/140	22/147	favours placebo over vardenafil (both dosages)
Flushing	0/140	19/140	21/147	favours placebo over vardenafil (both dosages)
Rhinitis	6/140	16/140	20/147	favours placebo over vardenafil (both dosages)
Dyspepsia	0/140	4/140	5/147	favours placebo over vardenafil (both dosages)
Nausea	0/140	1/140	5/147	favours placebo over vardenafil (both dosages)
Sinusitis	1/140	6/140	7/147	favours placebo over vardenafil (both dosages)
One or more severe adverse effects	3/140	7/140	5/147	

General comments -

(Montorsi *et al.* 2004)

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

Country: International, setting: Tertiary care

Inclusion criteria Men who had bilateral nerve sparing prostatectomy 1 to 4 years before study entry. Age 65 years or less at surgery. Erectile dysfunction (ED) which developed after

the surgery.

Exclusion criteria Less than 4 sexual intercourse attempts during the run-in period. Erectile dysfunction caused by other primary sexual disorders, significant penile deformity, penile implant; uncontrolled diabetes, hepatic or renal disease; unstable cardiovascular disease, previous pelvic surgery (other than NSRP), detectable PSA, radiotherapy, hormonal therapy, HIV infection or CNS injury.

Population number of patients = 303.

Interventions The study consisted of 2 periods. First, there was a 4 week run-in during which baseline erectile function was assessed. Patients were then randomised to receive either tadalafil (20 mg) or placebo for 12 weeks. The mean number of doses per week was 2.3 [SEM 1.5] for the tadalafil group and 2.1 [SEM 1.4] for the placebo group. Randomisation was stratified by ED severity, age, site, and status of postoperative penile tumescence.

Outcomes 3 primary outcomes: international index of erectile function, the percentage of successful attempts at vaginal penetration and the percentage of successful attempts at sexual intercourse. Adverse events categorised as severe, serious and others. Emergent adverse effects were defined as those occurring in 2% or more of patients.

Follow up 26/106 patients in the placebo arm discontinued treatment. 40/201 patients in the tadalafil arm discontinued treatment.

The proportion lost to follow up was 2.5% in the treatment arm and 2.9% in the placebo arm.

Results No severe adverse effects were reported.

COMPARISON in Men after nerve sparing prostatectomy	Tadalafil	Placebo	
International index of erectile function	IIEF increased by 5.3 [SEM 0.5]	IIEF increased by 1.1 [SEM 0.6]	In favour of tadalafil (p<0.001, ANCOVA)
Percentage of successful vaginal penetration attempts	Increase of 21.6% [SEM 2.4%]	Increase of 1.9% [SEM 2.5%]	In favour of tadalafil (p<0.001, ANCOVA)
Percentage of successful sexual intercourse attempts	Increase of 23.0% [SEM 2.3%]	Increase of 3.7% [SEM 2.3%]	In favour of tadalafil (p<0.001, ANCOVA)
Severe adverse events	10/201 (5%)	2/102 (2.0%)	No significant difference (p=0.55, ANCOVA).
Emergent adverse events	104/201 (52%)	27/102 (26.5%)	In favour of placebo (p<0.001, ANCOVA). Most common adverse events: headache, dyspepsia, myalgia, back pain, nasal congestion, fatigue, flushing, cough and gastroesophageal reflux

General comments Would a tadalafil vs. standard care comparison have been more useful than a placebo trial?

Systematic review of cohort studies

(Matthew *et al.* 2005)

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

Country: International, setting: Other

Inclusion criteria Included studies had to contain information on at least one of the following topics: the incidence of erectile dysfunction (ED) after RP, the efficacy and/or use of sexual assistive aids after RP, and the impact on quality of life or distress in patients with ED after RP.

Exclusion criteria Non-English language papers.

Population -

Interventions Radical prostatectomy for prostate cancer.

Outcomes Information was sought on the prevalence of ED, the use of assistive aids for sexual dysfunction and the prevalence of distress in this population.

Results The review concludes that despite apparent effectiveness between 30 and 50% of patients discontinue the use of sexually assistive aids within a year. This suggests that the achievement of erections is only one of the important factors in long term sexual adaptation after RP.

COMPARISON in Candidates for radical prostatectomy for PCa	Radical prostatectomy	
Erectile dysfunction	Reports of prevalence range from 25% to 75% in 11 studies	Review concludes that the rate in men with normal erectile function before RP is likely to be in the range 40 to 75%
Distress	Reports of prevalence range from 33% to 82% in 15 studies of post RP patients with ED	

General comments -

Prospective cohort study

(Stephenson *et al.* 2005)

Design: Prospective cohort study (therapy), evidence level:

Country: United States, setting: Community

Inclusion criteria Men diagnosed with prostate cancer randomly selected from cancer registries (SEER) for the Prostate Cancer Outcomes Study. Clinically localised disease. Men had to have completed at least the PCOS 6 month survey. Men were treated with either EBRT or RP between 1994 and 1995.

Exclusion criteria -

Population number of patients = 1977.

Interventions Treatment for erectile dysfunction, classified as vacuum erection device, penile injection, non-sildenafil medication, psychosexual counselling, penile prosthesis, sildenafil, or combinations of the above.

Outcomes The proportion of men using each ED treatment. The perceived helpfulness of the ED treatment, assessed by questionnaire. Sexual function, assessed by questionnaire. Comparisons were done for men using only one treatment.

Results 50.5% of the men had ever used ED treatment. Patient characteristics associated with the use of ED treatments were: age, a regular sexual partner at baseline and baseline sexual activity.

COMPARISON in Prostate cancer	Vacuum erection device	Penile injection	Psycho-sexual counselling (man only)	Penile prosthesis	Sildenafil	Non-sildenafil medication	
Proportion	mean 16.5% (SE 0.94)	mean 11.1% (SE 0.79)	mean 4.5% (SE 0.55)	1.9% (0.34)	Sildenafil only 16.7% (1.18), in combination with others 20.9% (1.21)	5.0% (0.54)	Figures are for ED treatment at any time during the 60 month period (except for sildenafil which only became available halfway through this period)
Perceived usefulness	71%	69%	40%	71%	47%	61%	Proportion who believed the ED treatment helped a lot or helped somewhat
Ability to achieve full erection	21%	39%	16%	42%	39%	25%	Proportion with full erection (vs. partial or none)

Ability to maintain erections	24%	42%	11%	67%	41%	31%	Proportion able to maintain erection during intercourse with little or no difficulty
One or more successful sexual intercourse attempts	68%	72%	40%	73%	69%	44%	

General comments Sildenafil became available in 1997 and was only included in the last survey (at 60 months). The comparisons of usefulness only include men using a single ED treatment.

Retrospective cohort study

(Schover *et al.* 2002b)

Design: Retrospective cohort study (therapy), evidence level: 2+

Country: , setting: Tertiary care

Inclusion criteria Men in the Cleveland Clinic prostate cancer registry. All men had been treated with definitive therapy for localised prostate cancer (46% RP and 54% radical radiotherapy). The earliest year of treatment was 1986 but 90% were treated between 1992 and 1999.

Exclusion criteria -

Population number of patients = 1236, age range 42 to 88 years, mean age = 67 years.

Interventions Patients in the Cleveland registry were sent a postal questionnaire about past and current sexual functioning

Treatment for ED was recorded as: sildenafil, psychosexual counselling, other oral medication (non-sildenafil), penile injections, intraurethral prostaglandin, vacuum device and penile prosthesis.

Outcomes Proportion of men with ED who had tried each treatment, who had experienced success and who continued using the treatment. A subset of the respondents were currently using ED treatment, in this group erectile functioning (EF) was assessed using the EF subscale of the IIEF measure. Response to sildenafil was analysed according to type of radical treatment for prostate cancer

Follow up The mean time since treatment was 4.3 years (SD 2.9 years). The return rate of the questionnaire was 49%, and demographic data suggested that the sample of responders was weighted toward men who were more interested in staying active sexually.

Results ED was a problem for 85% of men, and 59% of this group used at least I treatment for ED.

COMPARISON in Men with erectile dysfunction after radical prostatectomy	Sildenafil	Non-sildenafil medication	Penile injection	Vacuum erection device	Penile prosthesis	Prostaglandin E1 (alprostadil)	Psychosexual counselling (man only)

or EBRT								
Proportion who tried the option	549/1188 (52%)	21/1188 (2%)	179/1188 (18%)	197/1188 (19%)	16/1188 (2%)	Intraurethral 103/1188 (10%)	145/1188 (14%)	
Proportion continuing treatment	39%	47%	34%	41%	81%	21%	29%	
Any improvement with treatment	49% (16% greatly improved)	55% (11% greatly improved)	72% (29% greatly improved)	63% (19% greatly improved)	82% (44% greatly improved)	47% (6% greatly improved)	36% (7% greatly improved)	
Ability to achieve erections	53/99, 53% EF score 22 or more	3/4, 75% EF score 22 or more	22/32, 69% EF score 22 or more	6/18, 33% EF score 22 or more	1/1, 100% EF score 22 or more	1/3, 33% EF score 22 or more	not reported	data from the subgroup currently using ED treatment
COMPARISON in Men with erectile dysfunction after radical prostatectomy or EBRT	Bilateral nerve sparing prostatectomy	Unilateral nerve sparing prostatectomy	Non nerve sparing prostatectomy	Brachytherapy	3D-CRT or IMRT	Standard EBRT		
response to sildenafil	55% (47% still using it)	38% (32% still using it)	27% (15% still using it)	69% (59% still using it)	58% (48% still using it)	57% (32% still using it)		

General comments -

(Schover *et al.* 2002a)

Design: Retrospective cohort study (therapy), evidence level: 2+

Country: United States, setting: Tertiary care

Inclusion criteria Men in the Cleveland Clinic prostate cancer registry. All men had been treated with definitive therapy for localised prostate cancer (46% RP and 54% radical radiotherapy). The earliest year of treatment was 1986 but 90% were treated between 1992 and 1999.

Exclusion criteria -

Population number of patients = 1236.

Interventions A postal survey. The survey asked about demographic items, past and current sexual functioning, partner's sexual function and health, and a number of factors hypothesized to affect sex

Outcomes Standardized questionnaires included the Sexual Self-Schema ScaleMale Version, the International Index of Erectile Function (IIEF), urinary and bowel symptom scales from the Los Angeles Prostate Cancer Index, and the Short Form Health Survey (SF-36).

Follow up

The mean time since treatment was 4.3 years (SD 2.9 years). The return rate of the questionnaire was 49%, and demographic data suggested that the sample of responders was weighted toward men who were more interested in staying active sexually.

Results At the time they were diagnosed with prostate carcinoma, 36% of men had erectile dysfunction (ED) according to their oncologist. After treatment, erections became somewhat worse for 21% of men and much worse for 65%, with 85% reporting ED as a problem in the last 6 months. 66% of men reported that their partner had at least one sexual dysfunction.

61% of men were distressed about ED, 60% were distressed about sexual desire problems and 64% about orgasm problems.

General comments -

Prospective comparative study

(Kim *et al.* 2001)

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

Country: United States, setting: Tertiary care

Inclusion criteria 28 potent men, who had wide bilateral neurovascular bundle resection with nerve grafting (from 1997 onwards) during prostatectomy for prostate cancer at a single institution. Age 40 to 70 years. A control group of men who declined the nerve grafting procedure were include

Exclusion criteria Use of adjuvant or neoadjuvant therapy. History of ED or Peyronie's disease, peripheral neuropathy or psychiatric illness. Less than 1 year of follow-up data.

Population number of patients = 35.

Interventions Radical retropubic prostatectomy with deliberate wide bilateral neurovascular bundle resection and the placement of bilateral nerve grafts. A control group had radical retropubic prostatectomy with bilateral neurovascular bundle resection, but declined the nerve grafting procedure.

Outcomes International index of erectile function (IIEF), erectile function using a visual assessment scale (VAS), the patients partners were also questioned about the sexual relationship. Morbidity related to the nerve grafting procedure.

Follow up Patients had at least 1 year of follow up after prostatectomy. 5 eligible patients did not return their questionnaires after the nerve grafting procedure. The mean follow-up for those completed questionnaires was 23 months (range 12 to 36 months).

Results In the nerve graft group: 6/23 men (26%) achieved erections sufficient for unassisted intercourse, 6/23 (26%) achieved partial erections and 11/23 (48%) had no significant erectile activity. 10/23 (44%) were able to have intercourse unaided or using sildenafil.

COMPARISON in Candidates for radical prostatectomy for PCa	Bilateral nerve grafting during non-nerve sparing prostatectomy	Non nerve sparing prostatectomy	
IIEF - total score	mean score 33/75	mean score 18/75	in favour of nerve grafting (p=0.008)
IIEF - erectile function domain	mean score 10/30	mean score 3/30	in favour of nerve grafting (p=0.001)

General comments -

Prospective case series

(Baniel *et al.* 2001)

Design: Prospective case series (therapy), evidence level: 3

Country: Israel, setting: Tertiary care

Inclusion criteria Patients who had undergone radical retropubic prostatectomy (mostly non-nerve sparing) for prostate cancer at a single institution, and who complained of ED.

Exclusion criteria -

Population number of patients = 85.

Interventions All patients were initially treated with a vacuum erection device. Patients who did not continue with the device were treated with sildenafil citrate 25, 50 or 100 mg. If this was unsuccessful patients were given intracavernosal injection of papaverine, phentolamine and PGE1. If this failed a penile prosthesis was recommended.

Outcomes Ability to achieve erection suitable for vaginal penetration. Proportion of men choosing to continue to use an ED treatment under domestic conditions.

Results The progressive treatment method gave a positive response (ability to achieve an erection suitable for vaginal penetration) in 80 of the 85 patients (94%). After 1 year of follow-up, 76 of the 80 patients (95%) continued to respond. Of all the methods used, intracorporal injection was the most effective for ED after RRP

COMPARISON in Men with erectile dysfunction after radical prostatectomy	Vacuum erection device	Sildenafil	Penile injection	Penile injection plus vacuum device
Ability to achieve erections	78/85 (92%)	21/69 (30%)	51/60 (85%)	4/9 (44%)
Proportion continuing treatment	11/85 (13%)	14/69 (20%)	51/60 (85%)	not reported

General comments Patients only progressed to sildenafil and penile injections if they had failed the previous treatment, this could underestimate the efficacy of sildenafil and penile injection in the whole sample.

Prospective cross sectional study

(Perez *et al.* 1997)

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

Country: United States, setting: Tertiary care

Inclusion criteria Men who had undergone radical prostatectomy between 1990 and 1993 in a single institution, or who were awaiting prostatectomy for early-stage prostate cancer. Fluency

in English was required.

Exclusion criteria Too ill to complete questionnaires. Missing data

Population number of patients = 544.

Interventions Patients were mailed 2 questionnaires

Outcomes Quality of life was measured using a questionnaire developed for this study. Sexual function was assessed the Sexual History Form (SHF)

Follow up The mean time since prostatectomy was 1.9, 2.2 and 2.3 years for the nerve-sparing, erectile aid and standard prostatectomy groups respectively.

Results Overall quality of life and satisfaction with sexual functioning could range from 1 (worst) to 7 (best). There was little difference in QOL between the 4 groups. Significantly better outcomes in the sexual function questionnaire items were reported by patients who used erectile aids and in patients awaiting surgery, compared to the prostatectomy patients who did not use ED treatment.

COMPARISON in Candidates for radical prostatectomy for PCa	Preoperative prostatectomy patients	Patients using ED treatment	Nerve sparing prostatectomy	Non nerve sparing prostatectomy	
Quality of life	mean 6.02	mean 5.49	mean 5.35	mean 5.16	($p<0.04$,) not significant due to multiple comparisons
Satisfaction with sex life	mean 4.30	mean 4.14	mean 2.85	mean 2.52	($p<0.0001$) in favour of preop. and ED groups over the other groups

General comments Ad-hoc measure of QOL. There appeared to be differences between the groups in feelings of sexual desire. The group who used ED reported greater sexual desire than the other groups; this is likely to influence the sexual function measures.

Review

(Montorsi & McCullough 2005)

Design: Review (therapy), evidence level: 3

Country: International, setting: Other

Inclusion criteria Studies of sildenafil as monotherapy for erectile dysfunction after radical prostatectomy for PCa. MEDLINE and CANCERLIT (1998 to January 2004) were searched.

Studies included varying mixtures of nerve sparing and non-nerve sparing procedures. Four studies included patients who did not have prostatectomy.

Exclusion criteria -

Population mean age = 61 years.

Interventions Sildenafil as monotherapy for erectile dysfunction.

The typical dose ranged between 25 and 100 mg, although 2 studies allowed final doses of more than 100 mg. The majority of responders were taking 100 mg of sildenafil by the end of the study period. Treatment durations ranged from 4 weeks to 1 year.

Outcomes Efficacy of sildenafil. Six studies used informal patient reports of erections suitable for sexual intercourse. The other studies used structured questionnaire measures of erectile function (IIEF, CCPP and EDITS).

Results No randomised controlled trials were found. 10 of the included studies were case series, and one was a case control study. 7 of the 11 studies were included in a meta-analysis.

The response rate to sildenafil treatment after RP varied from 14% to 53%, the combined estimate was 35% [95% CI 24 to 48%].

COMPARISON in Prostate cancer	Nerve sparing prostatectomy	Non nerve sparing prostatectomy	
response to sildenafil	140/279 (5 studies combined)	6/83 (5 studies combined)	OR = 12.1 [95% CI 5.51 to 26.6]

General comments Different measures of efficacy used in the primary studies.

(Dubbelman *et al.* 2006)

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

Inclusion criteria Papers published between 1980 and 2005 about the rates of erectile dysfunction (ED) after radical prostatectomy for prostate cancer. Articles reporting haemodynamic changes after RP were also included.

Exclusion criteria Follow-up of less than 12 months, less than 50 patients in the case series,

Population -

Interventions Radical prostatectomy (classified as unilateral, bilateral or non nerve sparing).

Outcomes Erectile dysfunction. Potency (defined as the ability to achieve unassisted intercourse with vaginal penetration).

Follow up Not well reported, but a minimum of 12 months. Outcomes were reported at 1 and 5 years after surgery in some series,

Results 14 relevant articles were found. Not all studies used validated questionnaires to assess sexual function.

Reported potency rates before RP ranged from 64% to 100%.

Ranges of reported post-op potency rates

For bilateral nerve-sparing RP (18 to 76%), for unilateral nerve-sparing RP (13 to 56%) and for non-nerve sparing RP (0 to 34%).

Prognostic factors for post-op potency:

Neurogenic factors.

There was a strong correlation (figures not reported) between the number of preserved neurovascular bundles and post operative potency.

Vascular factors.

There was some evidence, from studies of penile blood flow, that vascular factors sometimes played a role in post-op ED.

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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3.8.3 Urinary incontinence

In men who have been treated with radical surgery or radical radiotherapy for prostate cancer, what are the effective interventions for incontinence

Short summary

Pelvic floor re-education

Systematic reviews of RCTs of pelvic floor muscle exercise (PME) training in men (Dorey ; Hunter *et al.* 2004) suggest that PME training using biofeedback is associated with earlier return to continence after radical prostatectomy. Continence rates at 1 year post prostatectomy, however, were similar in PME and non-PME groups. Two good quality RCTs published since the reviews (Burgio *et al.* 2006); Filocamo, *et al.* 2005) showed a benefit of early PMEs for post-prostatectomy incontinence

The systematic reviews (Dorey; Hunter *et al.* 2004) concluded that there was insufficient evidence to support enhancements (such as biofeedback and electrical or magnetic stimulation) to PMEs. An RCT conducted since these systematic reviews (Yokoyama *et al.* 2004) showed earlier return to post radical prostatectomy continence in men treated using external electrical or magnetic stimulation of the pelvic floor muscles than in those treated with PMEs.

Surgical treatment

A single RCT (Imamoglu *et al.* 2005) compared injection of urethral bulking agent with the AMS 800 artificial urinary sphincter in the treatment of post radical prostatectomy urinary incontinence. In men with total incontinence after prostatectomy, the artificial urinary sphincter was more effective in terms of number of pads used and grams of urine lost. In men with minimal incontinence, however, there was no significant difference between the two treatments.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
men treated with radical surgery or radical radiotherapy for prostate cancer	Interventions for urinary incontinence	No intervention	• Continence • Quality of life

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

Evidence Summary

<u>Conservative treatment</u>

Systematic reviews of RCTs of pelvic floor exercise (PME) training in men (Dorey; Hunter *et al.* 2004) suggest that PME training using biofeedback is associated with earlier return to continence after radical prostatectomy. Continence rates at 1 year post prostatectomy, however, were similar in PME and non-PME groups. Two good quality RCTs published since the reviews (Burgio *et al.* 2006; Filocamo *et al.* 2005) showed a benefit of early PMEs for post-prostatectomy incontinence. Figures below show combined results of the evidence from the systematic reviews and the more recent RCTs.

The systematic reviews (Dorey; Hunter *et al.* 2004) concluded that there was insufficient evidence to support enhancements (such as biofeedback and electrical or magnetic stimulation) to

PMEs. An RCT conducted since these systematic reviews (Yokoyama *et al.* 2004) showed earlier return to post radical prostatectomy continence in men treated using external electrical or magnetic stimulation of the pelvic floor muscles than in those treated with PMEs.

An RCT (Mishel *et al.* 2002) examined whether involving a man's partner or carer increased the effectiveness of a psycho educational post RP symptom control program. The authors reported that including the carer in the program was associated with better control of urine flow at 4 months RP, but not at 7 months post RP.

A randomised trial compared duloxetine with placebo in addition to pelvic floor muscle exercise after radical prostatectomy (Filocamo *et al.* 2007). There was a small benefit in favour of duloxetine (Filocamo *et al.* 2007) in terms of urinary continence. However, the effect was transient and at the expense of increased adverse events (15% vs. 2% for duloxetine and placebo groups respectively).

Surgical treatment

A single RCT (Imamoglu *et al.* 2005) compared injection of urethral bulking agent with the AMS 800 artificial urinary sphincter in the treatment of post radical prostatectomy urinary incontinence. In men with total incontinence after prostatectomy, the artificial urinary sphincter was more effective in terms of number of pads used and grams of urine lost. In men with minimal incontinence, however, there was no significant difference between the two treatments.

The search did not find any randomised trials involving the suburethal sling. Evidence about the safety and effectiveness of this procedure will rely on case series.

Quality of life

Conservative treatment

There was little evidence of the impact of PMEs on quality of life in this population. The systematic review of Hunter and co-workers (Hunter *et al.* 2004) identified a single small trial using validated QOL measures that found no difference between PME and control groups. Yokoyama and co-workers (Yokoyama *et al.* 2004) observed no significant difference in quality of life between external electrical or magnetic stimulation of the pelvic floor muscles or PME treatment groups.

Surgical treatment

An RCT (Imamoglu *et al.* 2005) compared injection of urethral bulking agent with the AMS 800 artificial urinary sphincter. In men with total incontinence after RP had significantly better quality of life when treated using the artificial urinary sphincter than those treated with injection. In men with minimal incontinence, however, there was no significant difference between the two treatments.

Adverse effects

Conservative treatment

There was reported evidence about adverse effects related to PMEs. A single patient in one trial reported rectal pain and stopped PME treatment (Dorey). There is some evidence (again from a single trial) that the Cunningham penile clamp significantly reduces penile blood flow (Hunter *et al.* 2004).

Surgical treatment

In the Imamoglu and co-workers RCT (Imamoglu *et al.* 2005) adverse event rate in the artificial sphincter group was 5/22 (infection, erosion and mechanical failure). In the injection group, the rate was 3/23 (urinary retention and urinary tract infection).

Figure 49 Continence at 3 months after prostatectomy (using authors' definitions of continence).

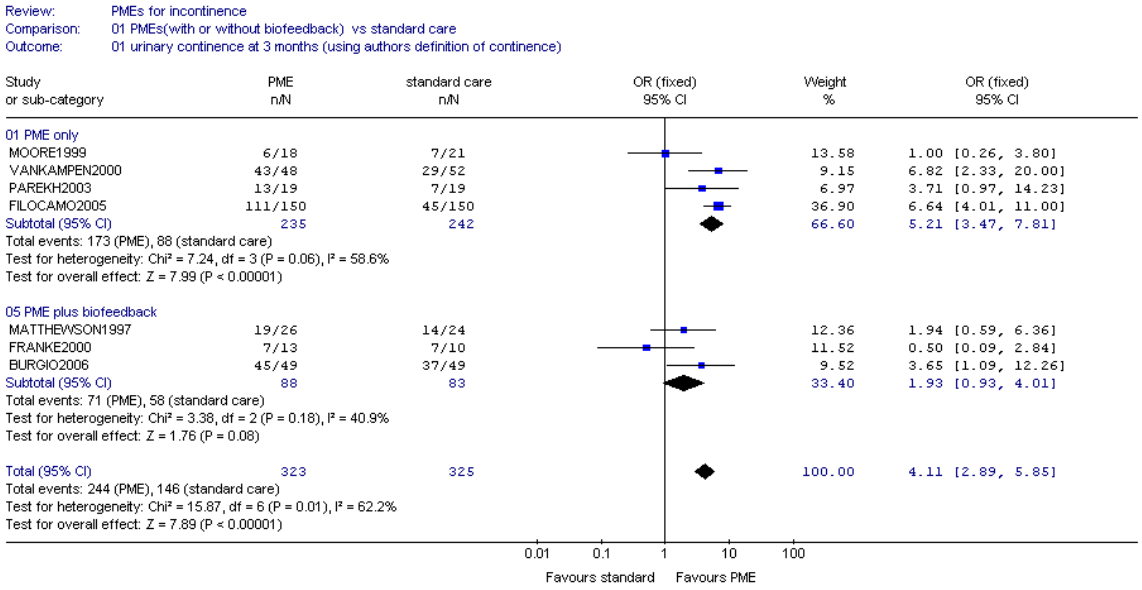
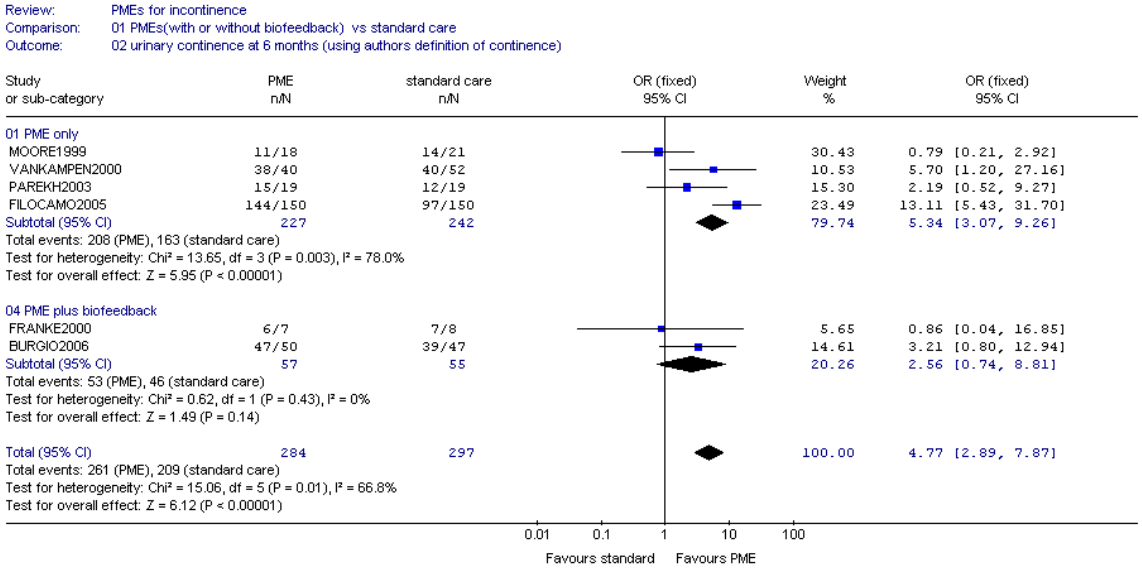


Figure 50 Continence at 6 months after prostatectomy (using authors' definitions of continence).



Evidence tables

Systematic reviews of RCTs

(Dorey)
Design: Systematic review of RCTs (therapy), evidence level: 1+ Country: , setting: Tertiary care **Inclusion criteria** RCTs reporting the use of pelvic floor muscle training (PMEs) to restore pelvic floor function. 11 studies were identified, which included men with urinary incontinence following radical prostatectomy or TURP and men with post micturation dribble. **Exclusion criteria** - **Population** - **Interventions** The PME treatment protocol varied, some trials used biofeedback in an attempt to enhance the exercises. One trial commenced PMEs some time after prostatectomy (up to 2 years after). The control groups in 5 of the trials were also given instruction on PMEs. The length of treatment varied between 3 and 12 weeks, but all trials stressed the importance of continuing PMEs at home **Outcomes** Urinary incontinence measure objectively with pad tests, and subjectively with questionnaires and bladder diaries. **Follow up** Outcome measures were recorded from between 1 week to 12 months after surgery. Drop out rate was generally low but one trial had a 50% drop out rate at 24 weeks post-operation. **Results** The author concluded that three of the eight trials showed a significant benefit of PMEs in men with radical prostatectomy. These benefits tended to be in the medium term, with an earlier return to continence in the PME group, while long term outcomes were similar in both groups. There was no evidence that biofeedback enhanced the treatment effect. In one trial, one subject experienced rectal pain and discontinued the PMEs. **General comments** Contains the same studies as the Hunter et al Cochrane review, except for one small RCT (Sueppel et al 2001) with 16 patients which showed a benefit in favour of PMEs in men with prostatectomy urinary incontinence.

(Hunter *et al.* 2004)
Design: Systematic review of RCTs (therapy), evidence level: 1++ **Inclusion criteria** Randomised controlled trials evaluating conservative interventions for uri-

nary continence after prostatectomy, published up to January 2004.

Exclusion criteria -

Population -

Interventions Conservative interventions for urinary continence after prostatectomy: pelvic floor muscle training, biofeedback, electrical nerve stimulation using surface electrodes, extracorporeal magnetic stimulation, lifestyle adjustment and external penile compression devices.

10 trials were included. In one trial patients had undergone transurethral resection of the prostate (TURP), in eight trials radical prostatectomy (RP) and in one trial either TURP or RP.

Outcomes Primary outcomes were: self report of urinary incontinence, number of pad or clothing changes per day, the frequency of incontinence (from self report or diary) and de novo urge symptoms. Standardised pad test measuring grams of urine lost.

Results In the table below, "standard care" refers to no treatment, placebo or sham treatment.

The authors concluded "The value of the various approaches to conservative management of post prostatectomy incontinence remains uncertain. There may be some benefit of offering pelvic floor muscle training with biofeedback early in the postoperative period immediately following removal of the catheter as it may promote an earlier return to continence. Long-term incontinence may be managed by external penile clamp, but there are safety problems."

COMPARISON in Men with urinary incontinence after radical prostatectomy	Pelvic floor muscle training	Standard care	
Standardised pad test, grams of urine lost	At 3 months or less of treatment, mean 87g (SD 123g); at 3-6 months, mean 74g (SD 131g); at 6-12 months, mean 70g (SD 114g)	At 3 months or less of treatment, mean 104g (SD 176g); at 3-6 months, mean 67g (SD 137g); at 6-12 months, mean 54g (SD 103g)	Results are from a single study. No significant difference at any time point.
Number not cured	With 3 months (or less) of treatment 13/48 (2 studies)	17/49 (combined figures from 2 studies)	RR 0.87 [95% CI 0.55 to 1.38] (no significant difference)
COMPARISON in Men with urinary incontinence after radical prostatectomy	Pelvic floor muscle training plus biofeedback	Standard care	
Standardised pad test, grams of urine lost	At 3 months or less of treatment. mean 120g (SD 250g)	At 3 months or less of treatment. mean 126g (SD 215g)	Results from a single study, no sig. difference between groups
Number not cured	At 3 months 63/154; at 3-6 months 28/148; at 6-12 months 5/114	At 3 months 86/155; at 3-6 months 39/153; at 6-12 months 15/118	At 3 months or less, in favour of treatment RR=0.74[95%CI 0.60 to 0.93]. At 3-6 months no sig. difference, RR=0.76 [95%CI 0.51 to 1.14]. At 3-6 months no sig. difference, RR=0.55 [95%CI 0.24 to 1.23]

COMPARISON in Men with urinary incontinence after radical prostatectomy	External penile compression devices	Standard care	
Standardised pad test, grams of urine lost	3 devices: U-Tex mean 53g (SD 66g), C3 mean 32g (SD 24g) and Cunningham mean 17g (SD 21)	Using no device mean was 123g (SD 131g)	All devices were significantly better than the control (no device group) at p<0.05.
Satisfaction with device	3 devices: U-Tex 0/12, C3 2/12 and Cunningham 10/12	0/12	More men were satisfied with the Cunningham device, however penile Doppler blood flow (mean systolic velocity) was significantly reduced (p<0.05) with this device.

General comments -

Randomized controlled trials

(Imamoglu *et al.* 2005)

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

Country: Turkey, setting: Tertiary care

Inclusion criteria Patients with post prostatectomy incontinence, despite conservative treatment following radical retropubic prostatectomy (RRP, n=12), transvesical prostatectomy (TVR, n=16) or transurethral prostatectomy (TURP, n=17). Incontinence was defined as more than one pad per day over the previous month. Minimum bladder capacity of 150 cc. Urethral pressure profiles below 20 cmH20 and leak point pressures below 40 cmH20. Randomisation was stratified according to the severity of incontinence (minimal incontinence or total incontinence, definitions were based on the number of pads used, the weight of the pads and quality of life measures).

Exclusion criteria Radiotherapy. Detrusor instability, hyperreflexia.

Population number of patients = 45.

Interventions Patients were randomised to an injection of urethral bulking agent (Macroplastique) or artificial urinary sphincter. A volume of about 5 to 7.5 cc of the bulking agent was applied submucosally above or around the striated sphincter at 3, 6 and 9 o'clock positions. In the artificial urinary sphincter group the AMS 800 (American Medical Systems Inc) was placed around the bulbar urethra, the pump in the scrotum and the reservoir balloon in the

space of Retzius. After 4 to 6 weeks the system was activated.

Outcomes The average number of pads used per day, the weight of the pads. Quality of life was assessed using the SEAPI QMM incontinence classification system. Complication rate.

Follow up Patients in the urethral bulking agent group were follow up for a mean of 48 months (range 6 to 84 months). Patients in the AUS group were followed up for a mean of 60 months (range 8 to 120 months). No loss to follow up was reported.

Results Subgroup analysis was done according to the pre-treatment severity of incontinence (minimal incontinence or total incontinence). Higher values on the quality of life scale indicate poorer QOL.

COMPARISON in Men with total urinary incontinence after prostatectomy	Urethral bulking agent	Artificial urinary sphincter	
Standardised pad test, number of pads	Baseline 2.46, post-treatment 1.41 (p<0.001)	Baseline 2.27, post-treatment 0.36 (p<0.001)	In favour of AUS (p<0.01)
Standardised pad test, grams of urine lost	Baseline 174.2, post-treatment 98.6 (p<0.001)	Baseline 153.1, post-treatment 25.9(p<0.001)	In favour of AUS (p<0.01)
Quality of life	Baseline 33.75, post-treatment 20.05 (p<0.001)	Baseline 33.3, post-treatment 9.2 (p<0.001)	In favour of AUS (p<0.01)
COMPARISON in Men with minimal urinary incontinence after prostatectomy	Urethral bulking agent	Artificial urinary sphincter	
Standardised pad test, grams of urine lost	Baseline 1.52, post-treatment 0.34 (p<0.001)	Baseline 1.33, post-treatment 0.09 (p<0.001)	Authors report no significant difference between groups
Standardised pad test, number of pads	Baseline 84, post-treatment 20.2 (p<0.001)	Baseline 76.3, post-treatment 4.1 (p<0.001)	Authors report no significant difference between groups
Quality of life	Baseline 29.9, post-treatment 8.95 (p<0.001)	Baseline 26.75, post-treatment 6.81 (p<0.001)	Authors report no significant difference between groups
COMPARISON in Men with urinary incontinence after prostatectomy	Urethral bulking agent	Artificial urinary sphincter	
Adverse events	3/23 (urinary retention, urinary infection)	5/22 (included infection, erosions, mechanical failure)	No direct comparison (different types of complications)

General comments Authors conclude that injection of a urethral bulking agent is recommended for minimal incontinence, but for total incontinence AUS is superior.

(Mishel *et al.* 2002)

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

Country: United States, setting: Community

Inclusion criteria Men with localised prostate cancer who were 2 weeks post catheter removal after RP or within 3 weeks of the start of radiotherapy. Men needed a telephone and an identifiable family member willing to participate. Men were recruited from 9 treatment centres.

Exclusion criteria Cognitive impairment, other cancer.

Population number of patients = 239, mean age = 64 years.

Interventions A psycho educational intervention by phone to the men with prostate carcinoma, with or without supplemented delivery to a close family member. The intervention was directed at managing uncertainty and improving symptom control. The intervention was a weekly structured telephone interview with a trained nurse every week for 8 weeks. During the interview symptoms and concerns were assessed and strategies were suggested. The control group received standard care only.

Outcomes Uncertainty and uncertainty management programs (not reported in this appraisal). Number of symptoms, symptom intensity, control over urine flow, ability to have an erection, satisfaction with sexual function.

Follow up Measurements were made at three time points: at entry into the study (baseline - T1), 4 months post baseline (T2) and 7 months post baseline (T3). Loss to follow up is not reported.

Results Control over urine flow was rated on a 1 to 5 scale, 5 being complete control over urine flow.

COMPARISON in Men with erectile dysfunction after radical prostatectomy or EBRT	Psycho educational counselling (man only)	Psycho educational counselling (man and carer)	Standard care	
Control over urine flow	Figures are group means (SD). At baseline 3.64 (1.16), at 4 months 4.52 (0.71) and at 7 months 4.56 (0.71)	At baseline 3.59 (1.19), at 4 months 4.59 (0.79) and at 7 months 4.73 (0.79)	At baseline 3.88 (0.93), at 4 months 4.41 (0.71) and at 7 months 4.51 (0.71)	In favour of the combined treatment groups at 4 months (Wilks lambda F=7.05; p=0.01), but no difference 7 months.

General comments Unclear who rated the symptoms (patient or nurse)

(Filocamo *et al.* 2005)

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

Country: Italy, setting: Tertiary care

Inclusion criteria Men who had undergone RRP for clinical stage T1 or T2 PCa at a single institution.

Exclusion criteria Prior bladder or prostate surgery, prior incontinence, neurogenic dysfunction of the lower urinary tract and preoperative history of overactive bladder.

Population number of patients = 300.

Interventions Patients were randomised to pelvic floor rehabilitation (Kegel exercises only, no biofeedback or electrical stimulation) or to a control group (standard care, no formal pelvic floor exercises). All patients who were incontinent after 6 months underwent urodynamic evaluation, and some received antimuscarinic therapy.

Outcomes Continence, defined using the 1 hour and 24 hour pad test and the incontinence section of the International Continence Society questionnaire.

Follow up Incontinence was assessed at 1, 3, 6 and 12 months after catheter removal. 2 patients in the control group were lost to follow up at the 12 month visit.

Results Multivariate analysis suggested that non-nerve sparing prostatectomy and increasing age were adverse prognostic factors for continence.

COMPARISON in Men after radical retropubic prostatectomy	Pelvic floor muscle training	Standard care	
Continence	19.3% at 1 mth , 74% at 3 mths, 96% at 6 mths and 98.7% at 12 mths	8% at 1 mth , 30% at 3 mths, 64.6% at 6 mths and 88% at 12 mths	favours pelvic floor exercises at all time points (p<0.01)

General comments The pad test results are not fully reported

(Filocamo *et al.* 2007)

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

Country: Italy, setting: Tertiary care

Inclusion criteria Men treated with standard retropubic radical prostatectomy for prostate cancer, between 2005 and 2006. Men had to have predominant symptoms of post prostatectomy stress incontinence, with at least 4 stress incontinence episodes per day and a positive

1 hour pad test.

Exclusion criteria Preoperative incontinence, history of overactive bladder symptoms. Post-operative urge incontinence.

Population number of patients = 112.

Interventions After catheter removal men were randomised to receive either the serotonin re-uptake inhibitor duloxetine (40 mg twice daily) or placebo. Both treatment arms also received pelvic floor muscle training. Treatment was started 10 days after catheter removal and continued for 16 weeks.

Outcomes Incontinence episode frequency (IEF - per day), pad use per day, and incontinence quality of life (I-QOL, assessed using a questionnaire). Adverse events.

Follow up Follow up included assessments at 4, 10, 16, 20 and 24 weeks after randomisation.102/112 men completed the 24 week study.

Results The adverse event rate was 9/59 (15%) in the duloxetine group and 1/53 (2%) in the placebo group. In 70% of cases the adverse event was nausea.

Incontinence Episode Frequency (IEF)

IEF was significantly lower during treatment in the duloxetine group than the placebo group. However, in the two months after stopping drug therapy, IEF was significantly higher in the duloxetine group. The absolute difference in IEF was small and both groups showed significant improvement in continence.

Results for pad use per day were similar to the IEF findings: fewer pads for the duloxetine group during therapy, but not maintained after the 16 week treatment period.

Incontinence related quality of life (I-QOL)

Both groups showed significant improvements in IQOL from the baseline value. IQOL was significantly higher in the

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General comments Adverse events poorly reported. Anti-depressant effects of duloxetine could confound the results.

(Yokoyama *et al.* 2004)

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

Country: , setting: Tertiary care

Inclusion criteria Patients with post prostatectomy incontinence, defined as more than 100g pad weight after the 24 hour pad test 1 day after removal of the catheter. No antocholinegic drugs were prescribed during the study.

Exclusion criteria -

Population number of patients = 36.

Interventions Patients were randomised to one of 3 treatment groups.

Anal functional electrical stimulation (FES) group: the electrode was inserted into the anus and pulse of 20-Hz square waves at 300 ms pulse duration and maximal current 24 mA were used for 15 minutes twice a day for one month.

Extracorporeal magnetic innervation (ExMI) group: the Neocontrol system (Neotonus) was used in treatment sessions of 20 minutes twice a week for 2 weeks. The frequency of the pulse field was 10 Hz intermittently for 10 minutes, followed by a pulse field using 50 Hz. The magnetic coil was set on an armchair such that the centre of the coil was position on the perineum.

Control group: pelvic floor muscle exercises were performed, using verbal feedback from the doctor and written instructions.

Outcomes 24 hour pad weight testing, bladder diaries and a quality of life measurement.

Follow up Measurements were made at 1, 2 and 4 weeks and 2,3,4,5 and 6 months after catheter removal. No loss to follow up was reported.

Results Continence was achieved earlier in the FES and ExMI groups than in the control groups but long term results (at 6 months) were similar in all three groups. The QOL of life measure was scored on a 0 to 100 scale, with 100 being the best QOL. No complications were reported in any of the groups.

The time points in the table below correspond to the time since catheter removal.

COMPARISON in Men with urinary incontinence after radical prostatectomy	Anal electrical stimulation	Extracorporeal magnetic innervation	Pelvic floor muscle training	
Standardised pad test (24hr), grams of urine lost	Around 700g on day 1, around 80g at 1 month, around 50g at 2 months and less than 5g at 6 months.	Around 700g on day 1, around 80g at 1 month, around 20g at 2 months and less than 5g at 6 months.	Around 700g on day 1, around 1700g at 1 month, around 90g at 2 months and less than 5g at 6 months.	In favour of ExMI and FES at 1 month and 2 months only ($p<0.05$)
Quality of life	Decreased to 55.1% at 1 week, around 90% at 6 months	Decreased to 57.8% at 1 week, around 90% at 6 months	Decreased to 51.6% at 1 week, around 90% at 6 months	No statistical difference between groups

(Burgio *et al.* 2006)

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

Country: United States, setting: Tertiary care

Inclusion criteria Men who elected for radical prostatectomy, between 1996 and 2001 at a university urology clinic. Patients had to ambulatory, continent (before surgery) and identified for the study at least one week before surgery.

Exclusion criteria Previous prostatectomy

Population number of patients = 125, age range 53 to 68 years, mean age = 61 years.

Interventions Patients in the treatment group received 1 preoperative session of biofeedback assisted behavioural training plus daily home exercise using written instructions. Biofeedback was provided using a rectal probe connected to a visual display. Patients in the control group received standard care, consisting of simple postoperative instructions to interrupt the urinary stream. Approximately 60% of prostatectomies in both groups preserved at least one neurovascular bundle.

Outcomes Duration of incontinence. A bladder diary. Quality of life was measured using the Hopkins Symptom Checklist and the Medical Outcomes Study Short Form Health Survey (SF-36).

Follow up The questionnaires were completed before surgery and 6 weeks, 3 months and 6 months after surgery. Surgery was cancelled in 13 patients and they were excluded from the intention to treat analysis. 6 month follow up data were available for 51/57 patients in the treatment group and 51/62 patients in the control group.

Results The treatment group returned to continence sooner than the controls (p=0.04, log rank test).

COMPARISON in Candidates for radical prostatectomy for PCa	Pelvic floor muscle training plus biofeed-back	Standard care	
Median time to conti-nence	3.5 months	not reached (>6 months)	
Days with no leakage	Mean at 6 months fol-low-up 72.6 (SD 0.39)	Mean at 6 months fol-low-up 54.2 (SD 0.39)	In favour of pelvic floor training p=0.04 (t test)
Wearing pads	At 6 months follow-up 16/50 (32%)	At 6 months follow-up 24/46 (52.2%)	In favour of pelvic floor training p<0.05 (Chi square)
Number of pads per day	Mean at 6 months fol-low-up 0.54 (SD 1.44)	Mean at 6 months fol-low-up 0.92 (SD 1.59)	No significant differ-ence (p=0.27)

General comments -

(Floratos *et al.* 2002)

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

Country: International, setting: Tertiary care

Inclusion criteria Patients incontinent after radical retropubic prostatectomy. Objectively confirmed incontinence. Good performance status.

Exclusion criteria Significant perioperative complications, preoperative incontinence,

Population number of patients = 42.

Interventions Patients were randomly assigned to 2 groups: pelvic floor muscle exercise (PME) training using either biofeedback or verbal feedback. The biofeedback group had 15 half hour sessions of EMG biofeedback, at a rate of 3 per week. In the verbal guidance group the instructor placed a finger in the patient's rectum during pelvic floor muscle exercises and gave the patient verbal guidance about technique. Both groups practised PMEs at home, up to 100 times daily.

Outcomes The 1 hour pad test was used to measure incontinence. A questionnaire was used to measure incontinence, pad use and symptoms.

Follow up Patients were evaluated at 1, 2, 3 and 6 months of treatment.

Results -

COMPARISON in Men with urinary incontinence after prostatectomy	Pelvic floor muscle training plus biofeedback	Pelvic floor muscle training	
Standardised pad test (1hour), grams of urine lost	Approximate values: at the start of treatment 40g, 1 mth 20g, 6 mth 5g	Approximate values: at the start of treatment 30g, 1 mth 10g, 6 month 5g	No significant difference at any time point
Number of pads used per day	Approximate values: at the start of treatment 4, 1 mth 3.5, 6 mth 0.5	Approximate values: at the start of treatment 4, 1 mth 2, 6 mth 0.5	No significant difference at any time point

General comments Small study, imprecise estimates of outcomes.

(Wille *et al.* 2003)

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

Country: Germany, setting: Tertiary care

Inclusion criteria Men with clinically localised prostate cancer scheduled for radical prostatectomy at a single hospital. Men had to agree to visits at 3 and 12 months postoperatively.

Exclusion criteria -

Population number of patients = 139.

Interventions Patients were randomised to three groups. (Pelvic floor muscle exercises (PME)) vs. (PME plus electrical stimulation (ES)) vs. (PME plus ES plus biofeedback (BFB)). Patients were trained in PME by a physiotherapist during the first 6 postoperative weeks. ES was done using a surface anal electrode connected to a bioimpluse generator (Haynl Elektronik). The same device was used to generate visual biofeedback in the third treatment group.

Outcomes Number of pads daily, symptoms and compliance were measured using a questionnaire. The 20 min pad test (Hahn and Fall) was use to assess continence.

Follow up Measurements were made at baseline and 3 and 12 months postop. At 3 months follow up was 79/139 for the pad test and 120/139 for questionnaires. At 12 months follow up was 124/139 for the pad test and 129/139 for questionnaires.

Results No treatment group differences were seen, and the authors concluded that the treatment program of ES and BFB enhanced PMEs did not affect continence after radical prostatectomy after 3 or 12 months.

COMPARISON in Candidates for radical prostatectomy for PCa	Pelvic floor muscle training	Pelvic floor muscle training plus anal electrical stimulation	Pelvic floor muscle training plus anal electrical stimulation plus biofeedback	
Continence (according to questionnaire)	Immediately postop 20.5%, at 3 mths 60% and at 12 mths 88%	Immediately postop 22.9%, at 3 mths 65% and at 12 mths 81%	Immediately postop 20.7%, at 3 mths 53% and at 12 mths 88.6%	No sig. differences at any time point
Continence (according to pad test)	Immediately postop 29%, at 3 mths not reported and at 12 mths 76.7%	Immediately postop 36.4%, at 3 mths not reported and at 12 mths 82%	Immediately postop 33%, at 3 mths not reported and at 12 mths 90.5%	No sig. differences at any time point

General comments -

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

Study	Comments
(Bales *et al.* 2000)	RCT included in the Hunter Cochrane review
(Franke *et al.* 2000)	RCT included in the Hunter Cochrane review
(Mathewson-Chapman 1997)	RCT included in the Hunter Cochrane review
(Moore *et al.* 1998)	RCT included in the Hunter Cochrane review
(Moore *et al.* 1999)	RCT included in the Hunter Cochrane review
(Parekh *et al.* 2003)	RCT included in the Hunter Cochrane review
(Porru *et al.* 2001)	RCT included in the Hunter Cochrane review
(van *et al.* 2000)	RCT included in the Hunter Cochrane review

Health Economic Summary

The literature search on interventions for urinary incontinence identified 184 potentially relevant papers. Nine of these papers were read in full but none were appraised as they did not include any economic evaluations. No economic modeling was attempted because there was considered to be insufficient clinical information on which to base a model.

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3.8.4 Follow-up

In men who have received treatment for prostate cancer, what is the most effective follow-up protocol?

Short Summary

Literature searches did not identify any studies comparing different follow-up strategies. Some authors have recommended strategies for follow-up (Carroll *et al.* 2001; Catton *et al.* 2003; Edelman *et al.* 1997; Yao & DiPaola 2003) but none comes from a systematic review of the evidence. Studies of the acceptability of follow-up outside hospital have not reported rates of disease recurrence and survival (Rose *et al.* 1996; Cathala *et al.* 2003; Booker *et al.* 2004)

PICO question

POPULATION	INTERVENTIONS	COMPARISONS	OUTCOMES
Men being followed up after, radical radiotherapy or prostatectomy, stratified by risk	• PSA test for biochemical relapse (definitions of relapse will depend on the radical therapy, see also topic 7A). • Clinical examination	Comparisons based on • Length of screening period • Frequency of screening • Place of screening • Person doing the screening (GP etc)	• Cost • Recurrence detection rates • Patient satisfaction • Overall survival

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

Evidence summary

Edelman et al (1997) reviewed the basic principles and available data on follow-up strategies for patients in complete remission following curative therapy for cancer (inc. prostate cancer – reported separately). Recommendations for a limited follow up regimen are made on the basis of cost and detection of recurrence: history/physical examination + PSA 6 monthly for 2 years & annually thereafter. Literature review with no reportable outcomes

Carroll et al (2001) published a best practice policy with regards PSA, and prostate cancer staging and follow-up. No reportable outcomes were provided and no recommendations made on the length, place and frequency of screening, or the person conducting the screening.

Rose et al (1996) evaluated a nurse-managed telephone interview service, designed to identify patient's symptoms 14-21 days after completion of radiotherapy for cancer (inc. prostate cancer – reported separately). Follow-up period was of insufficient duration, and designed to identify side effects of treatment and not those associated with disease recurrence.

Yao & DiPaola (2003) reviewed the evidence for follow up of patients with prostate cancer. The natural course of untreated prostate cancer, the complications of local therapy and delayed vs. early hormonal therapy are critically assessed and recommendations for a follow-up regimen are made. This paper is a literature review with no reportable outcomes.

Catton et al (2003) reviewed the evidence for follow-up strategies and management of patients with prostate cancer, following radical EBRT. The authors recommend that; 1) follow-up via regular PSA monitoring should be continued for life and that this may be done remotely (e.g. by the primary care physician), and 2) the necessary follow up frequency is influenced by individual patient factors. This paper is a literature review with no reportable outcomes.

Vicini et al (2005) reviewed the literature to evaluate the benefits and/or hazards of monitoring serum PSA in patients treated for non-metastatic prostate cancer with surgery or radiation therapy. They conclude that the overall benefit of monitoring serum PSA in these patients remains controversial. The review did not make any comparisons / recommendations with regards frequency / duration of follow-up.

Cathala et al (2003) conducted a feasibility study of an internet-based follow-up of patients with localised prostate cancer treated with laparoscopic radical prostatectomy. An online medical file was used as a physician-patient interface and patients were able to enter their PSA results and complete a quality of life questionnaire. The majority of patients connected regularly and were satisfied with this method of follow-up although no direct comparison was made with other standard methods.

Obek et al (1999) retrospectively analysed the data of 501 patients who had undergone a radical retropubic prostatectomy for prostate cancer. The authors report results for only the 4 patients in whom an abnormal DRE was noted; detectable PSA preceded an abnormal DRE by a mean of 12 months. They conclude that an abnormal DRE in these patients is always associated with a detectable PSA and therefore DRE as a part of routine follow-up in the absence of a detectable PSA may be unnecessary.

Ragavan et al (2005) conducted an audit to assess the factors which influence a change in the management of prostate cancer patients in a nurse led follow-up clinic. They found that a change in PSA trend is the most common factor influencing a change in management, while a change in DRE played only a limited role. The authors conclude that nurse specialists can run prostate cancer follow-up clinics in parallel to existing consultant clinics (thereby allowing the availability of medical personnel to perform DRE where deemed necessary) and DRE may be reserved only for patients with a PSA change / onset of new symptoms.

Booker et al (2004) evaluated a specialist nurse-led telephone service as a first post-intervention follow-up for patients following radical radiotherapy for prostate cancer. Follow-up duration was insufficient to detect recurrence (6 weeks) and was aimed at identifying post-treatment acute effects.

Evidence tables

Edelman, M.J., Meyers, F.J. & Siegel, D. (1997) The Utility of Follow-up Testing After Curative Cancer Therapy. Journal of General Internal Medicine 12(5), pp 318-331

Design: Critical review & economic analysis

Country: USA

Setting: N/A

Inclusion criteria

English language literature reviewed using MEDLINE headings for specific malignancies and the text word “follow-up”

Emphasis placed on prospective, randomised trials or large retrospective studies in which all patients who potentially could have been evaluated were accounted for.

Population

Patients in complete remission following curative therapy for prostate cancer

(review also evaluates Hodgkin’s’ disease, non-Hodgkin’s’ lymphoma, testicular, breast, colo-rectal, and lung cancer)

Interventions

Follow-up testing: PSA, bone scan, physical examination

Outcomes

Detection of recurrence

Cost

Follow up

Results

Authors’ conclusions:

- The utility of following PSA levels to monitor for recurrence remains uncertain
- Recommended follow-up testing:
  - History/physical examination and PSA level only
  - 6 monthly for 2 years, followed by annual follow-up thereafter.

OUTCOME OF INTEREST	Recommended follow up (see above)	Typical follow-up (+ CBC, CXR & annual bone scan)
Cost (of 10 year follow-up period)	$400,000 / 1,000 patients	$1.4 million / 1,000 patients

General comments

Literature review – no reportable outcomes

Best practice reports

Carroll, P., Coley, C., McLeod, D., Schellhammer, P., Sweat, G., Wasson, J., Zietman, A. & Thompson, I. (2001) Prostate-Specific Antigen Best Practice Policy – Part II: Prostate Cancer Staging and Post-treatment Follow-up.

Design: Best practice report

Country: USA

Setting: N/A

Population

Patients with prostate cancer

Interventions

PSA

Outcomes

Detection of recurrence

Follow up

Results

Authors' conclusions:

- Periodic PSA determinations should be offered to detect disease recurrence.

OUTCOME OF INTEREST	INTERVENTION	COMPARISON	RESULT

General comments

Best practice policy with no reportable outcomes.

No comparisons / recommendations made regarding length, frequency or place of screening, and person performing the screening.

Quality assurance projects

Rose, M.A., Shrader-Bogen, C.L., Korlath, G., Priem, J. & Larson, L.R. (1996) Identifying Patient Symptoms After Radiotherapy Using a Nurse-Managed Telephone Interview. Oncology Nursing Forum. Jan-Feb 23(1), pp 99-102

Design: Quality assurance project

Country: USA

Setting: Radiation therapy department in a community hospital in a large Midwestern city

Inclusion criteria

Patients with primary cancer of the prostate, head/neck, lung and breast who had completed the prescribed radiotherapy, spoke English and were able to be contacted by telephone

Population

111 patients treated by radiotherapy for primary cancer of the prostate, head/neck, lung and breast (49 patients with prostate cancer)

Age: mean = 66 years, range = 34 – 85 years

Interventions

Nurse-managed telephone interview

Outcomes

Symptoms at end of treatment & at telephone interview

Nursing assessments & interventions

Length of telephone interview

Follow up

14-21 days post-radiotherapy

Results

OUTCOME OF INTEREST	End of treatment (within last 5 days)	Telephone follow-up (14-21 days)
Prostate cancer patients only:		
• Experiencing ≥ 1 symptom	49/49 (98%)	42/47 (89%)
• Development of ≥ 1 new symptom		7/47
• Assessment of new / unresolved symptoms		40/47
• Education for symptom management		3/47
• Follow-up appt reminder		7/47
• Education for medication management		2/47
• Physician referral		1/47

Length of telephone calls, mean(range) = 4.42 (1.5 – 20) minutes (for all patients, not specific to prostate cancer patients)

General comments

A priori criteria for interventions and outcomes not met

Follow-up designed to assess the side effects of treatment with radiotherapy – time period not long enough to detect recurrence.

Literature reviews

Yao, S.L. & DiPaola, R.S. (2003) An Evidence-Based Approach to Prostate Cancer Follow-Up. Seminars in Oncology 30(3), pp 390-400

Design: Critical review

Country: USA

Setting: N/A

Population

Men treated with definitive therapy for prostate cancer with radiation or surgery

Results

Recommendations for follow-up in men treated for prostate cancer derived from review of data without attention to cost analysis or specific patient problems (to be modified for individual patients):

- International Prostate Symptom Score (IPSS) – every 6-12 months
- Quality of life – annually
- PSA – every 6 months during 1st 5 years, then annually thereafter
- DRE – annually
- Routine health maintenance inc. cardiovascular risk assessment / modification as appropriate

General comments

- Literature review with no reportable outcomes
- Review critically assesses the natural course of untreated prostate cancer, the complications of local therapy, issues regarding early versus delayed hormonal therapy and methods of determining eligibility for clinical studies.

Reviews

Catton, C., Milosevic, M., Warde, P., Bayley, A., Crook, J., Bristow, R. & Gospodarowicz, M. (2003) Recurrent prostate cancer following external beam radiotherapy: Follow-up strategies and management. Urologic Clinics of North America 30(4), pp 751-763.
Design: Review Country: Canada Setting: N/A **Population** Patients with prostate cancer, treated with radical external beam radiotherapy **Interventions** PSA, DRE, post-treatment biopsy of prostate & imaging techniques **Outcomes** Detection & treatment of recurrence **Results** Authors' conclusions: • There is no strong evidence that patients stop being at risk for recurrence at any time after treatment… it is recommended that periodic PSA measurements be continued for life. In the absence of a rising PSA, all other tests and visits are unnecessary. • Follow-up duties may be reasonably shared between the oncologist and the family doctor / urologist • It should be possible to follow patient remotely – by asking patients to have PSA tests done and forward the results to their physicians / by delegating follow-up to primary-care physicians with guidelines as to when referral back is required • Follow-up frequency, and the most beneficial follow-up investigations vary from scenario to scenario, and are influenced by the likelihood of relapse, time to relapse and planned intervention **General comments** Literature review – no reportable outcomes

Literature reviews

Vicini, F.A., Vargas, C., Abner, A., Kestin, L., Horwitz, E. & Martinez, A. (2005) Limitations in the use of serum prostate specific antigen levels to monitor patients after treatment for prostate cancer. The Journal of Urology 173(5) pp 1456-1462

Design: Literature review

Country: US

Setting: NA

Inclusion criteria:

Articles included:

- Trials published in English, in peer-reviewed journals (published studies & abstracts), specifically addressing the impact of monitoring serum PSA after treatment with RT or surgery for localised prostate cancer.

Search criteria:

- MEDLINE & CancerLit search (1990 to 2004)
- Search items included certain combined subject headings, including prostate neoplasms, radiotherapy, surgery, prostatectomy, prostate specific antigen and biochemical control (BC)/failure

Exclusion criteria

- Not all articles identified were used in analysis due to space limitations or duplicate publication
- Articles with insufficient follow up, small patient numbers or poor study designs were not analysed

Population

Patients treated with surgery or radiation therapy for non-metastatic prostate cancer

Interventions

Serum PSA levels

Outcomes

Articles reviewed to answer certain questions:

1) Can serial PSA monitoring after treatment provide an early surrogate assessment of cancer cure?
2) Do serial PSA measurements after treatment provide an early and accurate surrogate measurement of treatment failure?
3) If serial PSA measurements provide an early assessment of treatment failure, what is the magnitude of the lead time to clinical failure that this information provides?
4) Does any pattern in the PSA profile after treatment provide conclusive evidence of early local vs. systemic failure?

5) Are there any data to suggest that the early identification of BF with subsequent intervention may improve outcome?

Follow up Not reported

Results

QUESTION	NO. OF STUDIES	CONCLUSIONS
1	RT = 16; Surgery =?	No absolute PSA nadir level within first 4-5 years identified to definitively establish long-term biochemical control (cure)
2	RT = 21; Surgery =?	Inconsistent results & conclusions
3	6	No pattern of PSA kinetics has conclusively been associated with a specific recurrence site
4	6	Absolute lead time gained was variable. BF definitions in patients treated with RT appear to provide a 6-18 month lead time to clinical failure
5	6	Limited data to suggest early intervention of any type impacts survival

General comments

Literature review – no assessment of quality of studies, no reportable outcomes or meta-analysis

Authors conclusion: “The overall benefit of monitoring serum PSA after treatment for prostate cancer remains controversial”

Feasibility studies

Cathala, N., Brillat, F., Mombet, A., Lobel, E., Prapotnich, D., Alexandre, L. & Vallancien G. (2003) Patient follow-up after radical prostatectomy by internet medical file. The Journal of Urology 170(6) pp 2284-2287

Design: Feasibility study

Country: France

Setting: Patients' homes

Duration: 6 months

Population

Number of patients = 140

Patients with localised prostate cancer, treated with laparoscopic radical prostatectomy at the department between November 2000 & November 2001, who had computer access at home.

Mean age = 63 years (46 – 70)

Interventions

Website to be used as physician-patient interface for follow-up (inc. PSA data & quality of life questionnaire based on urinary continence & sexuality)

Outcomes

Patient use of online medical file

Patient satisfaction with method of follow-up

Follow up

Follow up via internet medical file

Results

OUTCOME OF INTEREST	RESULT
Patient use	95% regularly consulted website [mean = 8 connections per patient (1-22)]
Patient satisfaction (mail questionnaire)	98% patient satisfaction

- 11% had problems accessing site & 14% reported technical problems

General comments

- No reportable outcomes on QOL questionnaires and PSA
- Preliminary feasibility study found only 31% had internet access and only 48% were in favour of receiving medical file online

- 140/508 patients agreed to be included; 58% were senior executives / professionals (poor generalizability)
- Inconsistencies in reporting of patient numbers & percentages ("140 patients agreed to test the system" / "of these 100 patients"; "of these 100 patients 92 connected regularly" / "95% regularly consulted the website")

Diagnostic studies

Obek, C., Neulander, E., Sadek, S. & Soloway, M.S. (1999) Is there a role for digital rectal examination in the follow-up of patients after radical prostatectomy? Journal of Urology 162(3) pp 762-764

Design: Case series

Country: USA

Setting:

Recruitment: 1992 - 1998

Population

501 consecutive patients who underwent radical retropubic prostatectomy for clinically localised adenocarcinoma

Interventions

Digital rectal examination (DRE)

Comparator

PSA (biochemical recurrence; PSA>0.2ng/ml & increasing on at least 2 consecutive measurements)

Outcomes

Local recurrence defined as an induration or nodularity in prostatic fossa upon DRE

Follow up

Patients evaluated at 3 – 6 month intervals after surgery.

DRE & PSA performed at each visit

Mean follow-up = 25.4 +/- 20.8 months

Results

OUTCOME OF INTEREST	RESULT
Biochemical disease recurrence	72 / 501 (14.4%)

Local disease recurrence detected on DRE	4 patients (0.7% of overall population; 5.5% of 72 patients with biochemical recurrence)

In 3/4 patients a detectable PSA preceded an abnormal DRE (by 8, 9 & 19 months)

In 1/4 patients DRE and PSA were both abnormal at the same visit

General comments

Authors' conclusion: "Results suggest an abnormal DRE after radical prostatectomy is always associated with detectable PSA, which implies that performing a DRE in absence of detectable PSA may not be necessary"

Neoadjuvant hormonal therapy given in n = 138

Retrospective analysis, data only reported on 4/501 patients

Prospective Audits

Ragavan, N., Sangar, V., Gupta, S., Herdman, J., Matanhelia, S., Watson, M. & Blades, R. (2005) Is DRE essential for the follow up of prostate cancer patients? A prospective audit of 194 patients. BMC Urology 5(1) pp1-

Design: Prospective audit

Country: United Kingdom

Setting: Urology outpatients clinic

Recruitment: 2 month period: December 2002 – January 2003

Population

194 prostate cancer patients

Mean age = 74.8 years

Stages at initial diagnosis: T1 – T4 (n=73 (T1), 63(T2), 44(T3), 14(T4); 10 patients with metastatic disease)

Patients had undergone:

Hormonal manipulation (n = 68, 35%)

Orchidectomy (n = 8, 4.1%)

Radical radiotherapy with hormonal manipulation (n = 15, 7.8%)

Radical radiotherapy (n = 48, 24.6%)

Radical prostatectomy (n = 21, 10.8%)

Brachytherapy (n = 1, 0.5%)

Active surveillance (n = 33, 17%)

Interventions

Measurement of: PSA trend, lower urinary tract symptoms, bone pains, DRE findings, pruritis, altered renal functions, erectile dysfunction, bleeding per rectum

Outcomes

Change in management, defined as any alteration in follow-up pattern:

advancement or postponement of future appointments

need for further investigations or treatment

admission of patient

referral to different specialist

Results

OUTCOME OF INTEREST	RESULT
Change of management	47 / 194 (24%)
Factors influencing change in management:	
PSA trend	n = 27 (57.5%)
LUTS	n = 10 (21.3%)
Bone pain	n = 4 (8.5%)
Change in DRE finding	n = 2 (4.3%)
Abnormal renal function	n = 1 (2.1%)
Haematochezia	n = 1 (2.1%)
Pruritis	n = 1 (2.1%)
Erectile dysfunction	n = 1 (2.1%)

General comments

Authors' conclusion: "PSA is the most common factor influencing the change in management of these patients"

A priori criteria for population not met (not restricted to radical radiotherapy / prostatectomy or stratified by risk)

Pilot studie

Booker, J., Eardley, A., Cowan, R., Logue, J., Wylie, J. & Caress A. (2004) Telephone first post-intervention follow-up for men who have had radical radiotherapy to the prostate: evaluation of a novel service delivery approach. European Journal of Oncology Nursing 8(4) pp 325-333

Design: Pilot study

Country: United Kingdom

Setting: Telephone interviews

Recruitment: 47 men approached over 3 month period, 36/47 elected to receive telephone follow-up following verbal & written explanation of intervention

Population

36 men who had undergone radiotherapy treatment for prostate cancer

Interventions

Telephone follow-up by nurse to assess overall functional ability and physical symptoms following treatment

Outcomes

Patient perception of quality of service (open & closed question questionnaire):

Practicalities of telephone follow-up in terms of clear explanation, timeliness of call and convenience

Satisfaction with nurse knowledge & ability to deal with questions / concerns

Acceptability of nurse-led, telephone follow-up

Follow up

6 weeks post-treatment

Results

OUTCOME OF INTEREST	RESULT
Practicalities of telephone follow-up	35/36 patients satisfied
Nurse knowledge & ability	35/36 patients satisfied
Acceptability in comparison to standard follow-up:	
Telephone just as good	27/36
Telephone better	3/36
Telephone not as good	1/36
No strong feelings either way	5/36

Comments: 2 men did not have phones but had access to neighbour's phone

General comments

Authors' conclusion: "Telephone follow-up appears to have potential in this population and merits wider research-based consideration" A priori inclusion criteria for interventions not met

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.

Reference List

Booker, J., Eardley, A., Cowan, R., Logue, J., Wylie, J. & Caress, A. Telephone first post-intervention follow-up for men who have had radical radiotherapy to the prostate: evaluation of a novel service delivery approach. *European Journal of Oncology Nursing; 2004 Dec; 8(4):325-333,* 2004 Dec; 8: 325-333.

Carroll, P., Coley, C., McLeod, D., Schellhammer, P., Sweat, G., Wasson, J., Zietman, A. & Thompson, I. (2001) Prostate-specific antigen best practice policy--part II: prostate cancer staging and post-treatment follow-up. [Review] [38 refs]. *Urology,* 57: 225-229.

Cathala, N., Brillat, F., Mombet, A., Lobel, E., Prapotnich, D., Alexandre, L. & Vallancien, G. (2003) Patient followup after radical prostatectomy by internet medical file. *J Urol,* 170: 2284-2287.

Catton, C., Milosevic, M., Warde, P., Bayley, A., Crook, J., Bristow, R. & Gospodarowicz, M. (2003) Recurrent prostate cancer following external beam radiotherapy: Follow-up strategies and management. *Urol Clin North Am,* 30: 751-+.

Edelman, M. J., Meyers, F. J. & Siegel, D. (1997) The utility of follow-up testing after curative cancer therapy. A critical review and economic analysis. [Review] [133 refs]. *J Gen Intern. Med,* 12: 318-331.

Rose, M. A., Shrader-Bogen, C. L., Korlath, G., Priem, J. & Larson, L. R. Identifying patient symptoms after radiotherapy using a nurse-managed telephone interview. *Oncol Nurs.Forum; 1996.Jan-Feb; 23(1):99-102,* 1996 Jan-Feb; 23: 99-102.

Yao, S. L. & DiPaola, R. S. (2003) An evidence-based approach to prostate cancer follow-up. [Review] [56 refs]. *Semin. Oncol,* 30: 390-400.

4 Managing relapse after radical treatment

4.1 Defining biochemical relapse

In men who have had radical treatment for prostate cancer, what is the clinical importance of biochemical relapse after radical therapy and how should biochemical relapse be defined?

Short summary

Evidence from case series and clinical trials shows that that not all men with biochemical relapse after definitive prostate cancer therapy experience distant metastasis or death from prostate cancer (Vicini *et al.* 2005; Pound *et al.* 1999). Given this, studies have examined factors that signify clinically relevant biochemical recurrence. PSA-DT less than 3 months was an adverse prognostic factor for cancer specific survival (Freedland *et al.* 2005; D'Amico *et al.* 2004) and overall survival (D'Amico et al. 2004) in series of men with biochemical relapse. Gleason score was a prognostic factor for disease specific survival (Freedland *et al.* 2005; Kwan *et al.* 2006).

Definitions of biochemical relapse

After prostatectomy

Reviews report a variety of biochemical relapse definitions in the literature (Vicini 2005; (Cookson *et al.* 2007)), most commonly PSA of 0.2 ng/ml or more and rising and PSA of 0.4 ng/ml or more and rising (Cookson *et al.* 2007). Stephenson and co-workers (Stephenson et al. 2006) compared definitions of biochemical relapse in a large series of men following prostatectomy. The definition that best correlated with metastatic progression was PSA of 0.4 ng/ml or more and rising. A recent ASTRO consensus panel favoured a definition of 0.2 ng/ml or more and rising due to its greater sensitivity (Cookson *et al.* 2007).

After external beam radiotherapy

Meta-analysis of individual patient data was used to test 102 definitions of biochemical recurrence after external beam radiotherapy (Kuban *et al.* 2005b; Horwitz *et al.* 2005). The definitions with the best sensitivity and specificity for clinical and distant failure were those using a fixed PSA rise (2 or 3 ng/ml) above the current nadir value at call. The 2005 ASTRO consensus definition (PSA greater than current nadir + 2 ng/ml at call: (Roach *et al.* 2006)), had a sensitivity of 74% and specificity of 71% for any clinical failure.

After brachytherapy

Kuban and co-workers (Kuban et al. 2006) reported the most sensitive and specific practical definitions of biochemical recurrence after brachytherapy were the current nadir + 1 ng/ml and the current nadir + 2 ng/ml (ASTRO 2005). The sensitivity and specificity of the ASTRO 2005 definition were comparable to those seen in the radiotherapy cohort (Kuban *et al.* 2005b; Horwitz *et al.* 2005). The ASTRO 2005 definition had a false call rate of 2% due to PSA bounce in a large series of men after external beam radiotherapy or brachytherapy for prostate cancer (Pick-

les 2006).

PICO question

POPULATION	PROGNOSTIC FACTOR	OUTCOME
Men who have had radical treatment for prostate cancer	Biochemical relapse (comparing different definitions of biochemical relapse).	Accuracy of prediction of: • overall survival • disease-free survival • time till next intervention • quality of life • costs

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

Evidence summary

Clinical relevance of biochemical relapse (biochemical recurrence)

Biochemical relapse as a surrogate for clinical recurrence and survival

Evidence from case series shows that not all men with biochemical recurrence after definitive local therapy experience distant metastasis, and not all of those with distant metastasis experience prostate cancer specific mortality (Vicini et al. 2005). In the post-prostatectomy series reported by Pound (Pound et al. 1999), 34% of those with biochemical recurrence (single PSA of at least 0.2 ng/ml) went on to develop clinically evident metastases, at a median of 8 years after biochemical recurrence. Using serial PSA testing with current definitions of biochemical relapse, approximately 70% of cases of clinical recurrence after radiotherapy were preceded by biochemical relapse, in the cohort study of Horwitz and co-workers (Horwitz *et al.* 2005; Kuban *et al.* 2005b). The specificity of definitions of biochemical relapse was also imperfect, so not all of those with biochemical relapse went on to experience clinical recurrence.

Thus biochemical recurrence is an intermediate endpoint, and not necessarily a surrogate, for distant metastasis or disease specific survival.

Prognostic factors after biochemical failure (but before clinical recurrence)

Given that not all men with biochemical recurrence will experience clinical failure in their lifetime, some studies have looked at factors that signify clinically relevant biochemical recurrence. In a series of men treated with radiotherapy for prostate cancer (Kwan et al. 2006), biochemical recurrence was associated with reduced disease specific survival in men with intermediate or high risk disease (risk was based on Gleason score, tumour stage and serum PSA level). Biochemical recurrence was associated with reduced overall survival, but only in patients younger than 75 with high risk disease.

Freedland and co workers (Freedland et al. 2005) examined prognostic factors for prostate cancer specific mortality in men with biochemical recurrence (single PSA of 0.2 ng/ml or more) after prostatectomy. On multivariate analysis PSADT of less than three months, Gleason score of eight or more, and less than three years between surgery and biochemical recurrence were all adverse risk factors for prostate cancer specific mortality. In the series reported by D'Amico (D'Amico et al. 2004) a PSA-DT of less than three months was an adverse prognostic factor for prostate cancer mortality, and all cause mortality, in men with biochemical recurrence. Other

prospective (D'Amico *et al.* 2006) and retrospective (Tollefson *et al.* 2007) case series support the use of PSA doubling time as a predictor of risk of prostate cancer death.

Dotan and co workers (Dotan et al. 2005) published a nomogram to predict the probability of a positive bone scan in men with biochemical recurrence after prostatectomy. The predictive factors were: pathological features and Gleason sum of the prostatectomy specimen, pre-treatment PSA level, the PSA level that triggered the call of biochemical recurrence, PSA slope and PSA velocity.

Benefits of treatment before clinical recurrence.

If treatment at the time of biochemical recurrence results in better outcome than if it is deferred until clinical failure then diagnosis of biochemical recurrence is clinically relevant. There is only, however, only indirect evidence that treatment of PSA-only recurrence results in better outcomes than deferred treatment (see topic 7c).

Timing of biochemical recurrence.

The timing of biochemical recurrence could have clinical relevance if it discriminates local from distant failure. Vincenzi (Vicini et al. 2005) summarised six studies looking at time to biochemical recurrence as a predictive factor of local and distant recurrence and found that shorter time to biochemical recurrence was a predictive factor of distant metastasis. The review was unclear how this could be used to make decisions about salvage therapy.

Definition of biochemical relapse after external beam radiotherapy

The Vicini review (Vicini et al. 2005) reports a number of case series comparing definitions of biochemical relapse after radiotherapy. Results were inconsistent, but most found biochemical recurrence (using the ASTRO-1997 consensus definition) correlated with clinical recurrence. Those comparing definitions of biochemical recurrence did not find the ASTRO-1997 definition the most sensitive or specific.

The authors of some of these publications combined their datasets and tested 102 definitions of biochemical failure in the resulting series of 4839 men with T1 to T2 prostate cancer (Kuban *et al.* 2005b; Horwitz *et al.* 2005). The definitions with the best sensitivity and specificity for clinical and distant failure were those which used a fixed PSA rise (2 or 3 ng/ml) above the current nadir value at call. The 2005 ASTRO consensus definition (PSA greater than current nadir + 2 ng/ml at call: Roach, 2006), had a sensitivity of 74% and specificity of 71% for any clinical failure.

Definition of biochemical relapse after brachytherapy

Kuban and co-workers (Kuban et al. 2006) reported the most sensitive and specific definitions of BCR after brachytherapy were those using absolute thresholds (PSA of more than 2 or 3 ng/ml), but were impractical due to the gradual decrease of PSA after brachytherapy. The two definitions incorporating the nadir plus threshold value were the next most sensitive and specific (current nadir + 1 ng/ml; current nadir + 2 ng/ml – ASTRO 2005). The sensitivity and specificity of the ASTRO 2005 definition for the prediction of clinical failure were 70% and 89% respectively. These figures are comparable to those seen in the external radiotherapy cohort originally reported by (Kuban *et al.* 2005b; Horwitz *et al.* 2005) (72% and 83% respectively).

The impact of PSA bounce (after brachytherapy or external beam radiotherapy) on the accuracy BCR definitions was considered by Pickles (Pickles 2006) in a series of 2030 patients. The false call rates (false positive call of biochemical failure triggered by PSA bounce) were compared for

nine different BCR definitions. The definitions with the lowest false call rates were: current nadir + 3 ng/ml, current nadir + 2 ng/ml (ASTRO-2005), and threshold +3 ng/ml with false call rates of 2%, 2% and 4% respectively. Subgroup analysis did not reveal a significant difference between false call rates in terms of radiotherapy type (brachytherapy vs. EBRT).

Definition of biochemical recurrence after radical prostatectomy

The definition of biochemical recurrence after radical prostatectomy should be less complicated than for radiotherapy, since if all prostate tissue is removed serum PSA should be undetectable. In the Vicini review (Vicini et al. 2005) however, there did not appear to be consensus on the definition of biochemical recurrence after prostatectomy. Some studies used a threshold serum PSA level (any detectable, 0.2 or 0.4 ng/ml), some used consecutive values above a threshold value and others used rate of PSA rise (PSA doubling time). Biochemical failure (using the authors' definitions) correlated with clinical progression in six of the nine included studies. A recent ASTRO consensus panel favoured a definition of 0.2 ng/ml or more and rising due to its greater sensitivity (Cookson *et al.* 2007).

Stephenson and co workers (Stephenson et al. 2006) compared definitions of biochemical recurrence that best predicted metastatic disease progression, in a large series of men after radical prostatectomy. This study used multivariate analysis (to correct for disease characteristics), including preoperative PSA level, Gleason grade, surgical margin status, pathologic stage and use of secondary therapy as covariates. The definition that best correlated with metastatic progression was PSA of 0.4 ng/ml or more and rising: This definition was associated with relatively high probability of subsequent PSA progression within 4 years (91%) and secondary therapy or clinical failure within 7 years (62%). This was also the definition resulting in the fewest calls of biochemical recurrence

Evidence Tables

Systematic review of cohort studies

(Vicini *et al.* 2005)

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

Country: International

Inclusion criteria Studies of the use of serial PSA testing as a surrogate for clinical outcomes, published between 1990 and 2004. Studies had to be published in peer reviewed journals.

Exclusion criteria Repeat publication, insufficient follow-up, small patient numbers or poor study design (none of these criteria were defined in the review).

Population -

Interventions Studies were reviewed to determine

1) if serial PSA monitoring provides an early and accurate surrogate assessment of cancer cure or treatment failure,

2) if any pattern in the PSA profile after treatment provides conclusive evidence of early local vs. systemic failure,

3) the magnitude of the lead time to clinical failure that serial PSA monitoring may provide and

4) if the early identification of biochemical failure (BF) with earlier intervention improves outcome.

603 potentially relevant articles were identified from which 128 relevant studies emerged after screening. These relevant studies were further filtered to remove repeat publications and poor quality studies (on the basis of size, follow-up or study design).

Outcomes Biochemical failure (BF) variously defined, cancer specific survival (CSS) and distant metastasis (DM).

Results

Defining biochemical failure after RT

21 relevant studies, of which 13 were considered in more detail. There was inconsistency in the results and conclusions of these studies. Some studies found BF according to the ASTRO consensus definition to be a significant prognostic factor, others did not. In the four studies reporting multiple definitions, the ASTRO definition was not the most sensitive or specific.

Defining biochemical failure after surgery

Studies used a threshold value for BF, ranging from detectable PSA to 0.2 and 0.4 ng/ml. BF did not always predict clinical progression in the nine included studies. One study PSA doubling time (PSADT) to be a predictor of CSS.

Time to clinical failure

Short PSADT was a predictor of time to clinical failure after both EBRT and surgery (from 3 studies, n=2681 patients). Gleason score (in one study) and PSA level 1 to 3 ng/ml above the nadir value (in one study) were also prognostic factors for earlier clinical failure.

Impact of early intervention

Authors mention that after BF following surgery, RT is most effective if delivered early, but do not provided references. Six studies of initiation of androgen therapy at the time of BF, some of which suggest improved survival

Retrospective cohort studies

(Horwitz *et al.* 2005)

Design: Retrospective cohort study (diagnosis, screening), evidence level: 2-

Country: United States, setting: Multi-institutional

Inclusion criteria Men with clinical T1b to T2N0M0 prostate cancer, treated with EBRT between 1986 and 1995 at one of 9 participating institutions.

Exclusion criteria Neoadjuvant or planned adjuvant androgen suppression.

Population number of patients = 4389.

Interventions All men received at least 60 Gy of radiotherapy to the prostate. The sensitivity and specificity of 102 definitions of biochemical failure (BFD) for the prediction of distant failure (DF) and local failure (LF) were assessed.

Outcomes The sensitivity and specificity of the BF definitions using distant failure (DF) alone or clinical failure (CF), defined as local failure (LF) and/or DF.

Follow up Median follow-up was 6.3 years

Results 416 patients experienced local failure, and 329 experienced distant failure.

Predicting distant failure from BF

20 BF definitions were more sensitive and specific than the ASTRO definition, in the prediction of DF. The sensitivity and specificity of the ASTRO BFD were 55% and 68% respectively, compared to 76% and 72% for the definition using current nadir + 3 ng/ml (at call).

Hazard of distant failure in men with BF

The hazard ratio for DF in men with BF according to the current nadir + 3 ng/ml definition was 35.57 compared to 5.55 using the ASTRO definition.

Clinical failure (local failure and/or distant failure)

Three definitions were more sensitive and specific than the ASTRO consensus definition (see table below).

COMPARISON IN MEN AFTER EBRT FOR PCA	ASTRO-1997 CONSENSUS DEFINITION	PSA > CURRENT NADIR + 3 NG/ML (AT CALL)	PSA > CURRENT NADIR + 2 NG/ML (AT CALL)	2 CONSECUTIVE RISES OF AT LEAST 0.5 NG/ML, BACKDATED	OVERALL RESULT
Sensitivity for CF	60%	66%	74%	67%	
Specificity for CF	72%	77%	71%	78%	
Hazard ratio for CF	6.15	17.81	20.01	12.43	

General comments Overall definitions incorporating a fixed PSA rise above the current nadir value seemed to have the best sensitivity and specificity for DF and CF.

Definitions based on a single absolute PSA threshold were sensitive but had poor specificity.

Different definitions could be used depending on whether the aim is to diagnose cure or biochemical failure (the single definitions tend not to have both high sensitivity and specificity for BF).

(D'Amico *et al.* 2004)

Design: Retrospective cohort study (prognosis), evidence level: 3

Country: United States, setting: multi-centre study

Inclusion criteria Men entered in the CaPSURE or CPDR databases. The men had been treated with prostatectomy (n=5918) or radiotherapy (n=2751) for clinical stage T1c to T4NxM0 prostate cancer. Up to 3 months of neoadjuvant androgen therapy were permitted.

Exclusion criteria Patients receiving adjuvant therapy.

Population number of patients = 8669.

Interventions Serial PSA measurements, Agents; Hormonal; Blood; Combined Modality Therapy; Humans; Male; Met

Outcomes Prostate cancer specific mortality (PCSM), overall mortality. PSA doubling time (PSADT)

Follow up Follow-up started from the first day of treatment. Median follow up was 7.1 years

(range 0.5 to 14.3 years) for men treated with surgery. Median follow up was 6.9 years (range 0.8 to 14.5 years) for men treated with radiotherapy.

Results Patients treated with radiotherapy tended to be older, and have higher biopsy Gleason score and serum PSA level than those treated with surgery.

PSA recurrence was experienced by 611/5918 (10%) of patients treated with surgery and by 840/2751 (31%) of those treated with radiotherapy.

Overall there were 154 deaths of which 110 were attributed to prostate cancer. 29% of men with biochemical recurrence died of other causes.

On multivariate analysis PSADT of 3 months or less was an adverse prognostic factor for PCSM, ($p<0.001$). The authors argued that PSADT was a surrogate for PCSM as death was not dependent on other factors once a patient reached PSADT of 3 months or less.

General comments -

(Kuban *et al.* 2006)

Design: Retrospective cohort study (prognosis), evidence level: 3

Country: United States, setting: Multi-centre

Inclusion criteria Men treated with permanent prostatic implant brachytherapy as monotherapy for prostate cancer. This was a multicentre case series. Men were treated between 1988 and 1998.

A cohort of 4893 men treated using EBRT (previously reported in Kuban et al, 2005) were included for

Exclusion criteria Hormonal therapy before biochemical failure. Less than three post treatment PSA measurements.

Population number of patients = 2693.

Interventions Men were treated with permanent radioisotope implant (I-25 or Pd-103). 1831/2693 (68%) were treated with I-25 implants, at median prescribed dose of 160 Gy The remainder were treated using Pd-103 at median prescribed dose of 120 Gy.

Outcomes Clinical failure: defined as local, regional or distant. PSA of more than 25 ng/ml or initiation of hormonal therapy were also considered clinical failure.

Follow up Median follow up was 63 months.

Results The most sensitive and specific definitions of biochemical failure (BF) were those using absolute values (PSA of 2.0 or 3.0 ng/ml), but authors note that such definitions cannot be used immediately after radiotherapy, due to the gradual decrease in PSA. The nadir plus 1 or 2 ng/ml BF definitions were the next most accurate.

Similar results were seen when regression analysis was used to calculate the hazard ratio (HR) for clinical failure for each BF definition. The definitions based on a single threshold PSA

value had the highest HR for clinical failure, followed by the nadir + threshold definitions authors argue that the ASTRO 2005 consensus definition (nadir + 2 ng/ml) should be used after both brachytherapy and EBRT.

COMPARISON IN MEN AFTER BRACHYTHERAPY FOR PCA	NADIR + 2 NG/ML	NADIR + 1 NG/ML	PSA 3 NG/ML	PSA 2 NG/ML	OVERALL RESULT
Sensitivity for CF	70%	77%	81%	86%	
Specificity for CF	89%	82%	87%	82%	
COMPARISON IN MEN AFTER EBRT FOR PCA	NADIR + 2 NG/ML	NADIR + 1 NG/ML	PSA 3 NG/ML	PSA 2 NG/ML	OVERALL RESULT
Sensitivity for CF	72%	82%	78%	86%	
Specificity for CF	83%	71%	81%	71%	

General comments -

Prospective case series

(D'Amico *et al.* 2006)

Design: Prospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men with clinical stage T1b to T2b prostate cancer, enrolled on a randomised trial of adjuvant androgen deprivation therapy, who experienced biochemical failure (PSA >1.0 ng/mL, and increasing by more than 0.2 ng/mL on two consecutive measurements).

At trial entry men had one high risk feature (PSA level > 10 ng/mL, Gleason score 7 or higher, or T3 disease on MRI). Life expectancy 10 years or more, ECOG performance status 0 or 1.

Exclusion criteria -

Population number of patients = 81.

Interventions As initial curative therapy, all men received radiotherapy and were randomised to receive 6 months of androgen suppression therapy or no androgen suppression therapy.

After biochemical failure, salvage therapy was left to the discretion of the treating doctor, and was typically medical or surgical castration.

Outcomes Overall survival, disease specific survival, and time to initiation of salvage hormone therapy.

Follow up The median follow-up for living patients was 7.3 years from randomisation and 3 years after biochemical failure.

Results Overall mortality was 23/81 (28%) and 11/81 men (14%) died from prostate cancer.

Salvage hormone therapy was given at a median PSA level of 9.6 ng/mL (IQR 7.8 to 11.8 ng/mL). The median time to initiation of salvage hormone therapy significantly increased with increasing PSA-DT. For men with a PSA-DT <6, 6 to 12 and >12 months the median times were 0.2, 1.3 and 1.4 years respectively.

Multivariate analysis of predictive factors for mortality after biochemical failure. A PSA-DT < 6 months (p = 0.04) and age at the time of PSA failure (p = 0.009) were significantly associated with length of survival.

Adjusted hazard ratios: for age at PSA failure HR=1.1 (95% CI 1.03 to 1.26). For PSA-DT < 6 months, HR=4.9 (95% CI 1.1 to 23).

General comments -

(Kim-Sing *et al.* 2004)

Design: Prospective case series (prognosis), evidence level: 3

Country: Canada, setting: Tertiary care

Inclusion criteria Men treated with EBRT for prostate cancer at either of 2 institutions between 1994 and 2000, and entered into a prospective database.

Exclusion criteria Patients with simultaneous biochemical and clinical relapse were excluded from the analysis.

Population number of patients = 1499.

Interventions All patients were treated with EBRT. Those deemed at higher risk tumours were also treated with neoadjuvant or adjuvant androgen ablation, using LHRH agonist combined with an anti-androgen.

Biochemical relapse defined as the time when PSA rose above 1.5 ng/ml. The intervention PSA was defined as the last PSA recorded before secondary intervention (androgen ablation). PSADT was calculated from the first PSA greater than 1 ng/ml and the last PSA before intervention.

Outcomes Time to intervention (androgen ablation). Disease specific survival.

Follow up Median follow-up for clinical outcomes was 57 months and for survival was 71 months. Men were seen 6 weeks after the completion of EBRT, then twice a year for 3 years, then annually for 3 years and biannually thereafter.

Results Biochemical relapse occurred in 544/1499 (36%) of patients, 79 men had simultaneous biochemical and clinical relapse and were excluded from the analysis, leaving 465. Me-

dian time from EBRT to relapse in this group was 27 months.

215/465 men underwent a secondary intervention following biochemical relapse. The median time from biochemical relapse to intervention was 30 months in this group.

On multivariate analysis (Cox regression) the only significant predictor of time to intervention after biochemical relapse was PSADT (OR = 9.75 [95%CI 7.4 to 12.9], p<0.0001) with faster PSADT associated with earlier intervention. The time to biochemical relapse, T-stage, Gleason score and use of neoadjuvant or adjuvant hormonal therapy were not independent predictors of time to intervention.

On multivariate analysis of disease specific survival the significant independent predictors were PSADT (OR=2.4 [95%CI 1.4 to 4.0], p=0.0007) faster PSADT was an adverse prognostic factor, time of intervention (OR=0.94 [95%CI 0.91 to 0.97], p=0.0006) earlier intervention was an adverse factor and Gleason score (OR=1.35 [95%CI 1.1 to 1.7], p=0.018).

General comments -

(Kuban *et al.* 2005a)

Design: Prospective case series (prognosis), evidence level: 3

Country: , setting: Multicentre

Inclusion criteria Men entered into a multi database compiled to examine outcomes and failure definitions following EBRT for prostate cancer. All men had at least five years of follow-up after treatment. All were clinical stage T1b to T2c. All received their EBRT in the period 1986 to 1995.

Exclusion criteria -

Population number of patients = 4839.

Interventions All men had EBRT, none received adjuvant or neoadjuvant hormonal therapy as part of their definitive therapy. EBRT techniques varied with a trend towards higher doses and conformal techniques in later years.

Outcomes Biochemical failure (7 definitions were tested). Patients who started androgen suppression before the criteria for biochemical failure were met, were included as biochemical failures.

Clinical failure was defined as: local failure, distant failure, institution of hormonal therapy

Follow up Minimum follow-up was 5 years, median follow-up was 6.3 years and maximum follow-up was 14 years.

Results Disease free survival graphs (DFS) were drawn for each of the biochemical failure definitions. Compared to the Houston (nadir +2 and +3 ng/ml) and 3 rise call definitions, using the ASTRO definition resulted in an increased biochemical failure rate within the first 6 years after surgery, but reduced biochemical failure rate after 6 years (possibly due to backdating of failure). The PSA>0.2 and PSA>0.5 definitions resulted in greater biochemical failure rate than

the ASTRO (and all other) definitions at all times.

COM-PARI-SON IN MEN AFTER EBRT FOR PCA	ASTRO	0.5 X 2	ASTRO CALL-DATE	HOUS-TON +2	HOUS-TON +3	PSA >0.2	PSA >0.5	OVER-ALL RESULT
Sensitiv-ity	61%	68%	51%	74%	66%	91%	90%	
Specific-ity	80%	87%	80%	82%	86%	9%	26%	
5 year PSA-DFS	59%	66%	66%	68%	72%	15%	25%	
10 year PSA-DFS	49%	53%	41%	44%	8%	3%	11%	

General comments -

(Pickles 2006)

Design: Prospective case series (prognosis), evidence level: 3

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

Inclusion criteria Men treated with EBRT or brachytherapy for prostate cancer between 1998 and 2001 t of the staging

Exclusion criteria Men who relapsed within a year of primary therapy, men with fewer than three PSA measurements.

Population number of patients = 2030.

Interventions Men received either external beam radiation therapy (EBRT) or brachytherapy. Neoadjuvant or adjuvant deprivation therapy was given in cases with adverse risk factors for recurrence.

Outcomes False call (FC) rate was the primary outcome. FC was defined as a call of bio-chemical failure (false positive) triggered by PSA bounce. PSA bounce, defined as any rise in PSA that was followed by a fall of any size (before secondary therapy). The duration of the PSA bounce was defined as the time from the initiation of the bounce to its end.

Biochemical failure (BF) was defined using nine different definitions : ASTRO, Vancouver, threshold + n, and nadir + n. The false call (FC) rate was calculated for each definition.

Follow up Men were usually seen every six months for three years, then annually for 3 years, and biannually thereafter. At each visit PSA and testosterone were measured, and toxicity routinely assessed. Additional investigations were done only if clinically indicated.

Results Overall false call rates

The BF definitions with the highest FC rates were: threshold +0.5, threshold +1.0 and ASTRO (1997) definitions, with FC rates of 32%, 20% and 18% respectively.

The BF definitions with the lowest FC rates were: nadir +3, nadir +2 and threshold +3, with FC rates of 2%, 2% and 4% respectively.

The most robust definitions in terms of FC rate were the nadir +2 and nadir +3 definitions. There was no significant difference in FC rate between ADT groups and between radiotherapy modalities for these definitions.

COMPARISON IN MEN AFTER EBRT FOR PCA	EBRT (NO ADT)	EBRT (WITH ADT)	BRACHYTHERAPY (NO ADT)	BRACHYTHERAPY (WITH ADT)	OVERALL RESULT
PSA bounce rate (%)	66.4	55.3	71.4	88.9	
Median time to start of bounce	22 months	15 months	18 months	13 months	
Median duration of bounce	6.7 months	12 months	6.5 months	14.2 months	

General comments -

Retrospective case series

(Freedland *et al.* 2005)

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men who had radical prostatectomy at a single institution between 1982 and 2000, and had biochemical recurrence. Biochemical recurrence was defined as a single post operative PSA measurement of 0.2 ng/ml or more.

Exclusion criteria Men who had neoadjuvant therapy. Men who had successful salvage radiotherapy. Men without at least 2 PSA measurements at least 3 months apart (for the calculation of PSA doubling time).

Population number of patients = 379.

Interventions Serial PSA measurement. PSA doubling time (PSADT) was calculated using all values within 2 years after biochemical recurrence, but before subsequent therapy.

Outcomes Prostate cancer specific mortality.

Follow up The mean (SD) follow-up after surgery was 10.3 (4.7) years and median follow-up was 10 years (range, 1-20 years). After surgery, men were followed up with PSA assays and digital rectal examinations every 3 months for the first year, twice a year for the second year, and annually thereafter.

Results 66/379 (17%) patients died from prostate cancer. 15 men died of other causes and were censored in the disease specific survival analysis.

On multivariate analysis (Cox regression): PSADT (<3.0 vs. 3.0-8.9 vs. 9.0-14.9 vs. > or =15.0 months), pathological Gleason score (< or =7 vs. 8-10), and time from surgery to bio-chemical recurrence (< or =3 vs. >3 years) were all significant independent risk factors for prostate-specific mortality.

General comments Update of the Pound and co-workers (1999) series

(Pound *et al.* 1999)

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men with serum PSA elevation after radical prostatectomy. All patients were treated by a single surgeon at the same institution between 1982 and 1997.

Exclusion criteria Men who had adjuvant therapy prior to the development of metastasis were not included in the analysis of progression after PSA elevation. Men who had successful salvage radiotherapy (biochemical response of at least 2 years) were not included in this analysis.

Population number of patients = 1997.

Interventions Serial PSA measurement. Serial imaging, following biochemical relapse.

Outcomes Biochemical elevation, defined as a detectable serum PSA level of at least 0.2 ng/ml. Distant metastases were diagnosed by radionuclide bone scan, chest radiograph or other imaging, performed at the time of relapse and annually thereafter. Death was classified as: death with no evidence of disease, death with prostate cancer or death due to prostate cancer.

Follow up Median follow-up was 5.3 years, SD 3.7 years. Range was 0.5 to 15 years. After surgery, men were followed up with PSA assays and digital rectal examinations every 3 months for the first year, twice a year for the second year, and annually thereafter.

Results Metastasis free survival was 82% (95% CI, 76%-88%).

315/1997 (82%) of the men developed biochemical elevation, 11 of these were excluded from the analysis because of early adjuvant hormonal therapy.

104/315 (34%) of the men with biochemical elevation developed distant metastases. The median time to the development of metastases following PSA elevation was 8 years.

On univariate analysis (Wilcoxon-Gehan) prognostic factors for the development of distant metastases were: PSA doubling time of less than 10 months, prostatectomy Gleason score of 8 to 10, and short time to the PSA elevation (2 or less years after surgery) ($p<0.001$ for all prognostic factors).

44/105 (43%) of men who developed distant metastases died, in all cases the cause of death was prostate cancer. The only prognostic factor for death in this group was the time from surgery to development of metastases (the shorter the time the poorer the prognosis).

General comments Longer follow-up and more appropriate analysis of this series in Freedland (2005)

(Stephenson *et al.* 2006)

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men treated with radical prostatectomy for prostate cancer at a single institution between 1985 and 2004. Clinical stage was mainly T1 to T2, with 1% T3.

Exclusion criteria Neoadjuvant hormonal therapy or hormonal therapy before biochemical failure.

Population number of patients = 3125.

Interventions Men had radical prostatectomy case series (prognosis), evidence level: 3

Country: U

Outcomes Metastatic disease progression after post prostatectomy biochemical failure. Ten definitions of biochemical failure were evaluated to identify the one that best predicted metastatic progression. Secondary outcomes were the use of secondary therapy, continued PSA progression and PSA doubling time (PSADT).

Follow up PSA was measured every 3 months for the first three postoperative years, then every 6 months in years four and five and annually thereafter.

Results 75/3125 (2%) men developed metastases. The 10-year progression-free probability ranged from 63% to 79%, depending on biochemical failure definition.

Multivariate analysis was done for each BF definition for the prediction of metastases (including as covariates: preoperative PSA, prostatectomy Gleason grade, surgical margin status, pathological grade, and the use of secondary radiotherapy or androgen deprivation).

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	SINGLE PSA 0.6 OR MORE	SINGLE PSA 0.4 OR MORE	SINGLE PSA 0.2 OR MORE	RISING PSA 0.4 OR MORE	RISING PSA 0.2 OR MORE	RISING PSA 0.1 OR MORE	2 SUCCESSIVE RISES, FINAL 0.2 OR MORE	OVERALL RESULT
Association with metastatic progression	R squared 0.18; HR 35 [95% CI 16 to 76]	R squared 0.17; HR 30 [95% CI 14 to 65]	R squared 0.15; HR 21 [95% CI 10 to 45]	R squared 0.21; HR 31 [95% CI 19 to 50]	R squared 0.18; HR 22 [95% CI 13 to 37]	R squared 0.15; HR 14 [95% CI 7 to 25]	R squared 0.16; HR 16 [95% CI 8 to 30]	
10 year progression free probability	72% [95% CI 68 to 75%]	69% [95% CI 65 to 72%]	63% [95% CI 60 to 67%]	74% [95% CI 70 to 78%]	72% [95% CI 68 to 75%]	69% [95% CI 65 to 71%]	68% [95% CI 65% to 71%]	PSA of 0.4 ng/ml or more and rising was the most promising BCR definition

General comments No details about how the diagnosis of metastatic progression was made.

Authors argue that their use of covariates mean that patient characteristics are corrected for, and the BF definition is valid for all patients regardless of pathologic stage, Gleason grade or PSA.

(Tollefson *et al.* 2007)

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men treated with radical prostatectomy for prostate cancer at a single institution (1990 to 1999), who then experienced biochemical failure (PSA or 0.4 ng/mL or higher).

Exclusion criteria Neoadjuvant therapy.

Population number of patients = 1521.

Interventions All men initially had radical retropubic prostatectomy (RRP). A proportion of the

men were treated with radiotherapy (28%) and or hormonal therapy (34%) after biochemical failure.

Outcomes Local recurrence (identified using TRUS, DRE, MRI or biopsy) and systemic recurrence (metastatic disease on bone scan).

Follow up PSA-DT data were available for 1064/1521 men (70%).

Results Of the 1064 men with PSA-DT data, 322 (30%) had a PSA-DT of less than 1 year, 357 (34%) had a PSA-DT of 1 to 9.9 years, and 385 (36%) had a PSA-DT of 10 years or more.

Men with a PSA-DT of 10 years or more were at lower risk of local recurrence (hazard ratio [HR], 0.09; 95% confidence interval [CI], 0.06-0.14; compared with men with a PSA-DT of <1 year), systemic progression (HR, 0.05; 95% CI, 0.02-0.13), or death from prostate cancer (HR, 0.15; 95% CI, 0.05-0.43).

Consensus statements

(Cookson *et al.* 2007)

Design: Consensus statement (diagnosis, screening), evidence level: 4

Country: United States

Inclusion criteria Biochemical recurrence in men treated for clinically localised prostate cancer. Literature searches were performed to find papers published between 2001 and 2004 about definitions of biochemical recurrence.

Exclusion criteria -

Population -

Interventions 319 relevant publications were found, and definitions of biochemical recurrence after prostatectomy, radiotherapy were

Outcomes The frequency with which definitions of biochemical recurrence appear in the published literature.

Results A total of 166 different definitions of biochemical recurrence were used.

There were 145 studies identified for biochemical recurrence after radical prostatectomy, containing 53 different definitions of biochemical recurrence. The most commonly used definition was PSA > 0.2 ng/ml (used in 35 studies). The next most commonly used definitions were PSA >0.4 ml and detectable PSA (>0.2 ng/ml) after surgery (both used in 14 studies).

There were 208 studies identified for biochemical recurrence after radiotherapy, containing 99 different definitions of biochemical recurrence. The most commonly used definition was the ASTRO-1996 consensus definition (used in 70 papers)

There were 14 studies identified for biochemical recurrence after other therapy, containing 14 different definitions of biochemical recurrence.

General comments -

(Roach *et al.* 2006)

Design: Consensus statement (prognosis), evidence level: 4

Country: United States

Inclusion criteria -

Exclusion criteria -

Population -

Interventions A second consensus conference was sponsored by ASTRO and the Radiation Therapy Oncology Group in Phoenix, Arizona, on January 21, 2005, to revise the ASTRO 1997 consensus definition.

The consensus panel consisted of senior investigators considered experts on prostate cancer. It is not reported how they were selected.

There were seven presentations of data (large case series) for consideration by the consensus panel. Presentations included data about biochemical failure after EBRT, and brachytherapy, with and without androgen deprivation therapy.

Outcomes -

Results The consensus panel made two recommendations:

1) a rise by 2 ng/mL or more above the nadir PSA be considered the standard definition for biochemical failure after EBRT with or without hormonal therapy;

(2) the date of failure be determined "at call" (not backdated). They recommended that investigators be allowed to use the ASTRO Consensus Definition after EBRT alone (no hormonal therapy) with strict adherence to guidelines as to "adequate follow-up."

General comments -

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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4.2 Assessment of biochemical relapse

In men with biochemical relapse following radical treatment for prostate cancer, what staging investigations are effective?

Short Summary

The literature search found no studies reporting the impact of staging after biochemical recurrence on patient outcomes. Reported rates of positive biopsy in case series of men with biochemical recurrence after prostatectomy ranged from 41 to 55% (Scattoni et al. 2004). Men with eventual positive biopsy often required more than one biopsy session, suggesting a significant risk of false negative. An ASTRO consensus panel (Cox et al. 1999) considered evidence from case series about prostate biopsy after radiotherapy and concluded that routine biopsy of the prostate after radiotherapy was not recommended since it did not add to data provided by serial PSA measurements.

Small case series report good sensitivity and specificity of MRI for the detection of local recurrence after prostatectomy(Sella *et al.* 2004; Silverman & Krebs 1997), but not after radiotherapy (Sala *et al.* 2006; Coakley 2004).

The rate of bone scans positive for malignancy in men with biochemical recurrence after radical prostatectomy was 4 to 14% in four case series. The rate of suspicious or indeterminate (but ultimately non-malignant) scans was almost as high at between 3 and 8%, raising questions about the specificity of the bone scan. Trigger PSA, PSA slope, and PSA velocity were all significant predictors of bone scan result. The risk of a positive bone scan for men with PSA less than 10 ng/ml was between 1 and 3% in two series (Cher *et al.* 1998; Okotie *et al.* 2004), compared with 75% for PSA greater than 10 ng/ml (Okotie et al. 2004).

In one series salvage treatment decisions were sometimes changed on the basis of ProstaScint imaging (Jani 2004b), however there was inconsistent evidence that ProstaScint results could predict the outcome of salvage therapy (Levesque *et al.* 1998; Proano 2006; Mohideen 2002; Thomas *et al.* 2003; Nagda *et al.* 2007).

PICO question

POPULATION	INTERVENTIONS	COMPARISON	OUTCOME
Men with biochemical relapse following radical treatment	Biopsy of prostate bed MRI Bone scan ProstaScint	Reference standard staging investigation	Change in clinical decisions

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

Evidence Summary

Biopsy of prostate bed after prostatectomy

Scattoni (Scattoni et al. 2004) reviewed five case series (n=468) reporting biopsy of the vesicourethral anastamosis in men with biochemical recurrence after prostatectomy. The reported rates of positive biopsy ranged from 41 to 55%. Approximately one third of men with eventual positive biopsy required more than one biopsy session. This suggests a significant risk of false

negative biopsy, the true false negative rate, however, cannot be determined. It is also noted that negative biopsy does not preclude local recurrence and positive biopsy does not exclude systemic disease.

Biopsy of prostate after radiotherapy

An ASTRO consensus panel (Cox et al. 1999) considered evidence from four case series (n=1410) about the role of prostate biopsy after radiotherapy. They concluded that routine biopsy of the prostate after radiotherapy was not recommended since it did not add to data provided by serial PSA measurements. The panel concluded that prostate biopsy is appropriate, however, in patients with biochemical failure who were candidates for a local salvage therapy, or in the context of clinical research.

MRI

The literature search found only small case series reporting the sensitivity and specificity of MRI for local recurrence.

MRI after prostatectomy

Transrectal MRI (Sella *et al.* 2004; Silverman & Krebs 1997) had sensitivity between 95% and 100% and specificity 100% for the detection of local recurrence. The reference standard diagnosis of local recurrence was a combination of biopsy and clinical follow-up.

MRI after radiotherapy

Two case series looked at the role of MR following biochemical recurrence after radiotherapy. Coakley (Coakley 2004) reported a small series (n=21) of men who had endorectal MRI and MRS for the detection of local recurrence, using prostate biopsy as the reference standard. MR did not help in the detection of local recurrence: the corresponding area under the ROC curve was approximately 0.50.

Sala (Sala et al. 2006) reported the sensitivity and specificity of transrectal MRI for SVI and ECE in a series of 45 men, the prostatectomy specimen was the reference standard. Estimates of sensitivity and specificity of MRI for seminal vesicle invasion were 38 to 62% and 94 to 97% respectively. Estimates of sensitivity and specificity of MRI for extra capsular extension were 84 to 89% and 46 to 50% respectively.

Bone scan

The rate of bone scans positive for malignancy in men with biochemical recurrence after radical prostatectomy was 4 to 14% in four series (total n=594). The rate of suspicious or indeterminate (but ultimately non-malignant) scans was almost as high at between 3 and 8%, raising questions about the specificity of the bone scan.

Trigger PSA, PSA slope, and PSA velocity were all significant predictors of bone scan result. The risk of a positive bone scan for men with PSA less than 10 ng/ml was between 1 and 3% in two series (Cher *et al.* 1998; Okotie *et al.* 2004), compared with 75% for PSA greater than 10 ng/ml (Okotie et al. 2004). Dotan and co workers (Dotan et al. 2005) incorporated PSA variables (as well as information from the prostatectomy specimen) into a nomogram for the prediction of a positive bone scan after biochemical failure.

ProstaScint

Jani (Jani 2004b) examined the influence of a ProstaScint scan on clinical decision making in a series of 54 patients due to receive salvage radiotherapy after prostatectomy. Treatment decisions were changed on the basis of the ProstaScint scan in 10/54 cases. In 4 cases the decision to offer radiotherapy was changed and in 6 cases the radiotherapy treatment volume was increased to include the whole pelvis.

Case series reports looked at whether men with negative or apparently localised disease on ProstaScint scan had better outcome after salvage radiotherapy. One very small case series (Levesque et al. 1998) suggested that men whose clinical target volume covered the area of ProstaScint positivity tended to have better biochemical control. Proano (Proano 2006) reported that men with ProstaScint scans negative for local recurrence had better biochemical control after salvage radiotherapy. Mohideen (Mohideen 2002), however, found no difference between scan status and biochemical control. The ten patients whose scan suggested distant metastases were biochemically controlled after salvage radiotherapy. Similarly Thomas and co-workers (Thomas et al. 2003) found no significant difference in the two year biochemical control rate of men with positive and men with negative ProstaScint scans (31% vs. 38% respectively).

Evidence Tables

MRI

(Sella *et al.* 2004)
Design: Retrospective cohort study (diagnosis, screening), evidence level: 3 Country: United States, setting: Tertiary care **Inclusion criteria** Men who had endorectal MRI after radical prostatectomy for prostate cancer, at a single institution between 1997 and 2002. **Exclusion criteria** History of pelvic malignancy other than prostate cancer. **Population** number of patients = 82. **Interventions** All patients underwent radical prostatectomy, the interval from surgery to MR imaging ranged from 0.5 to 13 years (mean 3.5 years). Images were reviewed independently by 2 radiologists. The reference standard diagnosis was a combination of prostate biopsy, clinical follow-up, serial PSA measurements and serial MR imaging. **Outcomes** The sensitivity and specificity of MR imaging for the detection of local recurrence. **Follow up** In patients whose MR imaging findings were validated using clinical parameters the minimum clinical follow up was 1 year after MR imaging. **Results** 34/82 patients were excluded because they had incomplete follow-up data and their MR diagnosis could not be verified. Analysis is restricted to the remaining 48. MR findings 7/48 (14%) were negative for local recurrence, 39/48 (81%) were positive for local recurrence and 2/48 (2%) were indeterminate. The sensitivity and specificity of MR for local recurrence were 95% (95% CI 83% to 99%) and 100% (95% CI 59% to 100%) respectively. **General comments** -

(Silverman & Krebs 1997)
Design: Prospective case series (diagnosis, screening), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men after radical prostatectomy for prostate cancer, treated in a single institution.

Exclusion criteria Hormonal therapy.

Population number of patients = 41, age range 63 to 77 years, mean age = 71 years.

Interventions All men had prostatectomy. 35/41 had clinical and/or biochemical recurrence (> 0.4 ng/ml) and 6/41 were included as controls (no clinical or PSA evidence of recurrence).

All the men had negative bone scans. Sagittal and axial fat-saturated T2-weighted fast spin-echo as well as axial T1-weighted unenhanced and gadolinium-enhanced MR images of the prostatic bed were acquired in all patients using a transrectal surface coil. Images were interpreted by 2 experienced radiologists.

The reference standard diagnosis, biopsy of the prostate-bed (2 or more cores), was only done in those with biochemical recurrence. The other men were assumed to be recurrence free.

Outcomes The sensitivity and specificity of trans-rectal MR imaging for the detection of local recurrence.

Follow up MR was done a mean of 26 months after prostatectomy (range 8 to 60 months). The mean time between MR and prostate biopsy was 13 days (range 3 to 24 days). Men were followed-up clinically for a further 20 months for signs of local recurrence.

Results 31/41 patients had biopsy confirmed local recurrence. In all cases an iso-itense soft tissue lesion was seen on MR, giving a sensitivity of 100%.

4/41 patients had a palpable induration in the prostate bed, but not increased PSA or biopsy confirmed recurrence. In these cases no distinct abnormality was seen on MR. Biopsy results suggested fibrosis and clinical follow up did not observe PSA increase.

The 6 patients with no suspicion of recurrence had no suspicious nodule on MR.

Thus the specificity in this series was 100%.

(Coakley 2004)

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

Country: United States, setting: Tertiary care

Inclusion criteria Men treated at a single institution with definitive EBRT for prostate cancer, who then had endorectal MR and MRS and TRUS guided prostate biopsy (after suspected local recurrence). All men were imaging was done between 1996 and 2002

Exclusion criteria -

Population number of patients = 21, age range 45 to 80 years, mean age = 68 years.

Interventions All men had definitive EBRT for prostate cancer, then endorectal MR and MRS and TRUS guided prostate biopsy (within 1 year of the MR) after biochemical failure (ASTRO 1997 definition). 11/21 men had adjuvant hormonal therapy after EBRT.

Outcomes Sensitivity and specificity of MRI for the detection of local recurrence in left and right hemiprostate. MR images were rated by 2 readers on a 5 point scale from 1 (definitely not malignant) to 5 (definitely malignant). The reference standard diagnosis of local recurrence was prostate biopsy.

Follow up Median interval from EBRT to MR imaging was 29 months (range 14 to 48 months). The median interval from imaging to biopsy was 100 days (range 0 to 363 days).

Results Biopsy demonstrated local recurrence in 6/21 patients.

The area under the ROC curve (AUC) of MR for the prediction of local recurrence was 0.51 and 0.49 for the two readers respectively. These values indicate that MR does not help to diagnose local recurrence after EBRT.

General comments Considerable delay between MR and biopsy in some cases. The reference standard diagnosis, sextant prostate biopsy has limited sensitivity.

(Sala *et al.* 2006)

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

Country: United States, setting: Tertiary care

Inclusion criteria 45 consecutive men who had salvage radical prostatectomy for prostate cancer at one institution between 1998 and 2004. The primary curative therapy was radiotherapy. None of the men had evidence of distant metastases.

Exclusion criteria -

Population number of patients = 45, age range 43 to 76 years, median age = 62 years.

Interventions All men were initially treated with radiotherapy (33 EBRT, 3 brachytherapy and 9 both). Following biochemical failure (not defined) all men had endorectal MRI (before or after prostate biopsy) and then salvage prostatectomy .32% had chemotherapy or hormonal therapy before salvage prostatectomy.

Outcomes Sensitivity and specificity of endorectal MRI for tumour localisation, the detection of extracapsular extension (ECE) and the detection of seminal vessel involvement (SVI). A 5 point scale was used to evaluate each feature from 1 - tumour definitely absent to 5-tumour definitely present. 2 radiologists interpreted the MR reports separately.

The reference standard diagnosis was pathologic assessment of the prostatectomy speci-

men.

Follow up The median time from radiation therapy to surgery was 54 months.

Results Pathologic assessment of the prostatectomy specimen showed all men had tumour in at least one quadrant of the prostate gland. 19/45 (42%) had ECE and 13/45 (29%) had SVI.

A sensitivity of 62% (eight of 13) (95% CI: 33%, 84%) and a specificity of 97% (31 of 32) (95% CI: 80%, 100%) for detection of SVI at the patient level and a sensitivity of 89% (17 of 19) (95% CI: 65%, 98%) and a specificity of 50% (13 of 26) (95% CI: 31%, 96%) for detection of ECE at the patient level were recorded for reader 1. A sensitivity of 38% (five of 13) (95% CI: 16%, 67%) and a specificity of 94% (30 of 32) (95% CI: 77%, 99%) for detection of SVI at the patient level and a sensitivity of 84% (16 of 19) (95% CI: 60%, 95%) and a specificity of 46% (12 of 26) (95% CI: 28%, 66%) for detection of ECE at the patient level were recorded for reader 2.

For tumour detection, the area under the ROC curve (AUC) value for reader 1 was 0.75 (95% confidence interval [CI]: 0.67, 0.84), whereas the AUC value for reader 2 was 0.61 (95% CI: 0.52, 0.71). The AUC values for prediction of ECE were 0.87 (95% CI: 0.80, 0.94) for reader 1 and 0.76 (95% CI: 0.67, 0.85) for reader 2. The AUC values for prediction of SVI were 0.76 (95% CI: 0.62, 0.90) for reader 1 and 0.70 (95% CI: 0.56, 0.85) for reader 2.

8/45 (18%) men had lymph node involvement, however only 3/8 (38%) of these cases were detected on MRI.

General comments There may have been patients excluded from salvage prostatectomy on the basis of MRI results but these would not be included in this study.

Bone scan

(Cher *et al.* 1998)

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men who had a bone scan after biochemical failure following prostatectomy for prostate cancer. All were treated at a single institution between 1991 and 1996. Biochemical failure was defined as a detectable rising PSA level.

Exclusion criteria -

Population number of patients = 93.

Interventions All men had radical prostatectomy, then one or more bone scans following biochemical failure. 144 scans were done in 93 patients, 122 in men with no postoperative hormonal therapy (group 1) and 22 in men who received postoperative hormonal therapy (group 2). At least 12% of the men had neoadjuvant hormonal therapy and at least 21% had post operative radiotherapy.

Outcomes Metastatic disease: defined as a positive bone scan. The PSA measurement that prompted the clinician to obtain the bone scintigram was trigger PSA (tPSA). The rate of increase in PSA to tPSA was measured by tPSA/time from radical prostatectomy (slope 1) and tPSA/time from last undetectable PSA (slope 2).

Results The group 1 analysis is reported in this appraisal (men with no postoperative hormonal therapy), as group 2 contained only 22 men.

There were 5/122 (4%) positive bone scans, 3/122 were indeterminate and included in the 117 negative scans.

In univariate analysis tPSA ($p = 0.003$), slope 1 ($p = 0.005$) and slope 2 ($p = 0.004$) were significantly associated with the bone scintigram result but pathological stage, Gleason score, preoperative PSA and time to recurrence were not.

On multivariate analysis tPSA was the only significant predictor of bone scan result. For tPSA <10 ng/ml there was less than 1% chance of a positive bone scan, this probability increased slowly up to tPSA levels around 40 ng/ml, after which it increased rapidly.

General comments Low event rate (5 positive scans). tPSA threshold was up to the treating doctor.

(Dotan 2005)

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men who had bone scans after treatment with radical prostatectomy for prostate cancer at a single institution between 1985 and 2003.

Exclusion criteria Bone scans performed after androgen deprivation therapy (adjuvant or neoadjuvant).

Population number of patients = 239.

Interventions All men had radical prostatectomy, followed by serial PSA tests and bone scan after biochemical failure (PSA > 0.4 ng/ml or initiation of secondary treatment).

Outcomes Bone scan results: coded as positive or negative. Positive scans were further coded as malignant or non-malignant.

Follow up The recommended follow-up after surgery was every three months for the first year, every six months for the next two years, and annually thereafter.

Results 414 bone scans were performed in the 239 men. 60/414 (14%) were positive for metastatic cancer. 11/414 were positive but non-malignant and were reclassified as negative for the analysis.

Multivariate analysis of prognostic factors for positive bone scan considered the following variables: PSA velocity, ng/mL/mo ; PSA slope, log (ng/mL/mo) ; PSA doubling time, months ; Years from BCR to bone scan ; Months from operation to BCR ; Pathology Gleason sum ; Lymph node involvement (positive vs. negative) ; Seminal vesicle invasion (positive vs. negative) ; Extracapsular extension (positive vs. negative) ; Surgical margin (positive vs. negative) and Preoperative PSA, ng/mL.

The only statistically significant predictors of bone scan result were: PSA slope (odds ratio [OR], 2.71; P = .03), PSA velocity (OR, 0.93; P = .003), and tPSA (OR, 1.022; P < .001).

The authors constructed a nomogram for the prediction of a positive bone scan after biochemical failure. Using an internal validation method it was found to have a concordance index of 0.93. In contrast, using an absolute PSA threshold of 30 ng/mL at time of bone scan as the only predictor, the concordance index was 0.63.

General comments Bone scan following biochemical failure was at the discretion of the treating physician. Could bias results.

Too many predictor variables included in the multivariate analysis as the event rate was only 60.

(Okotie *et al.* 2004)

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men with biochemical failure after radical prostatectomy for prostate cancer, who had a bone scan and or CT after failure. All were treated at a single institution between 1986 and 2001. Biochemical failure was defined as a single PSA value more than 0.2 ng/ml.

Exclusion criteria It is not clear what the criteria were for bone scan or CT after biochemical failure in this institution.

Population number of patients = 128.

Interventions 97/128 patients had a bone scan and 71/128 had a CT scan.

Outcomes Metastatic disease: defined as a positive bone scan or CT. Preoperative clinical variables, pathological findings, serum prostate specific antigen (PSA) at postoperative imaging and postoperative PSA doubling time were compared between patients to identify factors that predicted positive imaging study results.

Follow up Not reported separately. The mean time from surgery to biochemical failure was 24 months in those with positive bone scans and 28 months in those with negative bone scans. The mean time from biochemical failure to imaging was 13 months in those with posi-

tive bone scans and 25 months in those with negative bone scans.

Results (CT results will not be discussed in this appraisal).

11/97 (11%) of the bone scans were positive.

On univariate analysis, men with positive bone scans had significantly shorter PSA doubling times (p=0.007), greater PSA at the time of imaging (p<0.001), higher incidence of extracapsular extension (p)and higher pathological stage than men with negative bone scans.

Men with PSA doubling time less than 6 months were at increased risk of a positive bone scan (26% vs. 3%). Men with PSA greater than 10 ng/ml were at increased risk of a positive bone scan (75% vs. 3%) compared to those with PSA less than 10 ng/ml.

General comments Very low event rate (11 positive scans) on which to base a prognostic model.

(Kane 2003)

Design: Retrospective cross sectional study (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men entered into the Centre for Prostate Disease Research (CPDR) database. All were treated with radical prostatectomy for clinically localised prostate cancer, at one of four participating institutions between 1989 and 1998. Only men with biochemical recurrence (2 PSA values greater than 0.2 ng/ml or a single value above 0.5 ng/ml). Only men who have bone scans or CT within 3 years of biochemical recurrence were included.

Exclusion criteria Men who received hormonal therapy before the bone scan or who did not have a PSA measurement within 3 months of the bone scan were excluded from the PSA analysis.

Population number of patients = 134.

Interventions All men had radical prostatectomy, followed by serial PSA testing and bone scan or CT after biochemical failure.

Outcomes Positive bone scan.

Follow up Post operative follow-up was done at 3,6, 9, and 12 months in the first year, every 6 months for the next 2 years and then annually.

Results 12/127 (9%) of bone scans were positive. 10/127 were suspicious but plain x-ray or MRI found no evidence of metastases.

On multivariate analysis both PSA and PSA velocity were significant predictors of bone scan result. Pretreatment PSA, pathologic stage and grade did not significantly predict bone scan

results. Authors concluded that most patients with a positive bone scan had a high PSA level (the average was 61.3 ng/ml) and high PSA velocity (more than 0.5 ng/ml/month). They argue that bone scan can be omitted for most men with biochemical recurrence of prostate cancer. **General comments** Low event rate.

ProstaScint (indium capromab pendetide)

(Jani 2004b
Design: Retrospective case series (diagnosis, screening), evidence level: 3 Country: United States, setting: Tertiary care **Inclusion criteria** 54 consecutive patients treated with radical prostatectomy for prostate cancer at a single institution between 1998 and 2002, and referred for ProstaScint scan after biochemical failure, to aid in the decision about salvage radiotherapy. **Exclusion criteria** - **Population** number of patients = 54. **Interventions** All men initially had radical prostatectomy. Following biochemical failure all had a ProstaScint scan to inform the decision about salvage radiotherapy. The radiotherapy recommendations were compared before and after ProstaScint to examine the influence of ProstaScint on treatment decisions. The two treatment decisions were radio-therapy or not, and whether to add whole pelvis radiotherapy to prostate-fossa radiotherapy **Outcomes** Influence of ProstaScint results on recommendations for salvage radiotherapy after prostatectomy, defined as the proportion of treatment decisions that changed following ProstaScint. **Results** The decision to offer EBRT was changed after ProstaScint in 4/54 cases (from yes to no). The decision to include the whole pelvis in the EBRT was changed after ProstaScint in 6/50

cases (the whole pelvis field was added in all 6 cases).

Thus overall treatment decisions were changed 10 times in 54 patients.

General comments It is not possible to say whether the changes in treatment decision were correct or not.

(Jani 2004a)

Design: Retrospective case series (other), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men due to receive salvage radiotherapy after prostatectomy for prostate cancer. All were treated in a single institution between 1999 and 2002.

Exclusion criteria -

Population number of patients = 25.

Interventions All men initially had radical prostatectomy. Following biochemical failure all had planning CT scan and ProstaScint scan to inform the decision about the radiotherapy clinical target volume (CTV).

CTVs were using CT only and using CT + ProstaScint to examine the influence of ProstaScint on the CTV.

Outcomes Clinical target volume (cm3). AUC (area under the curve - a measure of integral dose to an anatomical structure) and V60 (the volume of the structure that receives more than 60Gy)

Follow up Average follow-up was one year after salvage radiotherapy.

Results The mean CTV without using ProstaScint was 24.4 cm3 (SD 10.2 cm3) compared with 35.0 cm3 (SD 21 cm3) when the information from the ProstaScint scan was added. The volumes were significantly different (p=0.032).

Dosimetric analysis suggested that the AUCs for rectum and bladder were not significantly different for the two CTV methods. V60 for the rectum was not significantly different for the two CTVs, but there was a higher V60 for the bladder when the ProstaScint was incorporated in planning the CTV (p=0.015).

General comments Small case series

(Levesque *et al.* 1998)
Design: Retrospective case series (prognosis), evidence level: 3 Country: United States **Inclusion criteria** Men with biological recurrence of prostate cancer (2 PSA measurements more than 0.8 ng/ml) after prostatectomy. All surgery was done at one institution between 1985 and 1994. **Exclusion criteria** - **Population** number of patients = 48, age range 41 to 76 years, mean age = 63 years. **Interventions** All men had a ProstaScint scan and, within 8 weeks, a negative bone scan. Following staging investigations men were offered radiotherapy or watchful waiting. 13/48 had radiotherapy (59.4 to 68.4 Gy). Patients who maintained a PSA level of 0.2 ng/ml or less after radiotherapy were classed as responders. **Outcomes** ProstaScint scan results, coded as negative and positive in : prostate bed and extraprostatic sites. Response to radiotherapy. **Follow up** Mean duration from prostatectomy to relapse was 42 months, **Results** ProstaScint scan was positive in 38/48 and negative in 10/48. 3/38 scans were positive in the prostate bed only, 19/38 in the prostate bed and other sites and 16/38 in extraprostatic sites only. 6/13 patients treated with EBRT were non-responders to the therapy. In men with ProstaScint positivity outside the clinical target volume (CTV) the proportion of responders to non responders was 2/4. In men whose CTV covered the entire area of ProstaScint positivity the ratio of responders to non responders was 5/2. The number of cases is too small to draw conclusions **General comments** Small case series, only 13 had EBRT and there were only 6 failure events.

(Mohideen 2002)
Design: Retrospective case series (prognosis), evidence level: 3 Country: United States **Inclusion criteria** Men referred for radiotherapy after biochemical failure following prostatectomy. **Exclusion criteria** - **Population** number of patients = 49.

Interventions All men had a ProstaScint scan. All were treated with radiotherapy to the prostate bed (66.6 to 70.2 Gy in 1.8 Gy fractions).

Outcomes Result of the ProstaScint scan, coded as negative, positive in the prostate bed alone, positive in the lymph node regions and positive in metastatic or multiple sites.

Biochemical control at 3 years (not defined).

Follow up Mean follow-up after salvage radiotherapy was 2 years.

Results 13 scans were negative.

All ten patients with a positive scan suggesting distant metastases were biochemically controlled after radiotherapy.

COMPARISON IN MEN AFTER SALVAGE RADIOTHERAPY	PROSTASCINT POSITIVE IN PROSTATE BED ONLY	PROSTASCINT POSITIVE IN PELVIC NODES	PROSTASCINT POSITIVE OUTSIDE PROSTATE BED	NEGATIVE PROSTASCINT SCAN	OVERALL RESULT
3 year biochemical control rate (%)	80%	83%	89%	not reported	no significant difference between scan status and biochemical outcome

General comments Abstract only, limited follow-up, no definition of biochemical recurrence.

(Nagda *et al.* 2007)

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

Country: United States, setting: Tertiary care

Inclusion criteria Men with biochemical relapse after prostatectomy, treated at a single institution between 1996 and 2003. All had negative findings for distant metastases after CT and bone scan.

Exclusion criteria -

Population number of patients = 58, age range 48 to 80 years, median age = 66 years.

Interventions All men had a capromab pendetide scan as part of the evaluation of biochemical relapse. The results of the scan were classed as negative, positive in the prostate bed only, positive in metastatic sites or positive in multiple sites.

Regardless of the capromab pendetide results 57/58 men had local EBRT to the prostate bed (median dose 66 Gy, range 63 to 70.2 Gy, usually 3D-CRT). 7/58 men also had short term androgen deprivation for 3 to 6 months along with EBRT.

Outcomes Biochemical relapse free survival. Biochemical relapse was defined as PSA more than 0.2 ng/ml or above the nadir value. The positive predictive value of the capromab pendetide scan for detecting metastases outside the prostate was also calculated.

Follow up Median follow-up was 41 months (range, 6 to 92 months)

Results 21/58 men experienced biochemical relapse after salvage therapy. In this group the median time to failure was 18 months (range 3 to 50 months).

The capromab pendetide scan was reported as negative in 14 men, positive in the prostate bed only in 22 and positive elsewhere in 22.

Biochemical relapse rates were 5/14 (36%), 9/22 (41%) and 6/22 (27%) for men with negative, positive prostate bed only and positive elsewhere scan results respectively.

The PPV of the capromab pendetide scan was 27% (the proportion of people with a scan positive outside the prostate who experienced biochemical failure).

Biochemical relapse free survival (BCRFS)

The 4 year estimated BCRFS rates were 53%, 45% and 74% for negative, positive bed alone and positive elsewhere scans respectively. There was no significant difference in the BCRFS of these groups on Kaplan Meier analysis (p=0.51).

General comments -

(Proano 2006)

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

Country: United States, setting: Tertiary care

Inclusion criteria Men who had a ProstaScint scan at a single institution, following biochemical recurrence after prostatectomy for prostate cancer. All were treated between 1988 and 2004.

Exclusion criteria Men with insufficient follow-up data.

Population -

Interventions All men had radical prostatectomy. Following biochemical recurrence (not defined), all had ProstaScint imaging. This involved the injection of indium-capromab pendetide monoclonal antibody four days before SPECT and CT imaging of the pelvis and upper abdomen. The SPECT and CT images were fused digitally in 36/44 patients, and were interpreted by a single radiologist.

Salvage radiotherapy was delivered to the prostatic fossa (44/44 cases), and to the whole pelvis if ProstaScint suggested lymph node involvement (6/44 cases). The prostatic fossa fields were designed to incorporate the anatomical prostatic fossa including any areas of uptake indicated on the ProstaScint and CT fused image.

Outcomes Biochemical recurrence after salvage radiotherapy, defined using the ASTRO 1997 definition.

Follow up Mean follow up was 22 months after salvage therapy.

Results 10/44 patients had ProstaScint results negative for local recurrence, the remaining 34/44 had positive results. Patients with positive ProstaScint had significantly higher PSA at radiotherapy, were more likely to have had neoadjuvant hormonal therapy, but had longer radiotherapy PSA-doubling time.

43/44 patients experienced PSA decline after salvage radiotherapy.

15/44 experienced biochemical recurrence after salvage radiotherapy. 1/10 (10%) of those with negative ProstaScint scans experienced biochemical recurrence compared with 14/34 (41%) of those with positive ProstaScint (p=0.026).

General comments It is not clear from this analysis whether ProstaScint result is an independent predictor of outcome, since patients with negative scans had significantly lower PSA measurements than those with positive scans. Multivariate analysis is needed, but this series is too small.

(Thomas 2003)

Design: Retrospective cross sectional study (prognosis), evidence level: 3

Country: United States

Inclusion criteria Men who had ProstaScint scan between 1997 and 1999 at a single institution. All had post-prostatectomy biochemical relapse.

Exclusion criteria Men who did not elect to receive salvage radiotherapy. Radiographic evidence of metastatic disease at the time of biochemical relapse. PSA less than 0.2 ng/ml. Neoadjuvant salvage hormonal therapy before salvage radiotherapy. Interval of more than 7 months between ProstaScint and completion of EBRT.

Population number of patients = 30, age range 53 to 79 years, median age = 64 years.

Interventions All men had a ProstaScint scan, after biochemical recurrence (defined as PSA of 0.2 ng/ml or more) and before any secondary therapy.

Salvage radiotherapy was given to the prostate bed with a 1cm margin (64.8 to 70.2 Gy). Some patients had pelvic radiotherapy at 45 Gy. ProstaScint results were not used to inform the decision to offer salvage EBRT.

Outcomes Biochemical failure (BF), after salvage radiotherapy. BF was defined using the ASTRO-1997 consensus definition.

Follow up The interval between follow-up visits ranged from 1 to 7 months. The median follow-up after completion of salvage EBRT was 34.5 months

Results One patient was excluded because of inadequate follow-up.

14/29 men had a positive scan (in or outside the prostate-bed) and 15/29 had a negative scan.

COMPARISON IN MEN AFTER SALVAGE RADIOTHERAPY	PROSTASCINT POSITIVE	PROSTASCINT NEGATIVE	OVERALL RESULT
2 year biochemical control rate (%)	31% (SE 13%)	38% (SE 13%)	no significant difference

General comments Shows that men with positive and men with negative scans had similar outcomes after radiotherapy.

Biopsy

(Scattoni *et al.* 2004)

Design: Review (diagnosis, screening), evidence level: 4

Inclusion criteria Papers reporting TRUS guided prostate biopsy for the detection of local recurrence after radical prostatectomy. 5 case series (468 patients) were included. Indications for biopsy were not reported in this review.

Exclusion criteria -

Population -

Interventions TRUS guided prostate biopsy of the vesico-urethral anastamosis. Studies used different biopsy strategies in terms of number and location of cores. T

Outcomes The proportion of men with positive biopsy.

Results The rate of positive biopsy ranged from 41% to 55%.

Approximately one third of men with an eventual positive biopsy required 2 or more biopsy sessions, suggesting a significant risk of false negative biopsy. The true false negative rate, however, cannot be determined

The impact of the biopsy results on clinical decision making is not reported.

General comments -

(Cox *et al.* 1999)

Design: Consensus statement (diagnosis, screening), evidence level: 4

Country: United States

Inclusion criteria -

Exclusion criteria -

Population -

Interventions The panel aimed to role of re-biopsy to evaluate treatment success.

Results of prostate re-biopsy after radiotherapy from four large case series (total number of patients was 1410) were presented to the consensus panel by representatives from each institution. In three of the series radiotherapy was EBRT and in one series brachytherapy.

The median timing of the first re-biopsy after radiotherapy ranged from one to three years in the four series.

Outcomes -

Results In the four case series (n=1410), the prostate re-biopsy negative rates (at 2.5 years after radiotherapy) ranged from 62% to 80% for patients with stage T1-2 tumours.

The series from Memorial Sloan Kettering Cancer Centre provided data about the rate of positive biopsy according to PSA kinetics. In men with nadir PSA of 1 ng/ml or less, with non-rising PSA at the time of biopsy, the positive biopsy rate was 6%. In men PSA of 1 ng/ml or less, but rising PSA, the rate was 52%.

In the Wayne State series the strongest predictor of a positive re-biopsy was PSA level at the time of the biopsy

The consensus panel judged that prostate re-biopsy is not necessary as standard follow-up care. The absence of a rising PSA level after radiation therapy is the most rigorous indicator of total tumour eradication.

In patients with a rising PSA level, whose treatment options include a local treatment such as salvage radical prostatectomy , the panel concluded that re-biopsy would be useful to identify the persistence of cancer.

The panel stated that re-biopsy may be an important research tool.

General comments The criteria for re-biopsy and proportion of eligible patients who were re-biopsied was not consistently reported. Unclear how the consensus panel were selected.

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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4.3 Management of biochemical relapse

In men with biochemical relapse following radical treatment for prostate cancer, what salvage therapies for local recurrence are effective?

Short Summary

The literature search did not identify any randomised trials of the treatment of PSA-only recurrence. Indirect evidence comes from a systematic review (Wilt *et al.*) of four RCTs of immediate versus deferred hormonal therapy in men with advanced prostate cancer. Meta-analysis showed a small, but not statistically significant improvement in overall and disease specific survival at 1, 2 and 5 years, in favour of early therapy. The review concluded that there was insufficient evidence about the use of androgen suppression in men with clinically localised disease, who experience biochemical recurrence without other signs or symptoms. Moul and co-workers (Moul *et al.* 2004) considered the timing of hormonal therapy in a large case series of men with biochemical recurrence. There was no difference between the metastasis free survival of early and delayed hormonal therapy groups. A subgroup analysis, however, showed significantly better metastasis free survival for high risk patients treated with early hormonal therapy.

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

There was little evidence about salvage prostatectomy. Estimates of disease specific survival (Bianco *et al.* 2005; Ward *et al.* 2005; Sanderson *et al.* 2006) and complication rates (Stephenson *et al.* 2004a; Ward *et al.* 2005; Sanderson *et al.* 2006) come from case series. The NICE interventional procedures guidance on salvage cryotherapy (National Institute for Health and Clinical Excellence) reviewed seven case series with limited follow-up. Five year disease specific survival was 79%, in the only study reporting this outcome.

PICO question

POPULATION	INTERVENTIONS	COMPARISONS	OUTCOME
Men with biochemical relapse following radical treatment	Hormones after all Radiation after radical prostatectomy Radical prostatectomy Cryotherapy and HIFU after radiation	Surveillance (no immediate therapy)	• overall survival • disease-free survival • time till next intervention • quality of life • costs

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

Evidence Summary

The literature search did not identify any randomised trials of the treatment of PSA-only recurrence.

Hormonal therapy

Indirect evidence for treatment of biochemical recurrence comes from randomized trials of immediate versus deferred hormonal therapy in men with advanced prostate cancer.

The systematic review of Wilt and co-workers (Wilt *et al* 2001) identified four RCTs of immediate versus deferred androgen suppression in men with advanced prostate cancer. Meta-analysis suggested a small, but not statistically significant improvement in overall survival at 1, 2 and 5 years, in favour of early therapy. A significant benefit was seen at 10 years, but this was largely due to one trial. A similar pattern was seen with cancer specific survival. There were fewer adverse events due to disease progression with early hormonal therapy, but side effects of treatment were increased in this group.

The review concluded that there was insufficient evidence about the use of androgen suppression in men with clinically localized disease, who experience biochemical recurrence in the absence of additional signs or symptoms. Earlier initiation delays disease progression, but this must be balanced with the increased costs and treatment complications associated with early therapy.

Moul and co-workers (Moul *et al.* 2004) considered the timing of hormonal therapy in a large case series of men with biochemical recurrence. Early hormonal therapy was defined as that initiated at a PSA of 5 ng/ml or less. There was no difference between the metastasis free survival of early and delayed hormonal therapy groups. A subgroup analysis, however, showed significantly better metastasis free survival for high risk patients with early hormonal therapy.

Faria and co-workers (Faria *et al.* 2006) compared outcomes in a series of 178 men with asymptomatic biochemical failure after EBRT. They were either treated with hormonal therapy or managed with watchful waiting. There were no deaths due to prostate cancer in either group. At a median follow-up of 7 years, overall survival was 95% in the hormonal therapy group and 89% in the untreated group ($p<0.0001$).

No published trials of antiandrogen monotherapy for PSA-only recurrence were found.

Salvage prostatectomy

There was little evidence about salvage prostatectomy. Estimates of disease specific survival (Bianco *et al.* 2005; Ward *et al.* 2005; Sanderson *et al.* 2006) and complication rates (Stephenson *et al.* 2004a; Ward *et al.* 2005; Sanderson *et al.* 2006) come from case series.

Salvage radiotherapy

A systematic review (Nilsson *et al.* 2004) of ten retrospective case series, concluded that after radical prostatectomy (with adverse factors) adjuvant EBRT seems to result in better disease free survival than salvage or no postoperative EBRT. Similarly, salvage EBRT probably results in marginally better outcome than no EBRT. The treatment of PSA-only relapse was not addressed as a separate issue, and toxicity was not considered in detail.

Indirect evidence for early treatment comes from studies looking at pre-salvage radiotherapy PSA level as a predictor of response to therapy. Progression free survival was significantly better in men with lower pre-salvage therapy PSA levels (Nilsson *et al.* 2004) (Brooks *et al.* 2005; Pazona *et al.* 2005; Stephenson *et al.* 2004b; Buskirk *et al.* 2006; Stephenson *et al.* 2007; Neuhof *et al.* 2007). One review (Brooks *et al.* 2005) considered evidence from nine case series about the pre-salvage radiotherapy PSA level above which disease control is adversely affected. Estimates ranged from 0.6 to 2.5ng/ml.

Other adverse prognostic factors for response to salvage radiotherapy include: pre-treatment PSA-doubling time of less than 10 months, lymph node or seminal vesicle involvement and

Gleason score of 8 or more (Pazona *et al.* 2005; Stephenson *et al.* 2004b; Stephenson *et al.* 2007; Neuhof *et al.* 2007). Early salvage treatment is unlikely change these risk factors.

MacDonald and co-workers (Macdonald *et al.* 2004) compared outcomes after salvage radiotherapy in men with biochemical recurrence only and men with palpable recurrence. Five year overall survival was 95% in men treated for biochemical recurrence compared to 76% for men with palpable recurrence. Five year distant metastasis free survival was 90% in men treated for biochemical recurrence compared to 81% for men with palpable recurrence

In comparison, Pound (Pound *et al.* 1999) reported disease progression in a series of men with untreated biochemical failure after prostatectomy. At median follow-up of over five years, metastasis free survival was 66%.

There was very little evidence about salvage brachytherapy. One small case series (Grado *et al.* 1999) reported overall and disease specific survival, and toxicity in a group of 49 men. However, median follow-up was less than two years. Another small series reported outcomes after high dose rate salvage brachytherapy in a group of 21 men (Lee *et al.* 2007).

Salvage cryotherapy

The NICE interventional procedures guidance (National Institute for Health and Clinical Excellence) contains a review of seven salvage cryotherapy case series. Follow-up was limited, only two of the series had median follow-up of more than two years. Five year disease specific survival was 79%, in the only study reporting this outcome. Biochemical recurrence rate ranged from 26% to 63% depending on length of follow-up. Impotence, incontinence, ureteric obstruction and pelvic pain were all common complications.

Pisters and co-workers (Pisters *et al.* 2006) compared outcomes in a series of men who had either salvage prostatectomy or salvage cryotherapy for local recurrence. Only men with Gleason score less than 8 were included in the analysis. At median follow-up of 5 years, there was no difference in disease specific survival, but 29% of the salvage prostatectomy group experienced biochemical failure compared to 67% in the cryotherapy group.

Evidence Tables

HORMONAL THERAPY

Systematic review of RCTs

(Kumar *et al.* 2006)
Design: Systematic review of RCTs (therapy), evidence level: 1++ **Inclusion criteria** Randomised or quasi-randomised controlled trials of patients with localised or locally advanced prostate cancer, that is, stages T1-T4, any N, M0, comparing neo-adjuvant or adjuvant hormonal deprivation in combination with primary therapy (radical radio-therapy or radical prostatectomy) versus primary therapy alone were included in this review. **Exclusion criteria** - **Population** - **Interventions** Neoadjuvant or adjuvant hormonal therapy in combination with primary therapy (radical radiotherapy or radical prostatectomy) versus primary therapy alone. **Outcomes** Overall survival, disease specific survival, disease free survival, pathological tu-mour stage, surgical margin status, seminal vesicle invasion rate, lymph node involvement. Treatment related side effects, and quality of life measures. **Results** 21 studies were included, with 11149 patients. For neo-adjuvant hormonal therapy, there were 10 prostatectomy studies and four radiotherapy studies. For adjuvant hormonal therapy, there were three prostatectomy studies and four studies of radiotherapy. Adjuvant therapy with prostatectomy: Adjuvant androgen deprivation following prostatectomy did not significantly improve overall survival at 5 years (OR 1.50, 95% CI 0.79 to 2.85, P = 0.2); although one study reported a significant disease-specific survival advantage with adjuvant therapy (P = 0.001). In addition, there was a significant improvement in disease-free survival at both 5 years (OR 3.73, 95%CI 2.30 to 6.03, P < 0.00001) and 10 years (OR 2.06, 95% CI 1.34 to 3.15, P = 0.0009). Adjuvant therapy with radiotherapy: Adjuvant therapy following radiotherapy resulted in a significant overall survival gain apparent at 5 (OR 1.46, 95% CI 1.17 to 1.83, P = 0.0009) and 10 years (OR 1.44, 95% CI 1.13 to 1.84, P = 0.003); although there was significant heterogeneity (P = 0.09 and P = 0.07, respectively). There was also a significant improvement in disease-specific survival (OR 2.10, 95% CI 1.53 to 2.88, P = 0.00001) and disease-free survival (OR 2.53, 95% CI 2.05 to 3.12, P < 0.00001) at 5 years. Subgroup analysis could not be done because most studies did not report results by risk

groups.

General comments -

(Wilt *et al.* 2001)

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

Inclusion criteria Published randomized trials were included if they: randomized men with advanced prostate cancer to early versus deferred androgen suppression; reported overall, progression-free, and cancer-specific survival, and/or adverse events; did not utilize androgen suppression as adjuvant therapy to radiation treatment.

4 trials were included: (ECOG, MRC, VACURG-I and VACURG-II)

Exclusion criteria -

Population number of patients = 2167.

Interventions Androgen suppression: orchietomy LHRH agonist, oestrogen or diethylstilbestrol.

Trials compared early with deferred androgen suppression. Early was defined as: immediately at the time of diagnosis, immediately following surgery for clinically localized but pathologically advanced prostate cancer, for persistently elevated PSA levels following surgery, or immediately upon rising PSA levels in patients with previously undetectable PSA. Deferred androgen suppression was defined as withholding androgen suppression therapy until symptoms, clinical signs, or radiological evidence of clinical progression.

Outcomes Overall, progression-free, and cancer-specific survival. Adverse events and complications due to disease progression. Side effects of treatment.

Results Meta-analysis suggested a small, but not statistically significant improvement in overall survival at 1, 2 and 5 years, in favour of early therapy. A significant benefit was seen at 10 years, but this was largely due to a single trial (VACURG-1). A similar pattern was seen with cancer-specific survival. All trials noted improved 2 and 5 year progression free survival with immediate hormonal therapy. The VACURG-1 trial reported improved 10 year progression free survival with immediate therapy.

One trial reported adverse effects and complications due to disease progression. Cord compression, ureteric obstruction and extraskeletal metastases were significantly more likely if androgen suppression was delayed.

One trial considered side effects of treatment. Gynaecomastia weight gain, hot flashes, GI effects and haematological effects were significantly worse in the immediate androgen suppression group.

The review concluded that there was inadequate information about the use of androgen suppression in men with clinically localized disease, who experience biochemical recurrence in the absence of additional signs or symptoms. Earlier initiation delays disease progression, but this must be balanced with the increased costs and adverse events associated with early therapy.

COMPARISON IN MEN WITH ADVANCED PROSTATE CANCER	EARLY HORMONAL THERAPY	DELAYED HORMONAL THERAPY	OVERALL RESULT
5 year disease specific survival	460/659 (from 3 trials)	416/657 (from 3 trials)	In favour of immediate therapy, OR=1.54 [95% CI 1.04 to 2.28]
10 year disease specific survival	282/488 (from 3 trials)	241/494 (from 3 trials)	In favour of immediate therapy, OR=1.45 [95% CI 1.13 to 1.87]
5 year overall survival	344/787 (from 4 trials)	310/785 (from 4 trials)	No sig. difference, OR=1.19 [95% CI 0.95 to 1.50]
10 year overall survival	87/488 (from 3 trials)	61/494 (from 3 trials)	In favour of immediate therapy, OR=1.50 [95% CI 1.04 to 2.16]

General comments Authors comment that none of the included trials comes from the PSA-era.

In the MRC trial M0 patients tended to benefit more from immediate hormonal therapy than did M1 or Mx patients.

Retrospective cohort studies

(Moul *et al.* 2004)

Design: Retrospective cohort study (therapy), evidence level: 2+

Country: United States

Inclusion criteria Men in the Department of Defence Center for Prostate Disease Research multicentre prostate cancer registry, between 1988 and 2002. Men who had biochemical recurrence (BCR) after prostatectomy (PSA more than 0.2 ng/ml were included.

Exclusion criteria Less than 6 months postoperative follow-up, lack of PSA data or salvage radiotherapy after recurrence.

Population number of patients = 1352, mean age = 64 years, median age = 64 years.

Interventions Hormonal therapy (HT). HT included medical or surgical castration, with or with-

out and oral antiandrogen.

Early HT was defined as that administered at PSA levels of 5 ng/ml or less.

The high risk patient group was defined as: those with Gleason score more than 7 or with PSA doubling time (PSADT) of 12 months or less.

Outcomes Clinical metastasis free survival, bone metastasis free survival. Distant metastases were detected using nuclear and radiographic imaging studies.

Follow up The median follow up after prostatectomy was 4.7 years (range 0.5 to 13.0 years)

Results 355/1352 had hormonal therapy. 221/355 had early HT (initiated at PSA of 5ng/ml or less).

Overall 103/1352 patients experienced clinical metastasis; it is unclear how many patients on HT had clinical metastasis.

In the overall cohort, no benefit of early HT was seen in terms of clinical metastasis free survival. But subgroup analysis of high risk patients favoured early HT.

Multivariate analysis for risk factors for clinical metastasis in the entire cohort, found the only significant adverse prognostic factor was incurable disease.

In the high risk group, the timing of hormonal therapy and incurable disease were both independent risk factors for clinical metastasis.

COMPARISON IN MEN WITH BIOCHEMICAL RECURRENCE AFTER PROSTATECTOMY	EARLY HORMONAL THERAPY	DELAYED HORMONAL THERAPY	OVERALL RESULT
Bone metastasis free survival	90% at 5 years, 80% at 10 years	90% at 5 years, 86% at 10 years	HR (late vs. early HT) was 0.91 [95% CI 0.58 to 1.41] p=0.665
COMPARISON IN MEN WITH BIOCHEMICAL RECURRENCE AFTER PROSTATECTOMY, AND GLEASON SCORE > 7 OR PSADT LESS THAN 1 YEAR	EARLY HORMONAL THERAPY	DELAYED HORMONAL THERAPY	OVERALL RESULT
Bone metastasis free survival	84% at 5 years, 75% at 10 years	70% at 5 years, 56% at 10 years	HR (late vs. early HT) was 2.32 [95% CI 1.14 to 4.70] p=0.020

General comments Unclear what the event rate was for patients who had HT. Definition of early HT is PSA based (not time based). Definition of early HT was data driven, using PSA cut-offs of 1, 2, 3 and 4 ng/ml did not produce significant results.

(Sanderson *et al.* 2006)

Design: Retrospective case series (therapy), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men with clinically localised prostate cancer who had salvage RRP for recurrent disease, at a single institution between 1983 and 2002. Only men with life expectancy of at least 10 years and no evidence of distant metastases were offered salvage RRP.

Exclusion criteria -

Population number of patients = 51.

Interventions Salvage radical prostatectomy Primary curative therapy was EBRT (57%), interstitial brachytherapy (23%), EBRT plus brachytherapy (16%), brachytherapy plus cryotherapy (2%) and proton beam RT (2%).

Neoadjuvant hormonal therapy was used in 18% of patients. Adjuvant hormonal therapy was used in 37% of cases.

15/33 (45%) of the questionnaire respondents had an artificial urinary sphincter (AUS) .11/33 (33%) had an inflatable penile prosthesis (IPP).

Outcomes Overall survival, progression free survival (both from the date of salvage RRP), complications and HRQOL (measured using UCLA Prostate Cancer Index).

Follow up Median follow-up after salvage RP was 7.2 years (95% CI 0.8 to 20.2 years). 33/51 men were alive at the time of the study and completed the HRQOL questionnaires.

Results Overall survival

The median overall survival was 12.9 years (95% CI 7.6 to 19.1 years). The estimated 5 year overall survival probability was 85% (95% CI 80 to 90%) and the 10 year overall survival probability was 65% (57 to 73%).

Progression free survival

The median progression free survival (PFS) was 4.8 years (95% CI 2.0 to 18.1 years). The estimated 5 year PFS probability was 47% (95% CI 39 to 55%). No disease progression was reported after 5 years.

Complications

Bladder neck contracture (41%), rectal injury (2%).

HRQOL

Total continence (or occasional dribbling) was reported by 82% of men with an AUS, compared to 69% of those without. Sexual function scores were 13%, 38% and 66% of maximum

for men treated with standard RP, nerve sparing RP and RP+IPP respectively.

(Tefilli *et al.* 1998)

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

Country: United States, setting: Tertiary care

Inclusion criteria Men with local failure after definitive therapy for prostate cancer, who were treated with salvage radiotherapy or prostatectomy. Selection criteria for salvage surgery: positive needle biopsy, negative bone scan, pelvic and abdominal CT, and life expectancy of at least ten years.

For salvage radiotherapy the criteria were: negative bone scan, pelvic and abdominal CT.

Exclusion criteria -

Population number of patients = 70.

Interventions Salvage prostatectomy (n=27). Radical retropubic prostatectomy was done in 24 patients and cystoprostatectomy in 3.

Salvage radiotherapy (n=43) was administered with a mean cumulative dose of between 66 and 70 Gy to the prostate and seminal vesicle bed.

Outcomes Complications

Follow up Mean follow-up for the salvage RP group was 34 months and in the salvage RT group, it was 31 months.

Results The salvage radiotherapy group had a higher pre-salvage therapy PSA level than the salvage prostatectomy group. At the time of salvage treatment, the mean serum PSA levels were 9.1 and 1.1 ng/mL for the salvage RP and salvage RT groups, respectively (p = 0.0001). The mean time from tumour recurrence to salvage treatment was 15.6 months for the salvage RP group and 4.9 months for the salvage RT group (p = 0.0001).

COMPARISON IN MEN WITH LOCALLY RECURRENT PROSTATE CANCER, AFTER RADIOTHERAPY	SALVAGE PROSTATECTOMY	SALVAGE RADIOTHERAPY	OVERALL RESULT
Incontinence	17/27 (63%)	14/43 (29%)	p =0.01
Bladder neck contracture	3/37 (11%)	3/43 (7%)	p =0.67
Haematuria	1/27 (4%)	2/43 (5%)	p=0.9
Bowel dysfunction	2/27 (7%)	8/43 (19%)	p=0.29
rectal bleeding	1/27 (4%)	3/43 (7%)	p=0.87

General comments Important differences between the patient groups (before salvage therapy) make direct comparisons unreasonable.

(Bianco *et al.* 2005)

Design: Retrospective case series (therapy), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Consecutive patients who had salvage radical prostatectomy (RP) for biopsy confirmed locally recurrent prostate cancer, after radiotherapy. All men were treated between 1984 and 2003, at one of two institutions.

Selection criteria for RP were: life expectancy >10 years, clinically localised disease, no significant urinary problems, no proctitis.

Exclusion criteria Positive lymph nodes, if a staging lymphadenectomy had been done.

Population number of patients = 100.

Interventions Patients had radiotherapy as initial therapy: 58% EBRT, 13% brachytherapy and 29% both. All patients had salvage radical prostatectomy.

Outcomes Disease specific survival, progression free survival (not considered in this appraisal). Risk factors for disease progression were also considered.

Follow up Median follow-up after salvage RP was 5 years (range 1 to 20 years).

Results 10 year disease specific survival was 73%. The overall 5 year progression free survival (PFS) was 55%. For those with positive surgical margins 5 year PFS was 38%, 28% for those with pT3 tumours and 22% for those with positive lymph nodes.

In a multivariate analysis of risk factors for disease progression, preoperative PSA level, positive lymph nodes and positive seminal vesicles were all independent predictors of disease progression.

COMPARISON IN MEN WITH LOCALLY RECURRENT PROSTATE CANCER, AFTER RADIOTHERAPY	RADICAL PROSTATECTOMY	OVERALL RESULT
10 year disease specific survival	73%	
COMPARISON IN MEN WITH LOCALLY RECURRENT PROSTATE CANCER, AFTER RADIOTHERAPY	SALVAGE RADICAL PROSTATECTOMY	OVERALL RESULT
15 year disease specific survival	60%	

General comments No data about treatment morbidity.

(Stephenson *et al.* 2004a)

Design: Retrospective case series (harm), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men who had salvage radical prostatectomy (RP) for biopsy confirmed locally recurrent prostate cancer after radiotherapy. RP was done between 1984 and 2003 in a single institution.

Exclusion criteria -

Population number of patients = 100.

Interventions Initial therapy was radiotherapy (EBRT in 58% of cases and brachytherapy in 42%). 36% had pelvic lymph node dissection as part of initial therapy.

The technique of salvage prostatectomy depended on the initial therapy. When initial therapy was EBRT, retropubic radical prostatectomy was usually used. For men who had interstitial radiotherapy an abdominoperineal approach was usually used to facilitate dissection between the prostate and rectum. In selected later cases, nerve sparing procedures or nerve grafting was used.

Outcomes Major intraoperative and postoperative complications (defined as grade II or higher on a 5 point scale). Grade II complications required intravenous therapy. Risk factors for anastomotic strictures and urinary incontinence were also considered.

Results Subgroup analysis compared outcomes in the periods 1984 to 1992 and 1993 to 2003. The surgical technique tended to differ between the two periods; the later patients nearly all had standard retropubic radical prostatectomy.

Multivariate analysis of risk factors for anastomotic stricture found non-standard retropubic approach and poor urethrovesical anastomosis to be adverse risk factors. Risk factors for urinary incontinence were: non-standard retropubic approach, TRUS size greater than 25 cc and positive surgical margins.

23 patients required an artificial urinary sphincter, after moderate to severe urinary incontinence.

Overall potency at five years after surgery was 16%. The five year potency rate was 45% in those who were potent preoperatively.

COMPARISON IN MEN WITH LOCALLY RECURRENT PROSTATE CANCER, AFTER RADIOTHERAPY	SALVAGE PROSTATECTOMY (1984 TO 1992)	SALVAGE PROSTATECTOMY (1993 TO 2003)	OVERALL RESULT
Complications (grade II or more)	13 (33%)	8 (13%)	p =0.02
Rectal injury	6 (15%)	1 (2%)	p=0.01
Ureteral injury	2	3	
Haemorrhage	2	0	
Lymphocele	0	2	

Urinary extravasation	1	1	
Obturator nerve injury	0	1	
Sepsis	1	0	
Thromboembolism	1	0	
Re-operation	6 (15%)	2 (3%)	p=0.05
Anastomotic stricture	11 (28%)	19 (32%)	p=0.66
5 year continence rate	57% (one pad or less per day)	68% (one pad or less per day)	p=0.71

General comments Survival outcomes in this series are reported in Bianco et al (2005).

(Ward *et al.* 2005)

Design: Retrospective case series (therapy), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men who had salvage surgery for radiorecurrent prostate cancer between 1967 and 2000 at a single institution.

Exclusion criteria -

Population number of patients = 199, mean age = 65 years.

Interventions Primary therapy was EBRT alone in 89% of cases, the remainder involved brachytherapy. Salvage surgery was retropubic prostatectomy (RP) for 138/199 patients and cystoprostatectomy (CP) for 61/199 patients.

The median time from radiotherapy to salvage surgery was 3 years for RP patients and 5 years for CP patients.

Neoadjuvant hormonal therapy was used for 23% of RP patients and 70% of CP patients. Adjuvant hormonal therapy was used for 56% of RP patients and 74% of CP patients.

Outcomes Disease specific survival, progression free survival (not considered in this appraisal). Complications of surgery

Follow up Median follow up was 6 years for retropubic prostatectomy patients and 4 years for cystoprostatectomy patients.

Results -

COMPARISON IN MEN WITH LOCALLY RECURRENT PROSTATE CANCER, AFTER RA-	RETROPUBIC PROSTATECOMY	CYSTOPROSTATECTOMY	OVERALL RESULT

DIOTHERAPY			
Median disease specific survival	8.7 years	4.4 years	Favours RP (p<0.001, log rank test)
10 year disease specific survival	77%	38%	Favours RP (p<0.001)
Urinary extravasation	15%	3%	
Wound infection	4%	11%	
Bladder neck contraction	22%	not applicable	
Incontinence	48%	not applicable	
Respiratory infection	0%	13%	
Ileus	0%	18%	

General comments Series covers a 33 year period,

SALVAGE BRACHYTHERAPY

(Grado *et al.* 1999)

Design: Retrospective case series (therapy), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men with biopsy confirmed local recurrence of prostate cancer after radiotherapy. Before the biopsy, 36/49 cases had biochemical recurrence only, 13/49 cases also had clinical recurrence. One patient had distant metastases.

Exclusion criteria -

Population number of patients = 49, age range 53 to 87 years, median age = 73 years.

Interventions Primary therapy was EBRT in 46 men and brachytherapy in 3. The median time between primary therapy and salvage brachytherapy was 42 months (range 22 to 185 months). 11 of the patients had failed one or more secondary therapies (orchiectomy, antiandrogen therapy or prostatectomy). 16 had TURP.

Outcomes Overall survival, disease specific survival

Follow up Median follow-up amongst survivors was 23.2 months, (range 3 to 78 months).

Results Local failure occurred in 1/49 patients, and distant failure in 26/49 patients.

COMPARISON IN MEN WITH LOCALLY RECURRENT PROSTATE CANCER	SALVAGE BRACHYTHERAPY	OVERALL RESULT
3 year overall survival	75%, 95% C.I. 59 to 86%	
5 year overall survival	56%, 95% C.I. 36 to 71%	
3 year disease specific survival	89%, 95% C.I. 73 to 96%	
5 year disease specific survival	79%, 95% C.I. 58 to 91%	
TURP	7/49 (14%)	
Incontinence (after TURP)	3/49 (6%)	
Haematuria	2/49 (4%)	
Penile dysuria	3/49 (6%)	
Rectal ulcers	2/49 (4%)	
rectal bleeding	1/49 (2%)	

General comments -

(Lee *et al.* 2007)

Design: Retrospective case series (therapy), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men with locally recurrent prostate cancer after curative radiotherapy, who were unsuitable candidates for salvage RP, LDR brachytherapy or cryotherapy (or were unwilling to have these treatments). Men were treated between 1998 and 2005. Men had no evidence of distant metastases, biopsy confirmed local recurrence and at lest 5 years life expectancy.

Exclusion criteria -

Population number of patients = 21, age range 58 to 81 years, mean age = 68 years.

Interventions Salvage high dose rate brachytherapy (HDRBT). All me were treated with 36 Gy in six fractions using two separate HDR catheter implants, performed one week apart.

Outcomes Biochemical relapse (using the ASTRO-1997 definition). Treatment toxicity using the Common Terminology Criteria for Adverse Events (CTCAE version 3).

Follow up Median follow-up from original recurrence was 18.7 months (range 6 to 84 months).

Results 2/21 men (10%) experienced biochemical relapse. The two year Kaplan-Meier estimate of biochemical relapse free survival was 89%. No grade 4 treatment toxicity was re-

ported.

Genitourinary toxicity

18/21 men (86%) experienced grade1 or 2 urinary symptoms, but no incontinence was reported. 3/21 men (14%) experienced grade 3 genitourinary symptoms.

Gastrointestinal toxicity.

3/21 men (14%) experienced grade 1 or 2 gastrointestinal symptoms. There was no grade 3 GI toxicity in this series.

Sexual dysfunction

18/21 men (86%) experienced grade1 or 2 sexual dysfunction and 2/21 men (10%) experienced grade 3 sexual dysfunction.

SALVAGE EXTERNAL BEAM RADIOTHERAPY

(Buskirk *et al.* 2006)

Design: Retrospective case series (therapy), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men treated with salvage radiotherapy for biochemical failure after radical prostatectomy for prostate cancer. Men were treated between 1987 and 2003 at one of 3 clinics.

Exclusion criteria -

Population number of patients = 368.

Interventions Salvage EBRT, median dose to the prostate fossa was 64.8 Gy (range 54.0 to 72.4 Gy). 4/368 men also received radiotherapy to the pelvic lymph nodes (45.0 to 50.4 Gy).

Outcomes Biochemical recurrence (defined as PSA of 0.4ng/mL and above the post-RT nadir), overall survival and clinical disease free survival.

Follow up Median follow-up was 5 years (range 0.1 to 14.7 years)

Results Overall survival

Estimated 5 year overall survival was 92% (95% CI 89% to 95%).

Clinical disease free survival

Estimated 5 year clinical disease free survival was 96% (95% CI 94% to 99%).

Biochemical recurrence free survival

Estimated 5 year biochemical recurrence free survival was 46% (95% CI 41% to 53%).

Multivariate analysis identified the following risk factors for biochemical recurrence (BCR): pathological stage T3a or less vs. T3b (seminal vesicle involvement, p = 0.029), pathological Gleason score 7 or less vs. 8 or greater (p < 0.001) and pre-radiotherapy prostate specific antigen (p < 0.001). A prognostic scoring system for BCR was developed using these three variables.

(Nilsson *et al.* 2004)

Design: Systematic review of combined study designs (therapy), evidence level: 2++

Inclusion criteria A Medline search of published literature to January 2003 on radiotherapy in prostate cancer. After the initial screening, 820 articles remained. After reading the papers, 294 were included in the review.

Exclusion criteria Repeat publications, articles published before 1994, case reports, abstracts, lab studies.

Population number of patients = 853.

Interventions Adjuvant or salvage radiotherapy after radical prostatectomy, with or without hormonal therapy. Median RT dose in individual studies ranged from 52 Gy to 70 Gy, but was usually around 65 Gy. Some patients had hormonal therapy at the same time as radiotherapy.

Outcomes Biochemical control rates. Biochemical recurrence free survival. Some studies reported clinical recurrence rates. Limited analysis of treatment toxicity.

Follow up Where reported, median follow up ranged from 22 to 54 months.

Results -

COMPARISON IN MEN WITH LOCALLY RECURRENT PROSTATE CANCER AFTER PROSTATECTOMY	RESULTS	OVERALL RESULT
Adjuvant vs. salvage vs. no EBRT	Ten retrospective studies were included (853 patients in total). Most studies reported biochemical disease free survival / biochemical control rate.	After radical prostatectomy with adverse factors adjuvant EBRT seems to result in better disease free survival than salvage or no postoperative EBRT. Salvage EBRT probably results in

		marginally better outcome than no EBRT.
PSA level and salvage EBRT outcome	Five retrospective studies included (234 patients). Patients with pre-EBRT PSA of less than 1 ng/ml were more likely to experience biochemical control.	Lower pre-salvage therapy PSA values enhance long-term biological recurrence free survival.
Addition of androgen suppression to salvage EBRT	One randomised trial and two retrospective studies were included (300 patients). The use of adjuvant androgen suppression with salvage EBRT led to better biochemical control. One study reported an overall survival advantage at 10 years.	Androgen suppression combined with adjuvant EBRT may result in better biological recurrence free survival than EBRT alone.
Toxicity of salvage EBRT	Detailed toxicity data were not extracted. One prospective trial did not report an adverse effect of adjuvant EBRT on urinary continence.	Toxicity data are inadequate

General comments -

(Macdonald *et al.* 2004)

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

Country: United States, setting: Tertiary care

Inclusion criteria Men who had salvage radiotherapy for recurrent prostate cancer (detectable PSA) after prostatectomy. All were treated at one institution between 1993 and 1999.

Exclusion criteria Neo-adjuvant or adjuvant androgen deprivation therapy at the time of initial prostatectomy.

Population number of patients = 102.

Interventions Salvage radiotherapy, total dose ranged from 41 to 70 Gy (median 66 Gy), with daily dose between 1.8 and 2.0 Gy.

Subgroup analysis was done to compare outcomes after salvage radiotherapy in men with PSA-only recurrence, with those in men with palpable recurrence.

Outcomes Overall survival, distant metastasis free survival, biochemical recurrence free survival. Late radiation toxicity.

Follow up Median follow up was 4.2 years (range 0.2 to 9 years). Median time from prostatectomy to salvage radiotherapy was 2 years (range 0.2 to 10 years).

Results -

COMPARISON IN MEN WITH BIOCHEMICAL RECURRENCE AFTER PROSTATECTOMY	SALVAGE RADIOTHERAPY FOR PSA FAILURE ONLY	SALVAGE RADIOTHERAPY FOR PALPABLE FAILURE	OVERALL RESULT
5 year overall survival	95%	76%	Overall survival was better in men with PSA failure only (p=0.02, log rank test)
5 year distant metastasis free survival	90%	81%	DM free survival was better in men with PSA failure only (p=0.05, log rank test)
5 year biochemical failure free survival	48%	38%	no significant difference (p=0.1, log rank test)
Toxicity of salvage EBRT	--	--	Overall 46 late toxicities occurred. 17 patients had grade 1-2, and 3 had grade 3-4.

General comments -

(Neuhof *et al.* 2007)

Design: Retrospective case series (therapy), evidence level: 3

Country: Germany, setting: Tertiary care

Inclusion criteria Men treated with salvage radiotherapy for recurrent prostate cancer after radical prostatectomy, at a single institution between 1991 and 2004. At time of radiotherapy, no men had evidence of metastatic disease or nodal involvement.

Population number of patients = 171, age range 49 to 74 years, median age = 63 years.

Interventions All men received a dose of 56 Gy in 2 Gy daily fractions to the target volume, followed by a smaller boost field (to spare rectal tissue). The total dose was between 60 and 66 Gy.

Outcomes Biochemical failure after salvage RT (using ASTRO-1997 criteria), overall and clinical relapse free survival.

Follow up Median follow-up after salvage radiotherapy was 39 months (range 64 to 131 months).

Results 8/171 men (5%) died from prostate cancer. 1, 3 and 20 men had clinical evidence of local, nodal and distant relapse respectively (1%, 2% and 12% respectively).

On multivariate analysis only Gleason score (HR=3.02, 95% CI 1.02 to 8.97) and pre-RT PSA level (HR = 1.54, 95% CI 1.002 to 2.36) were found to be statistically significant predictors of PSA recurrence (at $p<0.05$).

(Pazona *et al.* 2005)

Design: Retrospective case series (therapy), evidence level: 3

Country: United States

Inclusion criteria Men who had radical retropubic prostatectomy, and then salvage radiotherapy for PSA progression (0.1 ng/ml or more). All were initially treated by the same surgeon between 1983 and 2003.

Exclusion criteria Men who had adjuvant therapy (hormonal therapy or radiotherapy). Men with missing follow up data.

Population number of patients = 223.

Interventions Salvage radiotherapy was given at different institutions. The details of EBRT were not available.

Outcomes PSA progression free survival.

Follow up Median time from RRP to PSA progression was 23 months (range 1 to 129). Median follow-up from RRP was 104 months (range 7 to 225). Median follow-up from salvage radiotherapy was 56 months (range 0 to 188).

Results Analysis was done to compare the progression free survival of subgroups based on PSA level at salvage therapy, seminal vesicle (SVI) or lymph node involvement (LNI), and PSA doubling time (PSA-DT).

COMPARISON IN MEN WITH BIOCHEMICAL RECURRENCE AFTER PROSTATECTOMY	SALVAGE RADIOTHERAPY WHEN PSA <1.3 NG/ML	SALVAGE RADIOTHERAPY WHEN PSA >1.3 NG/ML	OVERALL RESULT
5 year progression free survival	43%	32%	Better if PSA < 1.3 ng/ml (p=0.03, log rank test)
COMPARISON IN MEN WITH BIOCHEMICAL RECURRENCE AFTER PROSTATECTOMY	SALVAGE RADIOTHERAPY IN MEN WITH NO SVI OR LNI	SALVAGE RADIOTHERAPY IN MEN WITH SVI OR LNI	OVERALL RESULT
5 year progression free	46%	20%	Better if no SVI or LNI

survival			(p<0.01)
COMPARISON IN MEN WITH BIOCHEMICAL RECURRENCE AFTER PROSTATECTOMY	SALVAGE RADIOTHERAPY IN MEN WITH PSA-DT > 10 MONTHS	SALVAGE RADIOTHERAPY IN MEN WITH PSA-DT < 10 MONTHS	OVERALL RESULT
5 year progression free survival	48%	33%	Better if PSA-DT > 10 months (p=0.06)

General comments -

(Stephenson *et al.* 2004b)

Design: Retrospective case series (therapy), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men who had salvage radiotherapy for recurrent prostate cancer after prostatectomy, in one of 5 institutions. 96% has PSA level of 0.2ng/ml or more before salvage EBRT. All recurrence was believed to be local. All were treated between 1987 and 2002.

Exclusion criteria Adjuvant therapy at the time of the initial prostatectomy.

Population number of patients = 501, age range 40 to 79 years, mean age = 623 years.

Interventions All had salvage radiotherapy to the prostatic fossa in daily fractions of 1.8 to 2.0 Gy. 5% of patients had radiotherapy to the pelvic nodes.17% of patients had neoadjuvant androgen deprivation therapy, before salvage radiotherapy.

Outcomes PSA progression free survival.

Follow up Median follow up after prostatectomy was 85 months (range 5 to 192 months). Median follow up after salvage radiotherapy was 85 months (range 5 to 192 months)

Results 250/501 patients (50%) experienced disease progression after treatment, 49 (10%) developed distant metastases, 20 (4%) died from prostate cancer, and 21 (4%) died from other or unknown causes. The 4-year progression-free probability (PFP) was 45% (95% confidence interval [CI], 40%-50%).

On multivariate analysis, the following were adverse prognostic factors for PSA progression after salvage radiotherapy (SRT): pre SRT PSA of 2 or more, Gleason score 8 or more, negative surgical margins, PSA-DT of 10 months or less and seminal vesicle involvement.

COMPARISON IN MEN WITH BIOCHEMICAL RECURRENCE AFTER PROSTATECTOMY	SALVAGE RADIOTHERAPY WHEN PSA <1.1 NG/ML	SALVAGE RADIOTHERAPY WHEN PSA 1.1 TO 2.0 NG/ML	SALVAGE RADIOTHERAPY WHEN PSA >2.0 NG/ML	OVERALL RESULT

4 year biochemical progression free survival	53% [95% CI 46 to 60%]	49% [95% CI 38 to 61%]	21% [95% CI 12 to 29%]	Significant effect of PSA level, p<0.001 (Cox regression)

(Stephenson *et al.* 2007)

Design: Retrospective case series (prognosis), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men from 17 hospitals treated with salvage radiotherapy (SRT) for biochemical failure after radical prostatectomy. Biochemical recurrence was defined as PSA 0.2 ng/ml or more and rising, or a single value of 0.5 ng/ml or higher.

Exclusion criteria Adjuvant hormonal therapy after SRT (before or during SRT was acceptable).

Population number of patients = 1540, mean age = 62 years.

Interventions Salvage radiotherapy (not specified in detail). A nomogram to predict disease progression was developed using the following pre-SRT variables: prostatectomy PSA, Gleason score, SVI, surgical margins, LNI, persistently elevated postoperative PSA, pre-SRT PSA, PSA-DT, neoadjuvant ADT, and radiation dose.

Outcomes Disease progression after SRT, defined as serum PSA of 0.2ng/ml or more above the post SRT nadir followed by another higher value, continued rise in PSA, initiation of systemic therapy or clinical recurrence.

Follow up Median follow-up after the completion of salvage radiotherapy was 53 months (IQR 28 to 81 months).

Results 866/1540 (56%) of the men experienced disease progression after SRT. Six year progression free probability was 32% (95% CI 28% to 35%).

From survival analysis, an estimated 48% (95% CI 40 to 56%) of men who had SRT when their PSA was less than 0.5ng/mL were disease free at 6 years, compared with 40% (95% CI 34 to 46%), 28% (95% CI 20 to 35%) and 18% (95% CI 14 to 22%) for men treated at PSA levels of 0.51 to 1.00, 1.01 to 1.50 and greater than 1.51ng/mL respectively.

Multivariate analysis of prognostic factors for disease progression identified the following significant variables: PSA level before SRT (P < .001), prostatectomy Gleason grade (P < .001), PSA doubling time (P < .001), surgical margins (P < .001), androgen-deprivation therapy before or during SRT (P < .001), and lymph node metastasis (P = .019).

The nomogram for the prediction of six year progression free probability was validated internally using bootstrap resampling. The concordance index (similar to the area under the ROC curve - but for censored outcomes) was 0.69.

(Brooks *et al.* 2005)

Design: Retrospective case series (therapy), evidence level: 3

Country: United States

Inclusion criteria Patients who had salvage radiotherapy after prostatectomy, at two centres between 1991 and 2001. The criteria for salvage radiotherapy were persistent or increasing post-operative PSA of 0.2 ng/ml or greater.

The paper also summarises the results of ten published series of salvage radiotherapy after prostatectomy (including the present series), with 1464 patients.

Exclusion criteria Neo-adjuvant or adjuvant androgen suppression therapy at the time of the initial prostatectomy.

Population number of patients = 1464.

Interventions The median dose in the ten published series ranged from 64.0 Gy to 68.0 Gy.

Outcomes Optimal significant PSA cut-off (the pre-radiotherapy level that predicts the best outcomes), biochemical progression free survival, distant metastasis survival Toxicity, scored using the RTOG-EORTC criteria.

Follow up The median follow-up in the ten published series ranged from 36 to 75 months.

Results The paper summarised the results of ten published series of salvage radiotherapy after prostatectomy (including the present series).

COMPARISON IN MEN WITH BIOCHEMICAL RECURRENCE AFTER PROSTATECTOMY	SALVAGE RADIOTHERAPY
4 year biochemical progression free survival	between 39% and 50% in 4 studies (n=778)
5 year biochemical progression free survival	between 45% and 55% in 3 studies (n=232)
4 year distant metastasis free survival	between 82% and 83% in 2 studies (n=188)
Estimated pre-SRT PSA cut-off at which disease control is adversely affected	between 0.6 and 2.5 ng/ml in 9 studies (n=1298)
Genitourinary toxicity	13/144 had acute GU toxicity. 11/144 had late GU toxicity.

Gastrointestinal toxicity	26/144 had acute GI toxicity. 9/144 had late GI toxicity.

General comments -

(Faria *et al.* 2006)

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

Country: Canada (federal state, Commonwealth Realm)

Inclusion criteria Men with T1-3N0M0 prostate cancer initially treated with EBRT, who then experienced asymptomatic biochemical failure. All were treated at the same institution between 1992 and 2000.

Exclusion criteria Men with positive bone scans or pelvic CT at the time of biochemical failure. Men with missing follow up data.

Population number of patients = 178.

Interventions Initial therapy was EBRT. One group of patients (n=65) received hormonal therapy after biochemical failure, the others (n=113) were followed up without treatment. The types of hormonal therapy are not reported. The median

The decision to treat or not to treat was individualised and determined on the basis of PSA values, patient-doctor discussion or inclusion in a clinical trial.

Outcomes Disease specific survival (it is not reported how cause of death was ascertained), overall survival.

Follow up Median follow up was 102 months in the treated group and 83 months in the untreated group.

Results No patient in either group died of prostate cancer. In the untreated group 101/113 were alive an asymptomatic at the last follow-up visit and 12 had died of other causes. In the treated group, 3 men died of other causes.

COMPARISON IN MEN WITH ASYMPTOMATIC BIOCHEMICAL RECURRENCE AFTER RADIOTHERAPY	HORMONAL THERAPY	NO TREATMENT	OVERALL RESULT
Overall survival	62/65 (95%)	101/113 (89%)	Favours hormonal therapy (p<0.0001)

General comments Treatment toxicity is not reported.

SALVAGE CRYOTHERAPY

(Pisters *et al.* 2006)

Design: Retrospective case series (therapy), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria The study is a retrospective review of the cases of salvage cryosurgery and salvage radical prostatectomy (RP) from two institutions. All men had locally recurrent prostate cancer following initial treatment with radiotherapy.

Exclusion criteria Patients with pre-salvage treatment PSA more than 10 ng/ml. Patients with Gleason score greater than 8.

Population number of patients = 116.

Interventions Men had either salvage prostatectomy (n=56) or salvage cryotherapy (n=60). None had androgen deprivation therapy until post-salvage biochemical failure. Biochemical failure after salvage therapy was defined as 2 rises in PSA after nadir.

Outcomes Disease specific death, biochemical progression.

Follow up Mean follow up was 5.1 years for the cryosurgery group and 4.6 years for the radical prostatectomy (RP) group.

Results -

COMPARISON IN MEN WITH LOCALLY RECURRENT PROSTATE CANCER, AFTER RADIOTHERAPY	SALVAGE PROSTATECTOMY	SALVAGE CRYOTHERAPY	OVERALL RESULT
Death due to prostate cancer	3/56	5/60	no significant difference
Biochemical progression	16/56	40/60	p=0.0002, in favour of prostatectomy

General comments Abstract only. No data about complications.

(National Institute for Health and Clinical Excellence)

Design: Systematic review of combined study designs (therapy), evidence level: 2+

Inclusion criteria Papers published before June 2004, containing safety or efficacy data about salvage cryotherapy for recurrent prostate cancer.

Exclusion criteria -

Population -

Interventions Seven relevant studies were identified.

Outcomes Efficacy: disease specific survival biochemical disease free survival, negative biopsy rate. Complications (according to individual author's definitions).

Follow up Only two of the seven case series had median follow up of more than two years.

Results A single study reported disease specific survival.

The highest complication rates were invariably seen in the older studies, using outdated second generation machines.

COMPARISON IN MEN WITH LOCALLY RECURRENT PROSTATE CANCER	SALVAGE CRYOTHERAPY	OVERALL RESULT
5 year disease specific survival	79%	Data comes from 1 study, (n=131)
Incontinence	Overall 35% (range 8 to 73%)	Data from 6 studies (n=422)
Impotence	Overall 71% (range 66 to 72%)	Data from 2 studies (n=164)
Obstruction	Overall 25% (range 5 to 44%)	Data from 4 studies (n=307)
Rectal or pelvic pain	Overall 23% (range 6 to 39%)	Data from 4 studies (n=245)
Sloughing	Overall 14% (range 5 to 22%)	Data from 3 studies (n=282)
Fistula	Overall 2% (range 0 to 4%)	Data from 6 studies (n=422)
Scrotal swelling	Overall 1% (range 0 to 11%)	Data from 6 studies (n=422)
Biochemical recurrence	Ranged from 26% to 63% (median follow-up ranged from 1 to 6.8 years)	Data from 7 studies (n=553)
Negative biopsy rate	Ranged from 77% to 100%	Data from 3 studies (n=454)

General comments The authors of the review could not draw any conclusions about the efficacy of the procedure, due to the lack of relevant outcome data and short follow up. They note that complication rate may be underestimated due to the use of physician records rather than validated questionnaires.

(Spiess *et al.* 2006)

Design: Retrospective case series (therapy), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men treated with cryotherapy for recurrent prostate cancer at a single institution between 1980 and 2004. Primary treatment was EBRT in all cases.

Exclusion criteria Neoadjuvant or adjuvant hormonal therapy with cryotherapy. A minimum of 3 PSA measurements before and after cryotherapy.

Population number of patients = 49, age range 58 to 81 years, median age = 66 years.

Interventions Men were treated with salvage cryotherapy (not described in detail)

Outcomes Overall survival, disease specific survival, clinical recurrence and biochemical recurrence (increasing PSA, at least 2 ng/mL above the postsalvage nadir).

Follow up Median follow-up was 5.7 years

Results 26/49 men (53%) experienced biochemical failure. 11/49 men (22%) experienced distant metastases. 18/49 men (37%) died from prostate cancer, after a median disease specific survival duration of 9.4 years (range 7.8 to 12.6 years). Overall mortality was 20/49 (41%).

On multivariate analysis of prognostic factors for biochemical failure free survival, pre-salvage PSA-DT <16 months was an adverse prognostic factor (RR = 0.43, p=0.06) and pre-salvage serum PSA > 10 ng/ml was a favourable prognostic factor (RR=1.12, p=0.002).

General comments Series spans two decades, cryotherapy technique is likely to have changed substantially.

Health Economic Summary

The literature review on the management of biochemical relapse identified 20 potentially relevant papers but none were obtained for appraisal as they did not include any economic evaluations. Since case studies represented the highest quality clinical evidence, the evidence base was considered too weak to warrant any further consideration of cost-effectiveness and de novo economic modelling.

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5 Locally Advanced Prostate Cancer

5.1 Combined hormone and radiotherapy

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

Short Summary

Adjuvant therapy with radical prostatectomy

Randomised trials report significant toxicity with adjuvant therapy in addition to prostatectomy (Kumar *et al.* 2006). With the exception of one small trial in node-positive men (Messing, 1999), these trials have not demonstrated significant benefit in overall survival. It is possible that modest survival benefits will emerge with longer follow-up. Evidence about adjuvant radiotherapy comes from two randomised trials (Bolla *et al.* 2005; Thompson, Jr. *et al.* 2006).

Evidence Summary

Adjuvant hormonal therapy with prostatectomy

Evidence comes from three randomised trials included in the Kumar and co-workers (Kumar *et al.* 2006) review. Men treated with adjuvant hormonal therapy had significantly better disease free survival at 5 and 10 years after surgery. In meta-analysis there was no difference in overall survival at 5 years after surgery, although Messing and co-workers (1999, 2006) reported a significant survival benefit with adjuvant hormone therapy. In the Wirth study (Wirth *et al.* 2004), men treated with adjuvant hormonal therapy had significantly lower overall survival at 10 years after surgery, than the standard care group.

The Messing study (Messing *et al.* 1999) reported a significant increase in grade 1 and 2 side effects in the adjuvant hormone group. The Wirth study (Wirth *et al.* 2004) noted that discontinuation due to adverse effects was twice as likely in the adjuvant hormone group.

Adjuvant radiotherapy with prostatectomy

Evidence comes from two randomised trials (Bolla *et al.* 2005; Thompson, Jr. *et al.* 2006). There was no significant effect of adjuvant radiotherapy on overall or disease specific survival, although follow-up in the Bolla trial is not yet long enough to establish survival outcomes. Biochemical failure and clinical failure were significantly less likely in the group receiving adjuvant radiotherapy. Complications were significantly increased in those receiving adjuvant radiotherapy when compared to standard care.

Evidence Tables

Kumar, Shelley, Harrison, Coles, Wilt & Mason. Neo-adjuvant and adjuvant hormone therapy for localised prostate cancer [protocol for a Cochrane review]. Cochrane Database of Systematic Reviews 2006 Issue 2. [2]. 2006. Chichester (UK), John Wiley & Sons, Ltd.
Design: Systematic review of RCTs (therapy), evidence level: 1+ **Inclusion criteria** Study types: Randomised controlled trials or quasi-randomised trials reporting on neo-adjuvant and adjuvant hormonal therapy for localised or locally advanced prostate cancer. Also RCTs that compare schedules of neo-adjuvant or adjuvant hormonal therapy were eligible. Only peer reviewed published articles were included. Participants: Men with stage T1 - T4, N1, M0 prostate cancer, according to the WHO 1997 TNM classification. Interventions: Primary therapies included radical prostatectomy, radical radiotherapy, brachytherapy or cryotherapy. Neo-adjuvant or adjuvant hormonal therapies consisting of combination hormonal therapy with LHRH agonists plus anti-androgens, or single agent hormone deprivation therapies. Hormonal therapies of any duration were considered. Only studies of either adjuvant or neo-adjuvant hormones were included and not those that are looking at both. Neo-adjuvant and adjuvant hormonal therapies were taken to include those that overlap or were concurrent with radiotherapy treatment. **Interventions** Neoadjuvant hormonal therapy with prostatectomy. Adjuvant hormonal therapy with prostatectomy. Neoadjuvant hormonal therapy with radiotherapy. Adjuvant hormonal therapy with radiotherapy. **Outcomes** Overall survival, biochemical relapse free survival, clinical relapse free survival, treatment toxicity. **Results**.

(Messing *et al.* 2006)
Design: Randomized controlled trial (therapy), evidence level: 1+ Country: United States, setting: Tertiary care **Inclusion criteria** Men who had radical prostatectomy and pelvic lymphadenectomy for clinically localised prostate cancer, and who had confirmed pelvic nodal metastases. **Exclusion criteria** No radiological evidence of metastases, no previous hormonal therapy **Population** number of patients = 98, age range 45 to 78 years, median age = 66 years. **Interventions** All men had radical prostatectomy and pelvic lymphadenectomy. Men were ran-

domised to receive either immediate hormone therapy (choice of 3.6 mg goserelin monthly or bilateral orchidectomy) or no hormone treatment until disease progression.

Outcomes Overall and disease specific survival. Disease recurrence (PSA or clinical recurrence).

Follow up Median follow-up was 11.9 years (range 9.7 to 14.5 for survivors). Men were followed up every three months for the first year, with clinical examination and PSA tests, and bone scans at alternate visits. Follow-up frequency changed to 6 months after the first year.

Results Multivariate analysis (Cox proportional hazards) was used to adjust for the effect of Gleason score on the outcomes.

COMPARISON IN MEN AFTER RADICAL RETROPUBIC PROSTATECTOMY, WITH ADVERSE RISK FACTORS	IMMEDIATE HORMONE THERAPY	DELAYED HORMONE THERAPY	OVERALL RESULT
Overall survival	17/47 men died (36%)	28/51 men died (55%)	Favours immediate therapy, adjusted HR for death (deferred vs. immediate) 1.84 (95% CI 1.01 to 3.35)
Disease specific survival	7/47 men died from prostate cancer (15%)	25/51 men died from prostate cancer (49%)	Favours immediate therapy, adjusted HR for death from PCa (deferred vs. immediate) 4.09 (95% CI 1.76 to 9.49)
Disease progression	22/27 (47%)	44/51 (86%)	Favours immediate therapy, adjusted HR for progression (deferred vs. immediate) 3.42 (95% CI 1.96 to 5.98)

General comments Study closed early due to accrual problems (due to changes in clinical practice).

Bolla, van, Collette, van, Vekemans, Da, de Reijke, Verbaeys, Bosset, van, Marechal, Scalliet, Haustermans, Pierart & European Organization for Research and Treatment of Cancer. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). [See comment]. Lancet 366[9485]. 2005.

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

Country: International, setting: Tertiary care

Inclusion criteria EORTC trial 22911. Men with previously untreated prostate cancer with a

clinical tumour stage T0 to T3, nodal stage N0 and no distant metastases. Pathological stage pT2-T3 pN0 and at least one of the following risk factors: tumour growth beyond the capsule, positive surgical margins or invasion of the seminal vesicles.

Men had to be younger than 76 years, with WHO performance status of 0 or 1.

Exclusion criteria Inappropriate disease stage, previous or concurrent cancer, prior treatment, lack of baseline data or incomplete initial workup.

Population number of patients = 1005, median age = 65 years.

Interventions All men had radical retropubic prostatectomy.

After surgery men were randomly assigned to receive radiotherapy or to a wait and see policy, where treatment was delayed until biochemical or clinical failure.

Radiotherapy within 16 weeks after surgery. A dose of 50 Gy was given in 25 fractions over 5 weeks, to a volume that included the surgical limits. A 10 Gy boost was given in 5 fractions over a week to a smaller volume.

113/503 (22%) of patients in the observation group received radiotherapy for biochemical or clinical relapse.

Outcomes Clinical progression free survival (survival with no clinical, radiological or scintigraphic evidence of recurrence). Biochemical progression free survival, defined as an increase of more than 0.2 ng/ml over the lowest post operative value measured on 3 occasions at least 2 weeks apart.

Adverse effects from radiation, and late complications (using the EORTC scale).

Follow up clinical examinations, with DRE and PSA tests, were done at 2, 4 and 12 months after surgery, then every 6 months until the end of the 5th year, then yearly until death. Median follow-up was 5 years.

Results 220/ 503 in the wait-and-see group and 131/502 in the radiotherapy group experienced biochemical relapse.

113/ 503 in the wait-and-see group and 75/502 in the radiotherapy group experienced clinical progression or death.

15/ 503 in the wait-and-see group and 8/502 in the radiotherapy group experienced death due to prostate cancer.

Acute adverse effects of radiation were mild to moderate in most patients. The following grade 3 acute effects were reported: acute diarrhoea (5.3% of patients), frequency passage of urine (3.3%), dysuria (1.1%) and skin (0.4%).

COMPARISON IN MEN AFTER RADICAL RETROPUBIC PROSTATECTOMY, WITH ADVERSE RISK FACTORS	ADJUVANT RADIOTHERAPY	NO RADIOTHERAPY	OVERALL RESULT
5 year biochemical progression free survival	74.0% [98% CI 68.7 to 79.3%]	52.6% [98% CI 46.6 to 58.5%]	Favours radiotherapy, p<0.0001 (log-rank test)
5 year clinical progres-	92.2% [98% CI 87.8 to	81.0% [98% CI 76.4 to	Favours radiotherapy,

sion free survival	94.6%]	85.5%]	p<0.0001 (log-rank test)
5 year overall survival	93.1% [98% CI 90.1 to 96.2%]	92.3% [98% CI 89.1 to 95.5%]	No sig. difference, p =0.6796 (log rank test)

General comments -

Thompson, Jr., Tangen, Paradelo, Lucia, Miller, Troyer, Messing, Forman, Chin, Swanson, Canby-Hagino & Crawford. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. JAMA 296[19]. 2006.

Design: RCT (therapy) evidence level: 1++

Country: United States, setting: Tertiary care

Inclusion criteria Men treated with prostatectomy for stage pT3 N0 M0 prostate cancer. Men had to have adequate bone marrow and liver function and performance status of 0 to 2.

Exclusion criteria positive bones scan result. Urinary incontinence, rectal injury, pelvic infection or urinary extravasation. Previous chemotherapy or radiotherapy were not permitted

Population number of patients = 425.

Interventions Men were randomised to receive either adjuvant radiotherapy or observation after radical prostatectomy. Radiotherapy was given within 17 weeks of radical prostatectomy, at a dose of 60 to 64 Gy in 30 to 32 fractions. 70/211 (33%) of patients in the observation arm received radiotherapy for biochemical or clinical relapse.

Outcomes Metastasis free survival, overall survival, biochemical relapse free survival (only defined for men with post surgical PSA of less than 0.4 ng/ml as PSA greater than 0.4 ng/ml), time to hormonal treatment and complication rate.

Follow up Median follow-up was 10.6 years (IQR 9.2 to 12.7 years). Toxicity was monitored weekly during radiotherapy. Follow up visits were every 3 months for 1 year, every 6 months for the next 2 years and then annually.

Results -

COMPARISON IN MEN AFTER RADICAL RETROPUBIC PROSTATECTOMY, WITH ADVERSE RISK FACTORS	ADJUVANT RADIOTHERAPY	OBSERVATION AND SALVAGE RADIOTHERAPY IF INDICATED	OVERALL RESULT
Distant metastasis free survival	Median 14.7 years. 76/214 had metastatic disease or died	Median 13.2 years. 91/211 had metastatic disease or died	No sig. difference, HR = 0.75 (95% CI 0.55 to 1.02), p=0.06
Biochemical recurrence	122/175.	60/172	Favours adjuvant radiotherapy (p<0.001,

			HR = 0.43, 95% CI 0.31 to 0.58)
Clinical recurrence	84/214	111/211	Favours adjuvant radiotherapy (p=0.001, HR = 0.62, 95% CI 0.46 to 0.82)
Overall survival	71/214 died	83/211 died	No sig. difference (HR=0.80, 95%CI 0.58 to 1.09, p=0.16)
Complications	51/214	25/211	Favours observation (RR=2.01, 95%CI 1.37 to 2.23)

General comments -

Which patients with non-metastatic prostate cancer benefit from a combination of hormones and external beam radiotherapy?

Rationale

External beam radiotherapy (EBRT) is a standard treatment for localised non metastatic prostate cancer. Hormone therapy which blocks androgen stimulation to the prostate cancer cells also suppresses tumour growth and may control prostate cancer for some years. Resistance to hormone therapy is inevitable and it is therefore not seen as a long term definitive treatment in a patient whose life expectancy is likely to extend beyond the duration of response, typically two to three years. The advantage of hormone therapy however is that as a systemic treatment it will affect prostate cancer cells outside the prostate gland and will be active on micrometastases. It will also reduce the tumour burden in the prostate if given before EBRT thus potentially reducing the number of viable cells which radiotherapy has to eliminate. Combining the two treatments may therefore provide optimal local and distant tumour control, but is only relevant to those patients where EBRT alone would not encompass and eliminate the full extent of the prostate cancer.

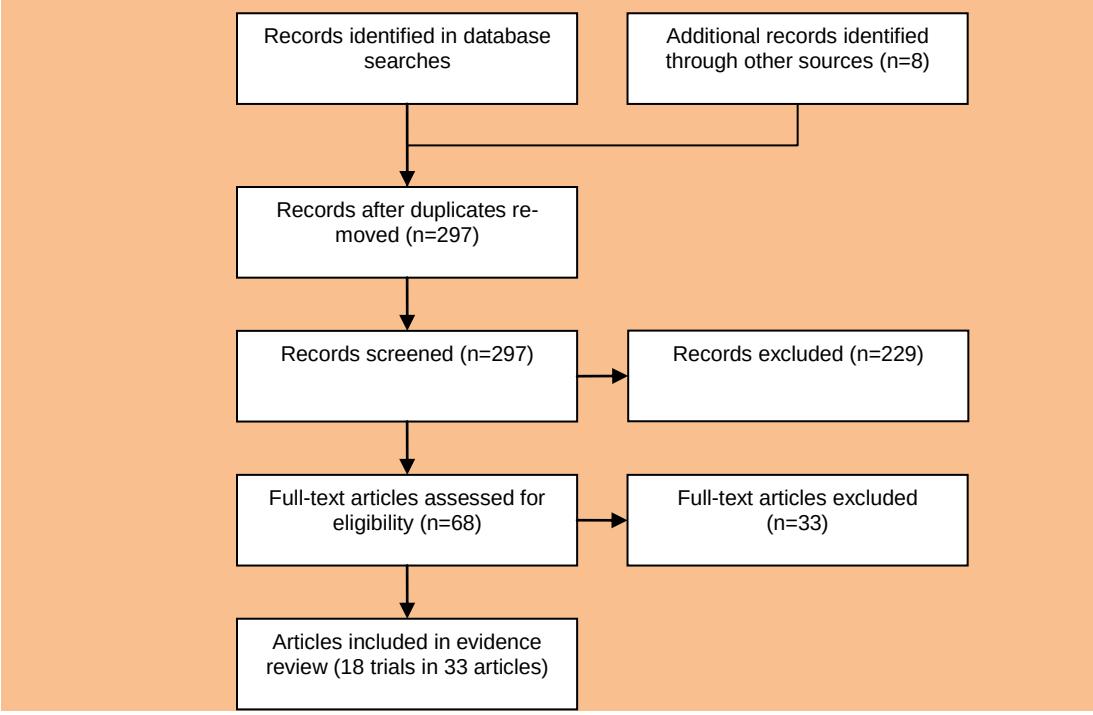
EBRT is a defined event within a specific time frame, typically 7 to 8 weeks when external beam is used alone. Hormone therapy may be given for a variable length of time and may precede radiotherapy (neoadjuvant treatment, NAH), be given during radiotherapy and for a period following radiotherapy. The optimal timing and overall duration is uncertain; typically, patients with 'intermediate to high-risk' localised disease receive NAH for 3-6 months before EBRT, while patients with 'locally advanced' cancers might receive hormone treatment for 2 years or longer, with NAH often , but not always, being part of that treatment. Although most trials of hormone therapy used in association with EBRT have used androgen deprivation therapy (ADT), some, including the SPCG-7 study for locally advanced disease, have used anti-androgens. Which patients should receive hormone therapy, when, what type and for how long have not been clearly defined.

In addition, as prolonged hormone therapy has significant morbidity associated with it, it can only be justified if long duration hormone therapy is clearly superior to short duration, in those patients in whom it is indicated, in terms of tumour control and survival.

PICO question

Population	Intervention	Comparison	Outcomes
Men with non-metastatic prostate cancer Subgroups by risk (low, intermediate, high & locally advanced)	Hormones + RT	• RT alone • Hormones alone	• Overall survival • Disease-free survival • Metastases free survival • Biochemical disease-free survival • Treatment-related morbidity • Cardiovascular events • Health-related quality of life

Results of the search



Of the 18 trials that were included, four compared radiotherapy alone to radiotherapy followed by hormone therapy (Bolla 2010, See (EPC trials 23, 24, 25), Efstathiou/Pilepich (RTOG 85-31), Zagars 1988), four compared radiotherapy alone to hormone therapy followed by radiotherapy (Roach 2008 [RTOG 8610], Denham 2011 [TROG 96.01], Laverdiere 2004 [L 101], Jones 2011), three compared radiotherapy alone to neoadjuvant, concomitant and adjuvant hormone therapy + radiotherapy (Granfors 2006, Laverdiere 2004 [L 101], D'Amico 2004) and three compared hormone therapy alone to hormone therapy + radiotherapy (Mottet 2010, Warde [PR07], Widmark 2009). One additional trial was included which compared hormone therapy alone, radiotherapy alone and combined hormone and radiotherapy treatment to each other (Fellows 1992). It is however unclear in which order the hormone and radiotherapy treatments were given in the combined treatment group in this trial.

The hormone therapy used in the studies consisted of goserelin acetate and flutamide (Denham 2011, Jones 2011, Roach 2008), goserelin acetate and cyproterone acetate (Bolla 2010), leuprolide acetate, goserelin acetate and flutamide (D'Amico 2004), goserelin acetate (Efstathiou/Pilepich [RTOG 85-31]), leuprorelin (Mottet 2010), leuprorelin and flutamide (Widmark 2009), biccalutamide (See [EPC trials 23, 24, 25]), a luteinizing hormone-releasing hormone agonist plus an antiandrogen agent (Laverdiere 2004), a luteinizing hormone-releasing hormone agonist or orchiectomy (Warde [PR07]), orchiectomy alone (Fellows 1992, Granfors 2006) and diethylstilbestrol (Zagars 1988)

Details of the study characteristics and risk of bias assessments for each included study are reported in the evidence tables at the end of this document. The tables below outline the results for the outcomes that were not meta-analysed (i.e., all the outcomes for the studies comparing hormone therapy alone to hormone therapy + radiotherapy, and the adverse events, cardiovascular events and health-related quality of life for the studies comparing radiotherapy alone to radiotherapy + hormone therapy). The figures below illustrate meta-analyses for overall survival,

disease-free survival, distant metastasis-free survival and biochemical-free survival for the studies comparing radiotherapy alone to radiotherapy + hormone therapy, with the exception of the data from Fellows (1992) which could not be extracted in such a way that it could be included in the relevant meta-analyses (overall survival and distant metastasis-free survival).

Evidence statements

Radiotherapy alone v radiotherapy + hormone therapy

Compared to treatment with radiotherapy alone, treatment with radiotherapy + hormone therapy is associated with longer overall survival (9 studies/5994 patients; HR = 1.3, 95% CI = 1.2-1.41; LOW QUALITY), longer disease-free survival (7 studies/3892 patients; HR = 1.49, 95% CI = 1.37-1.62; VERY LOW QUALITY), longer distant metastasis-free survival (5 studies/4332 patients; HR = 1.63, 95% CI = 1.43-1.85; VERY LOW QUALITY), comparable rates of adverse events (5 studies/4813 patients; not pooled; VERY LOW QUALITY), comparable rates of cardiovascular events (5 studies/3988 patients; not pooled; VERY LOW QUALITY), and lower health-related quality of life (1 study/1979 patients; VERY LOW QUALITY).

Radiotherapy alone v radiotherapy followed by hormone therapy

Compared to treatment with radiotherapy alone, treatment with radiotherapy followed by hormone therapy is associated with longer overall survival (4 studies/2725 patients; HR = 1.32, 95% CI = 1.17-1.47; LOW QUALITY), longer disease-free survival (4 studies/2808 patients; HR = 1.48, 95% CI = 1.33-1.64; LOW QUALITY), longer distant metastasis-free survival (2 studies/1360 patients; HR = 1.73, 95% CI = 1.46-2.06; VERY LOW QUALITY), and longer biochemical-free survival (1 study/5903 patients; HR = 1.62, 95% CI = 1.39-1.88; VERY LOW QUALITY).

Radiotherapy alone v hormone therapy followed by radiotherapy

Compared to treatment with radiotherapy alone, treatment with hormone therapy followed by radiotherapy is associated with longer overall survival (3 studies/2972 patients; HR = 1.25, 95% CI = 1.12-1.39; LOW QUALITY), longer disease-free survival (2 studies/993 patients; HR = 1.47, 95% CI = 1.28-1.68; VERY LOW QUALITY), longer distant metastasis-free survival (3 studies/2972 patients; HR = 1.49, 95% CI = 1.22-1.82; LOW QUALITY), and longer biochemical-free survival (4 studies/3109 patients; HR = 1.65, 95% CI = 1.48-1.83; LOW QUALITY).

Radiotherapy alone v neoadjuvant, concomitant and adjuvant hormone therapy + radiotherapy

Compared to treatment with radiotherapy alone, treatment with neoadjuvant, concomitant and adjuvant hormone therapy + radiotherapy is associated with longer overall survival (2 studies/297 patients; HR = 1.72, 95% CI = 1.25-2.39; VERY LOW QUALITY), longer disease-free survival (1 study/91 patients; HR = 2.51, 95% CI = 1.32-4.76; VERY LOW QUALITY), and longer biochemical-free survival (2 studies/338 patients; HR = 2.53, 95% CI = 1.75-3.67; VERY LOW QUALITY).

Hormone therapy alone v hormone therapy + radiotherapy

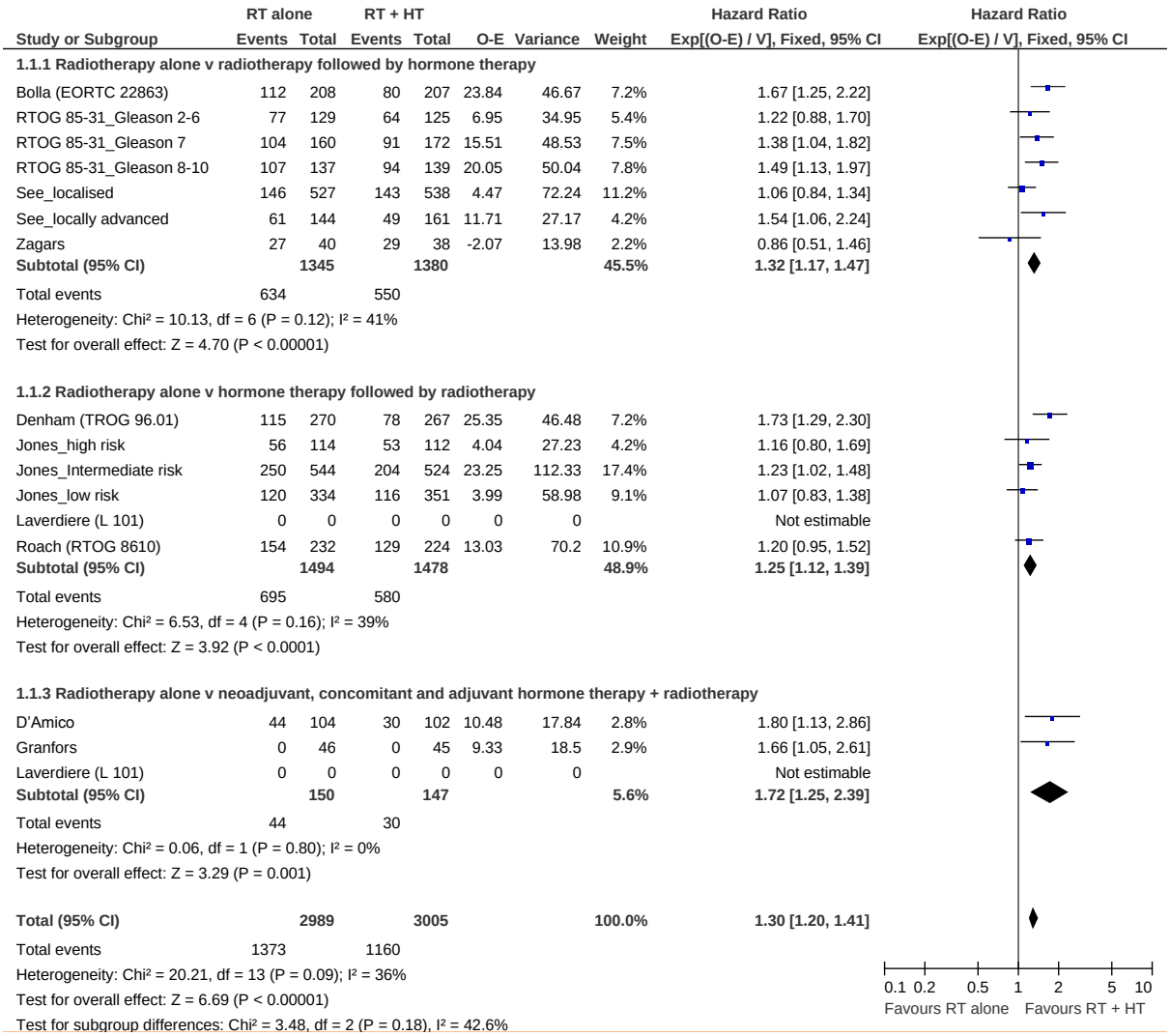
Compared to treatment with hormone therapy alone, treatment with hormone therapy + radiotherapy is associated with similar or longer overall survival (4 studies/2533 patients; not pooled; MODERATE QUALITY), longer disease-free survival (2 studies/1469 patients; not pooled; LOW QUALITY), similar distant metastasis-free survival (2 studies/452 patients, LOW QUALITY), longer biochemical-free survival (2 studies/1139 patients; not pooled; LOW QUALITY), comparable rates of adverse events (2 studies/2080 patients; not pooled; LOW QUALITY), comparable rates of cardiovascular events (1 study/263 patients; MODERATE QUALITY), and comparable health-related quality of life (2 studies/2080 patients; not pooled; LOW QUALITY).

Table 109 Radiotherapy alone v radiotherapy + hormone therapy

Outcome	Study/ies	Results
Radiotherapy alone vs radiotherapy followed by hormone therapy		
Overall survival	Bolla; RTOG 85-31; See; Zagars	Meta-analysis
Disease-free survival	Bolla; RTOG 85-31; See	Meta-analysis
Metastases-free survival	Bolla; RTOG 85-31; Zagars	Meta-analysis
Biochemical disease-free survival	See	Meta-analysis
Cardiovascular events	Bolla	Cardiovascular mortality: Group 1 – CVD at study entry: RT=11/63 vs RT/HT=8/53; HR 0.78 (95% CI 0.31-1.95); p=0.60 Group 2 – No CVD at study entry: RT=6/145 vs RT/HT=14/154; HR 1.75 (95% CI 0.67-4.56); p=0.25
	RTOG 85-31	Cardiovascular mortality at 9 years: RT=11.4% vs RT/HT=8.4%; HR 0.77 (95% CI 0.53-1.11); p=0.16
	See	Death from myocardial infarction: RT=23/664 vs RT/HT=18/694 Cerebrovascular accident: RT=9/664 vs RT/HT=11/694 Heart arrest: RT=5/664 vs RT/HT=6/694 Heart failure: RT=5/664 vs RT/HT=4/694
	TROG 96.01	Fatal cardiac events: RT=7.5% vs RT/HT=6.4% (p=0.65) (6-month neoadjuvant HT arm)
Adverse events	See	Diarrhea: RT=14% vs RT/HT=15.6%. Asthenia: RT= 9.8% vs RT/HT=13.5%. Impotence: RT=9.9% vs RT/HT=12.7%. Decreased libido: RT=1.4% vs RT/HT=4%. Hot flashes: RT=5.4% vs RT/HT=9.8.7%. Back pain: RT=13.9% vs RT/HT=12%. Pharyngitis: RT=11.1% vs RT/HT=11.4%. Rectal haemorrhage: RT=11.3% vs RT/HT=11.4%. Constipation: RT=9.2% vs RT/HT=11.1%. Rash: RT=8.9% vs RT/HT=10.8%. Haematuria: RT=12.7% vs RT/HT=9.5%. Arthralgia: RT=11.1% vs RT/HT=8.6%. Abnormal liver function: RT=1.8% vs RT/HT=2.2%. Withdrawal due to AE: RT=11% vs RT/HT=31.4%
Health-related quality of life	Not reported	
Radiotherapy alone vs hormone therapy followed by radiotherapy		
Overall survival	Denham; Jones; Roach	Meta-analysis
Disease-free survival	Denham; Roach	Meta-analysis
Metastases-free survival	Denham; Jones; Roach	Meta-analysis
Biochemical disease-free survival	Denham; Jones; Laverdiere; Roach	Meta-analysis
Cardiovascular events	Denham	Cardiac deaths at 10 years: RT=3 vs HT/RT=6
	Roach	Fatal cardiac event at 10 years: RT=9.1% vs HT/RT=12.5%; p=0.32

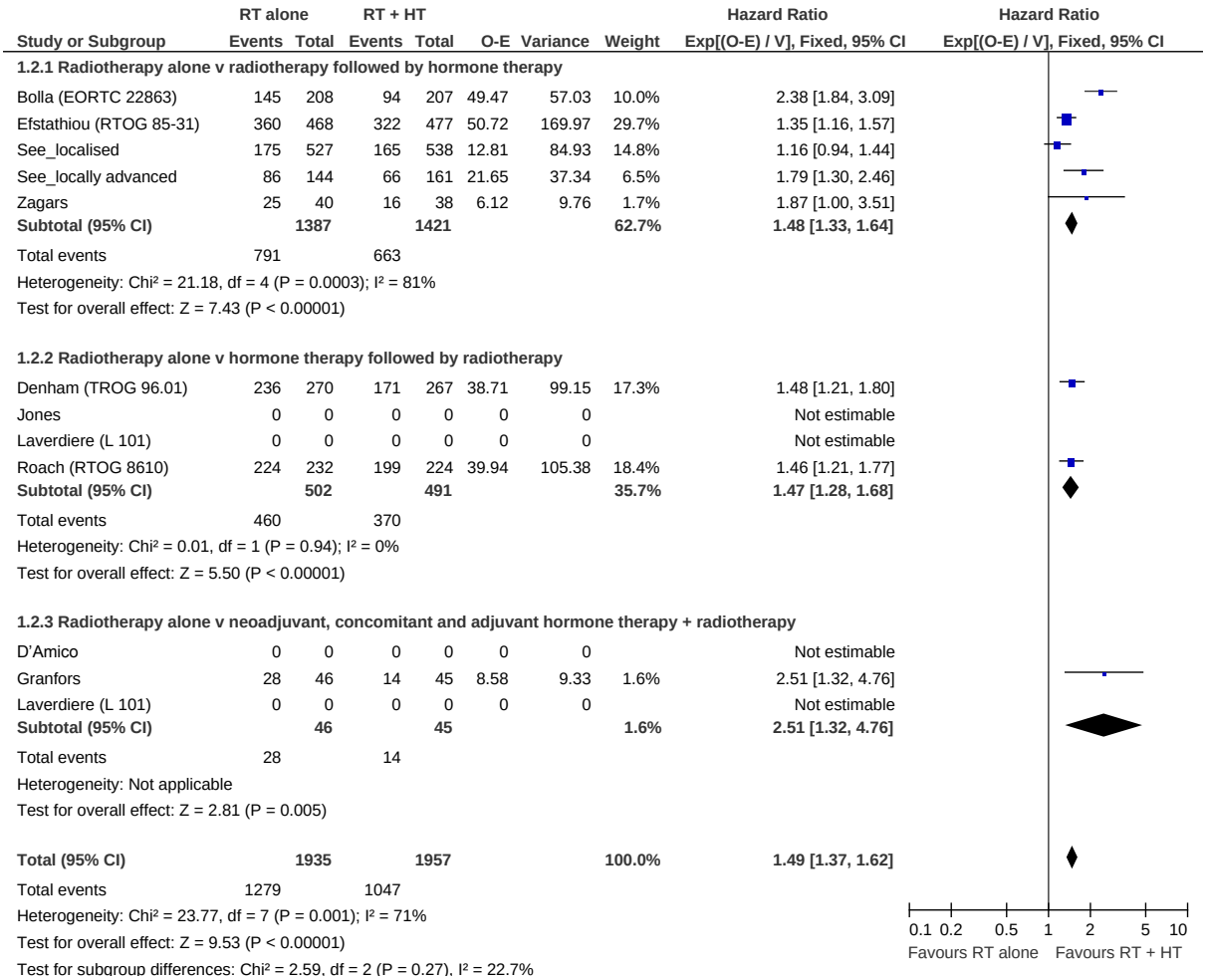
Adverse events	Denham	HT group: AE were temporary and confined to the period of androgen depletion. HT had no adverse effect on morbidity due to RT. N = 124 discontinued flutamide due to diarrhoea and abnormal liver function
	Jones	Acute hepatic toxic effects grade 3-4 up to 90 days after start of RT: HT/RT= 3-4%. Late hepatic toxic effects grade 3-4: RT=0% vs HT/RT>1%. Acute and late gastrointestinal toxic effects grade ≥3: RT=3% vs HT/RT=1%. Acute and late gastrointestinal toxic effects grade 5: RT=2 vs HT/RT=1. Acute genitourinary toxic effects grade ≥3: RT=2% vs HT/RT=2%. AE during HT (grade 1): Hot flashes (55%); Rash (3%); hepatic toxic effects (16%); decreased haemoglobin levels (16%); elevated white cell counts (4%); cardiac toxic effects within 2 years after treatment (1%)
	Roach	Grade 3 RT toxicity: ~4% in both groups Acute grade 3 toxicity: RT=4% vs HT/RT=2% Late grade 3 toxicity: 8% in both groups Late grade 4 toxicity: RT=3% vs HT/RT=1%
Health-related quality of life	Jones	Erectile function at 1 year (when sexually excited, are you able to get an erection?): Always/almost always: RT=85/274 vs HT/RT=59/284; Sometimes: RT=62/274 vs HT/RT=66/284; Almost never/never: RT=69/274 vs HT/RT=94/284; Did not try: RT=55/274 vs HT/RT=58/284; Not applicable/answered: RT=4/274 vs HT/RT=13/284.
Radiotherapy alone vs neoadjuvant, concomitant and adjuvant hormone therapy + radiotherapy		
Overall survival	D'Amico; Granfors	Meta-analysis
	Fellows	7-year: RT=67/88 vs HT/RT=64/99 (non-significant).
Disease-free survival	Granfors	Meta-analysis
Metastases-free survival	Fellows	7-year: RT=71/88 vs HT/RT=59/99 (significant), favouring HT/RT
Biochemical disease-free survival	D'Amico; Laverdiere	Meta-analysis
Cardiovascular events	Not reported	
Adverse events	D'Amico	Urinary incontinence (complete): N=1 in both groups. Urinary incontinence (stress)/anal fibrosis/gyneco-mastasia: N=0 in both groups. Haematuria: N=3 in both groups. Diarrhoea: RT=3 vs RT/HT=1. Rectal bleeding: RT=2 vs RT/HT=3. Impotence: RT=21 vs RT/HT=26. Liver dysfunction: RT=2 vsRT/HT=0.
	Fellows	See in entry below in the "Study outcomes and results" table for "HT alone v HT + RT"
Health-related quality of life	Not reported	

Figure 51 Overall survival



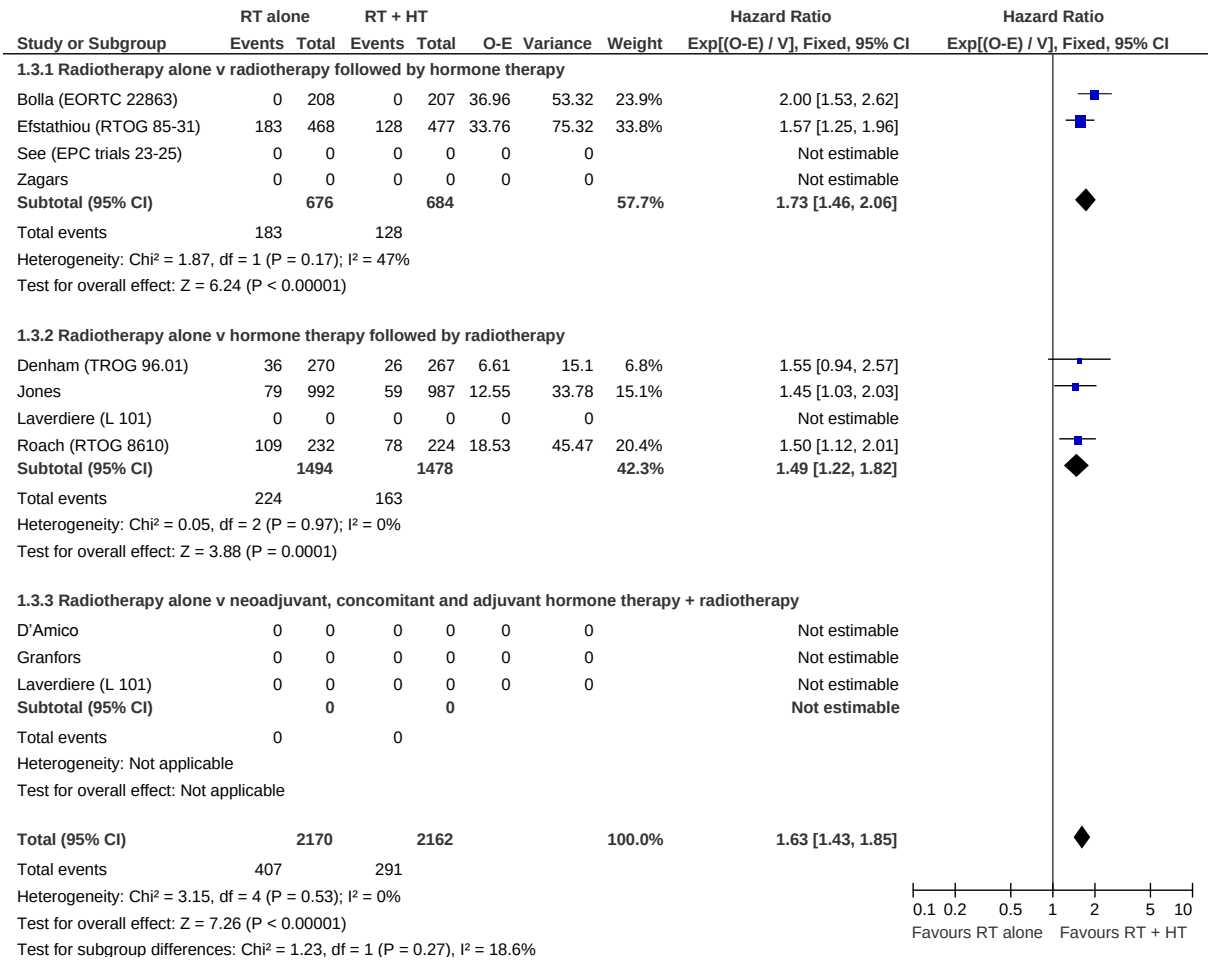
Please note "0" indicates "not reported". The events entered are number of deaths. For See, the hazard ratios used to calculate o-e appear to be adjusted for trial, randomized treatment, initial PSA level, tumour grade and stage, whereas for the rest of the studies, unadjusted estimates were used. The data entered for Denham are for RT alone versus 6 months HT + RT. Denham also compared RT alone to 3 months of HT + RT (10-year all cause mortality = 42.5% for RT alone and 36.7% for HT3 /RT; p = 0.2).

Figure 52 Disease-free survival



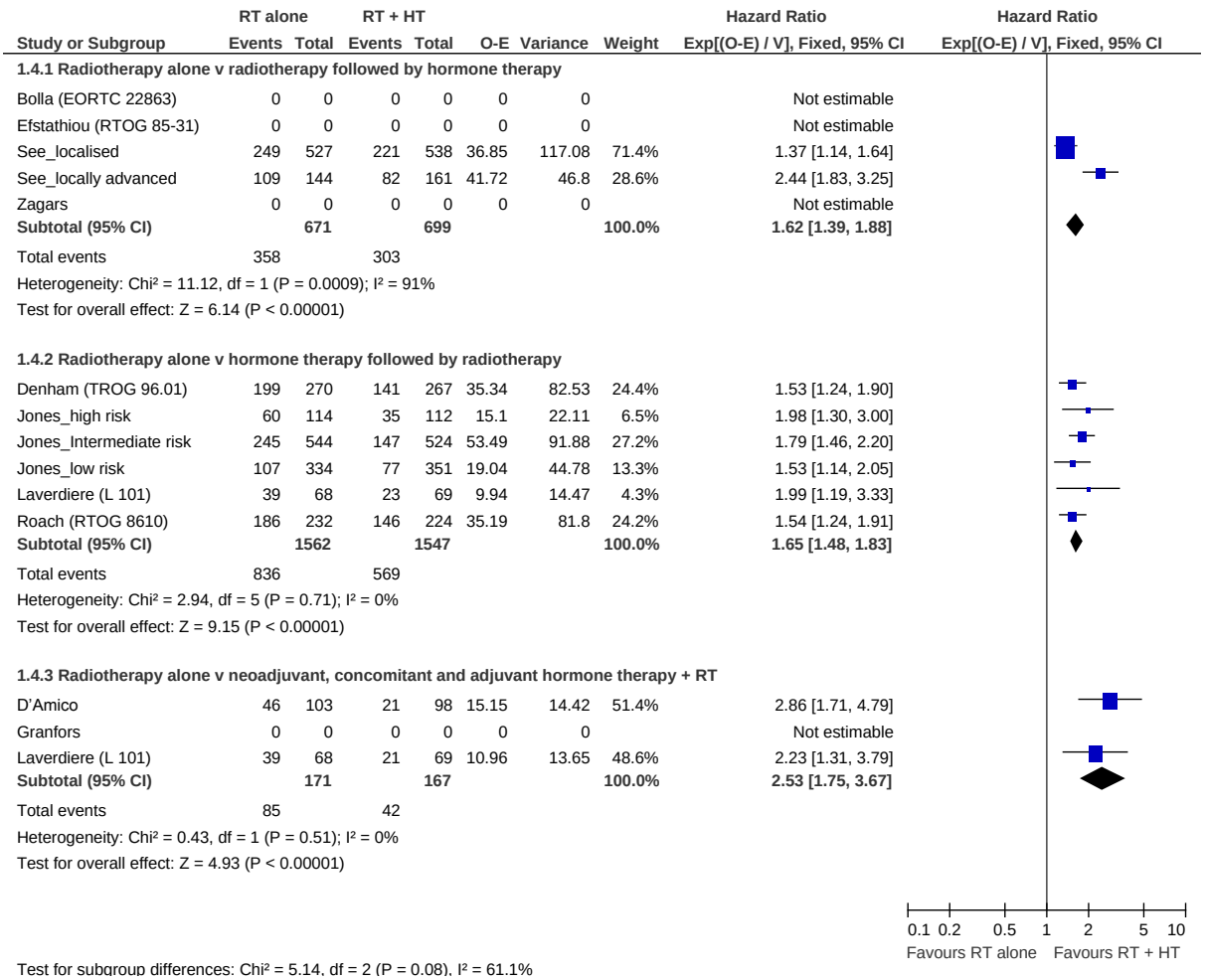
Please note: "0" indicates "not reported". The events entered are number of failures. For See, the hazard ratios used to calculate o-e appear to be adjusted for trial, randomized treatment, initial PSA level, tumour grade and stage, whereas for the rest of the studies, unadjusted estimates were used. The data entered for Denham are for RT alone versus 6 months HT + RT. Denham also compared RT alone to 3 months of HT + RT (10-year DFS = 12.7% for RT alone and 28.8% for HT3 /RT; p < 0.0001). Heterogeneity is high overall and in the radiotherapy alone v radiotherapy followed by hormone therapy subgroup; this may be due to combining data from different risk groups.

Figure 53 Distant metastasis-free survival



Please note "0" indicates "not reported". The events entered are number of failures. The data entered for Denham are for RT alone versus 6 months HT + RT. Denham also compared RT alone to 3 months of HT + RT (10-year distant progression = 13.5% for RT alone and 14.5% for HT3 /RT; p = 0.82).

Figure 54 Biochemical-free survival



Please note "0" indicates "not reported". The events entered are number of failures. For See, the hazard ratios used to calculate o-e appear to be adjusted for trial, randomized treatment, initial PSA level, tumour grade and stage, whereas for the rest of the studies, unadjusted estimates were used. The data entered for Denham are for RT alone versus 6 months HT + RT. Denham also compared RT alone to 3 months of HT + RT (10-year PSA progression = 73.8% for RT alone and 60.4% for HT3 /RT; p = 0.0009). The data from D'Amico is based on N = 103 and 98 instead of N = 104 and 102, for the RT and RTR/HT groups, respectively. No overall estimate is provided because the same data from the RT alone group in the study by Laverdiere are used in two subgroups. Heterogeneity is high in the radiotherapy alone v radiotherapy followed by hormone therapy subgroup; this may be due to combining data from different risk groups.

Additional analyses based on study-reported risk groups:

Efstathiou/Pilepich (RTOG 85-31): Disease-free survival restricted to patients with PSA < 1.5ng/ml: RT (385/431) < RT/HT (314/440), p < 0.0001 (favouring RT/HT).

Bolla: Overall survival analysis restricted to T3-4 patients (90% of the whole sample): HR = 0.56 (95% CI 0.41-0.75, p = 0.0001), favouring RT/HT (10-year OS rates = 58.8%) over RT (10-year OS rates = 37.7%).

Table 110Hormone therapy alone v hormone therapy + radiotherapy

Outcome	Study	Results
Overall survival	Fellows	7-year: HT=58/90 vs HT/RT=64/99 (non-significant).
	Mottet	5-year: HT=71.5% vs HT/RT=71.4%
	PR07	8-years: HT=260/602 vs HT/RT=205/603; HR 0.70 (95% CI 0.57-0.85, p = 0.0003) favouring HT/RT
	SPCG-7/SFUO-3	7-years: Absolute risk difference = 3.6% (95% CI -1.7 to 8.8%; non-significant) favouring HT/RT 10-years: Absolute risk difference = 9.8% (95% CI 0.8-1 8.8%; significant) favouring HT/RT Relative risk of overall death: 0.68 (95% CI 0.52-0.89; p = 0.004) favouring HT/RT
Disease-free survival or distant metastases-free survival	Mottet	Disease-free survival - median (days): HT=641 vs RT/HT=2804 (p = 0.0001) 5-year: HT=8.5% vs HT/RT=61%
	PR07	Progressive disease: HT=251 vs HT/RT=95. Median time to progression: HT=6.8 years (inter-quartile range 3.4–not reached) vs HT/RT=Not reached (inter-quartile range 8.2–not reached); HR 0.30, 95% CI 0.23–0.39; p = 0·0001) favouring HT/RT.
Metastases-free survival	Fellows	Distant metastasis-free survival , 7-year: HT=55/90 vs HT/RT=59/99 (non-significant).
	Mottet	Metastases at median 67 months follow-up: HT=10.8% vs HT/RT=3.0% (p=0.018)
Biochemical disease-free survival	Mottet	PSA progression at median 5.6-year follow-up: (ASTRO criteria) HT=78.5% vs HT/RT=17.3%. (ASTRO-Phoenix) HT=68.5% vs HT/RT=14.3% 5-year progression-free survival: significantly lower for HT/RT
	SPCG-7/SFUO-3	7-year cumulative incidence: HT=71.1% (95% CI 66.3-75.9%) vs HT/RT=17.6% (95% CI 13.6-21.5%). 10-year cumulative incidence: HT=74.7% (95% CI 69.6-79.8%) vs HT/RT=25.9% (95% CI 19.3-32.6%). Relative risk of PSA recurrence: 0.16 (95% CI 0.12-0.2; p < 0.0001) favouring HT/RT
Cardiovascular events	Mottet	Median of 67 months follow-up: HT=10 vs HT/RT=17
Adverse events	Fellows	HT-related AE: Hot flushes (N=28), rectal bleeding, frequency and urgency of micturition (all N=1). RT-related AE: Bowel symptoms (N=35), urinary symptoms other than transient frequency (N=15), both (N=2), severe rectal bleeding (N=4). N=2 who died had radiation proctitis.
	Mottet	*At median of 67 months follow-up:* Genitourinary (GU) & gastrointestinal (GI) toxicities (notably diarrhoea, pollakiuria & dysuria) were more common with HT+RT than HT (250 vs 30) Of patients receiving RT: grade 2-3 GI toxicity = 25%; grade 2-4 GU toxcicity = 13%; grade 2-3 dermatologic toxicity = 6%
	PR07	Severe (> grade 3) late side-effects: Diarrhoea: HT=4 vs HT/RT=8. Rectal bleeding: HT=3 vs HT/RT=2. Genitourinary: HT=14 vs HT/RT=14. Grade>2 proctitis: HT=0.3% vs HT/RT=1.0%
	SPCG-7/SFUO-3	*At 5 years:* Bladder obstruction/sclerosis, urinary frequency per day > 10, intestinal symptoms (moderate/severe), sexual activity: HT=HT/RT Urethral stricture, urgency, urinary incontinence, erection problems: HT < HT/RT *(though none are significant if Bonferroni*

		correction applied to alpha level) Serious adverse events: HT=11 vs HT/RT=7
Health-related quality of life	PR07	Overall, 6 months: HT>RT/HT. Overall, 36 months: HT=RT/HT. Physical functioning, 6 and 36 months: HT=RT/HT. Urinary functioning, 6 months: HT<RT/HT. Urinary functioning, 36 months: HT=RT/HT. Bowel or rectal, 6 and 36 months: HT = RT/HT. Diarrhoea, 6 months: HT<RT/HT. Diarrhoea, 36 months: HT=RT/HT. *Bonferroni-correction has been applied for multiple comparisons*
	SPCG-7/SFUO-3	*At 4 years:* Physical/role/emotional/cognitive function, global health/QoL, fatigue, nausea/vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, financial difficulties: HT = HT/RT Social function, diarrhoea: HT/RT worse *(though none are significant if Bonferroni correction applied)*
Analyses by risk group	SPCG-7/SFUO-3	*Subgroup analyses conducted on absolute risk reduction (95% CI) in 10-year cumulative incidence of prostate-cancer specific mortality:* T1b-T2: 16% (3.7-28.2) (favouring HT/RT) T3: 10.6% (2.1-19) (favouring HT/RT) PSA < 20 ng/ml: 7.22% (-1.8 – 16.2) (non-significant) PSA > 20 ng/ml: 17.3% (6-28.5) (favouring HT/RT) Age < 67 years: 9.8% (-1.1 – 20.7) (non-significant) Age > 67 years: 12.9% (3.4-22.5) (favouring HT/RT)

Evidence tables:

Study: Bolla (EORTC 22863)

Methods	Study design: RCT (multicentre phase 3) Country: International Study period: 1987-1995 Inclusion criteria: Aged < 80 years, WHO performance status 0-2, newly diagnosed histologically proven T1-2 prostatic adenocarcinoma with WHO histological grade 3, or T3-4 prostatic adenocarcinoma of any histological grade. Exclusion criteria: History of malignant disease apart from adequately treated basal-cell carcinoma of the skin, or evidence of distant metastases, incl involvement of common iliac or para-aortic lymph nodes. Length of follow up (median and inter-quartile range): 9.1 (5.1-12.6) years.
Participants	No. in trial arm: RT: N = 208; RT/HT: N = 207 Age (median, inter-quartile range): RT: 70 (65-75) years; RT/HT: 71 (67-75) years. WHO performance status: RT: 0 (N = 164), 1 (N = 38), 2 (N = 4), not documented (N = 2); RT/HT: 0 (N = 162), 1 (N = 37), 2 (N = 7), not documented (N = 1). WHO histopathological grade: RT: G1 (N = 39), G2 (N = 96), G3 (N = 68), not documented (N = 5); RT/HT: G1 (N = 44), G2 (N = 98), G3 (N = 63), not documented (N = 2). Gleason total score: RT: 2-4 (N = 16), 5-6 (N = 40), 7-10 (N = 71), not documented (N = 81); RT/HT: 2-4 (N = 11), 5-6 (N = 50), 7-10 (N = 66), not documented (N = 80). Clinical T classification: RT: T1 (N = 2), T2 (N = 20), T3 (N = 167), T4 (N = 18), not documented (N = 1); RT/HT: T1 (N = 2), T2 (N = 18), T3 (N = 167), T4 (N = 20), not documented (N = 0). N classification: RT: N0 (N = 183), N1 (N = 5), N2 (N = 1), N4 (N = 1), NX (N = 18); RT/HT: N0 (N = 184), N1 (N = 4), N2 (N = 5), N4 (N = 0), NX (N = 14). T according to grade (stratification): RT: T1-2 G3 (N = 20), T3-4 any G (N = 188); RT/HT: T1-2 G3 (N = 20), T3-4 any G (N = 187). Baseline PSA concentration: RT: < 4 µg/L (N = 10), 4 to < 10 µg/L (N = 23), 10 to < 20 µg/L (N = 36), 20 to < 40 µg/L (N = 49), > 40 µg/L (N = 67), not documented (N = 23); RT/HT: < 4 µg/L (N = 16), 4 to < 10 µg/L (N = 24), 10 to < 20 µg/L (N = 29), 20 to < 40 µg/L (N = 47), > 40 µg/L (N = 72), not documented (N = 19). Chronic disease: RT: None (N = 100), cardiovascular (N = 63), other (N = 42), not documented (N = 3); RT/HT: None (N = 111), cardiovascular (N = 53), other (N = 43), not documented (N = 0).
Interventions	Radiotherapy alone (RT) v radiotherapy + immediate androgen sup-

	pression (RT/HT) Radiotherapy (both groups): Patients were treated once a day/5 days a week/ 7 weeks and consisted of planning target vol 1 (the whole pelvis irradiated up to 50 Gy) and planning target volume 2 (the prostate and the seminal vesicles irradiated with an additional 20 Gy). Hormone therapy: 3.6 mg goserelin acetate administered subcutaneously every 4 weeks starting the first day of pelvic RT and continued for 3 years. Cyproterone acetate administered orally for 1 month, 50 mg three times a day starting a week before goserelin.
Outcomes	Clinical disease-free survival, overall survival, distant metastasis-free survival, cause-specific mortality and locoregional control. QoL was not obtained in this study.
Notes	The groups appear to be comparable at baseline. RT: 203/208 started treatment and 200/203 completed treatment; RT/HT: 198/207 started RT/HT treatment, 201/207 completed RT treatment, 150/198 completed HT treatment. ITT analyses undertaken.

Study: Bolla (EORTC 22863)

Bias/Quality item	Authors' judgement (Low/Unclear/ High risk of bias)	Support for judgement
Random sequence generation (selection bias)	Low	Central randomization. Randomisation used the minimisation technique with institution, clinical stage (T1-2 WHO grade 3 v T3-4 WHO grade 1-3), results of pelvic-lymph-node dissection (N0 v N1), and irradiation fields extension (extended v limited fields) as minimisation factors.
Allocation concealment (selection bias)	Low	
Blinding of outcome assessment (detection bias): Objective outcomes	Unclear	No information reported apart from "Cause of death was prospectively documented by the treating physician and was not subjected to central independent review".
Blinding of outcome assessment (detection bias): Subjective outcomes	Unclear	
Incomplete outcome data (attrition bias)	Low	The data from all the randomized patients have been analysed for all reported outcomes.
Selective reporting (reporting bias)	Unclear	No adverse events reported

Study: D'Amico

Methods	Study design: RCT (multicentre) Country: USA Study period: 1995-2001 Inclusion criteria: T1b-T2b, Nx, M0 centrally reviewed adenocarcinoma of the prostate, PSA 10-40 ng/ml or Gleason score ≥ 7, ECOG performance status 0-1, white blood cell count ≥ 3000/µl, hemacrit > 30%, platelet count > 100 X 10^3/µl, life expectancy ≥ 10 years (excl death from prostate cancer) at study entry, negative bone scan and pelvic lymph node assessment using MRI or CT within 6 months of randomisation. Low risk patients with radiographic evidence using endorectal coil MRI of extracapsular extension or seminal vesicle invasion. Exclusion criteria: History of malignant disease apart from non-melanoma skin cancer, any history of hormone therapy. Length of follow up (median): 8.2 (inter-quartile range 7-9.5) years (PSA recurrence), 7.6 (range 0.5-11) years (overall survival).
Participants	No. in trial arm: RT: N = 104; RT/HT: N = 102 Age (median, range): RT: 73 (51-81) years; RT/HT: 72 (49-82) years. ECOG performance status: RT: 0 (N = 101), 1 (N = 3); RT/HT: 0 (N = 95), 1 (N = 7). Baseline PSA level (median, range; ng/ml): RT: 11 (0.9-40); RT/HT: 11 (1.3-36). Gleason total score: RT: 5 or 6 (N = 27), 3+4 (N = 37), 4+3 (N = 24), 8-10 (N = 16); RT/HT: 5 or 6 (N = 30), 3+4 (N = 35), 4+3 (N = 23), 8-10 (N = 14). Clinical T classification: RT: T1b (N = 3), T1c (N = 41), T2a (N = 26), T2b (N = 34); RT/HT: T1b (N = 1), T1c (N = 54), T2a (N = 20), T2b (N = 27). Treatment stratification: RT: PSA of 20-40 ng/mL (N = 13), Gleason score ≥ 7 (N = 64), PSA of 20-40 ng/mL and Gleason score ≤ 6 (N = 24), Low risk and endorectal MRI category T3 (N = 3); RT/HT: PSA of 20-40 ng/mL (N = 12), Gleason score ≥ 7 (N = 64), PSA of 20-40 ng/mL and Gleason score ≤ 6 (N = 24), Low risk and endorectal MRI category T3 (N = 2).
Interventions	Radiotherapy alone (RT) v radiotherapy + androgen suppression therapy given neoadjuvantly (2 months), concurrently (2 months) and adjuvantly (2 months) (RT/HT) Radiotherapy: Patients were treated once a day/5 days a week at a daily dose of 1.8 Gy for the initial 25 treatments and 2 Gy for the final 11 treatments totaling 70.35 Gy to the prostate (and seminal vesicles?) plus a 1.5 cm margin using a 4-field 3D-CRT technique. Hormone therapy: Leuprolide acetate (N = 88) was delivered intramuscularly each months at a dose of 7.5 mg or 22.5 mg every 3 months.

	3.6 mg goserelin (N = 10) was administered subcutaneously each month (or 10.8 mg every 3 months). Flutamide (N = 98) every 8 hours at a dose of 250 mg starting 1-3 days before leuprolide acetate/goserelin. Flutamide was discontinued if if either aspartate aminotransferase or alanine aminotransferase exceeded 2 times the upper limit of normal or the patient developed drug-induced diarrhea or anemia causing clinical symptoms. The treating physician assessed potency at randomisation.
Outcomes	PSA recurrence, overall survival, cause-specific mortality, adverse events.
Notes	The groups appear to be comparable at baseline, although not sure if the T stage is slightly higher in the RT patients compared to the RT/HT patients. Information on treatment adherence available for 103/104 RT patients and 98/102 RT/HT patients. RT: All patients had RT per protocol. All RT/HT patients completed 6 months of leuprolide/goserelin, but 27/98 did not complete 6 months of flutamide treatment due to adverse events. ITT analyses undertaken.

Study: D'Amico

Bias/Quality item	Authors' judgement (Low/Unclear/ High risk of bias)	Support for judgement
Random sequence generation (selection bias)	Low	Central randomization with stratification for baseline PSA level and Gleason score. A permuted blocks randomisation algorithm was used with a block size of 4.
Allocation concealment (selection bias)	Low	
Blinding of outcome assessment (detection bias): Objective outcomes	Unclear	No information reported.
Blinding of outcome assessment (detection bias): Subjective outcomes	Unclear	No information reported.
Incomplete outcome data (attrition bias)	Low	The data from all the randomized patients have been analysed for all reported outcomes apart from adverse events where data from 103/104 RT patients and from 98/102 RT/HT patients included.
Selective reporting (reporting bias)	Unclear	Distant metastasis-free survival and loco-regional control not reported

Study: Denham (TROG 96.01)

Methods	Study design: RCT (multicentre) Country: Australia and New Zealand Study period: 1996-2000 Inclusion criteria: Men with T2b-T4 prostatic adenocarcinoma. Exclusion criteria: Significant intercurrent medical conditions, prior malignancies or metastases. Length of follow up (median and range): 10.6 (0.1-13.9) years.
Participants	No. in trial arm: RT: N = 270; HT3/RT: N = 265; HT6/RT: N = 267 Age (median, range): RT: 67 (51-80) years; HT3/RT: 68 (47-80) years; HT6/RT: 68 (41-87) years. PSA (µg/L; median, range): RT: 16.4 (0.6-165); HT3/RT: 14.4 (0.5-154.2); HT6/RT: 14.5 (1.1-203.9). Stage: RT: T2b (N = 72), T2c (N = 92), T3-4 (N = 106); HT3/RT: T2b (N = 67), T2c (N = 87), T3-4 (N = 111); HT6/RT: T2b (N = 68), T2c (N = 94), T3-4 (N = 105). Gleason score: RT: 2-6 (N = 114), 7 (N = 115), 8-10 (N = 41); HT3/RT: 2-6 (N = 118), 7 (N = 94), 8-10 (N = 53); HT6/RT: 2-6 (N = 123), 7 (N = 101), 8-10 (N = 43). Risk group: RT: Intermediate (= all not “high risk”) (N = 48), High (= PSA > 20, or Gleason > 7, or T2c-T4) (N = 222); HT3/RT: Intermediate (N = 39), High (N = 226); HT6/RT: Intermediate (N = 43), High (N = 224).
Interventions	Radiotherapy alone (RT) v hormone therapy for 3 months followed by radiotherapy (HT3/RT) v hormone therapy for 6 months followed by radiotherapy (HT6/RT) Radiotherapy: 2 Gy a day/5 days a week/6.5-7 weeks to a dose of 66 Gy to the prostate and the seminal vesicles. Hormone therapy: 3.6 mg goserelin acetate administered subcutaneously every month and 250 mg flutamide given orally 3 times a day. Hormone therapy started 2 months before radiation nin group HT3/RT and 5 months before radiation in group HT6/RT.
Outcomes	Overall survival, distant progression, prostate cancer-specific mortality, secondary therapeutic intervention, event-free survival, local progression.
Notes	The groups appear to be comparable at baseline. RT: 268/276 received RT; HT3/RT: 264/270 received HT3; HT6/RT: 266/272 received HT6. Paper states that ITT analyses undertaken.

Study: Denham (TROG 96.01)

Bias/Quality item	Authors' judgement (Low/Unclear/ High risk of bias)	Support for judgement
Random sequence generation (selection bias)	Low	"Patients were randomised by the minimisation technique at the TROG Central Trials Office in Newcastle".
Allocation concealment (selection bias)	Low	
Blinding of outcome assessment (detection bias): Objective outcomes	Unclear	No information reported.
Blinding of outcome assessment (detection bias): Subjective outcomes	Unclear	No information reported.
Incomplete outcome data (attrition bias)	Low	RT: 270/276 analysed; HT3/RT: 265/270 analysed; HT6/RT: 267/272 analysed.
Selective reporting (reporting bias)	Unclear	No adverse events reported

Study: Efstathiou/Pilepich (RTOG 85-31)

Methods	Study design: RCT (multicentre phase 3) Country: USA Study period: 1987-1992 Inclusion criteria: Histologically confirmed adenocarcinoma of the prostate with either grossly palpable tumour beyond the confines of the prostate (clinical stage T3) or documented involvement of the regional lymphatics. Patients with primary tumour confined to the prostate (clinical stage T1-2) were eligible if there was evidence of spread to the regional lymph nodes either radiographically or histologically. Bulky primary lesions (product of palpable tumour dimensions ≥ 25 cm) were not eligible for this study, but were for a parallel study (RTOG 86-10). Exceptions were those with evidence of spread to lymphatics outside the pelvis (common iliac and/or paraaortic) who were eligible regardless of the size of the primary tumour. Patients who had undergone radical prostatectomy were eligible if penetration through the prostatic capsule to the resection margin and/or to the seminal vesicles was histologically documented. The Karnofsky performance status had to be >60%. Exclusion criteria: None listed beyond those above.

	Length of follow up: 13-18 years.
Participants	No. in trial arm: RT: N = 468; RT/HT: N = 477 Age: RT: < 70 years (N = 223), ≥ 70 years (N = 245); RT/HT: < 70 years (N = 230), ≥ 70 years (N = 247). Gleason score (central): RT: 2-6 (N = 129), 7 (N = 160), 8-10 (N = 137), missing (N = 42); RT/HT: 2-6 (N = 125), 7 (N = 172), 8-10 (N = 139), missing (N = 41). Clinical stage: RT: A/B (N = 127), C (N = 341); RT/HT: A/B (N = 141), C (N = 336). Nodal involvement: RT: No (N = 345), Yes (N = 123); RT/HT: No (N = 337), Yes (N = 140). Prostatectomy: RT: No (N = 400), Yes (N = 68); RT/HT: No (N = 406), Yes (N = 71). Acid phosphatase: RT: Not elevated (N = 316), Elevated (N = 152); RT/HT: Not elevated (N = 318), Elevated (N = 159). Prevalent cardiovascular disease: RT: No (N = 345), Yes (N = 120), Unknown (N = 3); RT/HT: No (N = 342), Yes (N = 133), Unknown (N = 2).
Interventions	Radiotherapy alone with hormone therapy only at recurrence (RT) v radiotherapy followed by hormone therapy (RT/HT) Radiotherapy (both groups): Patients were treated with 1.8-2 Gy a day/4-5 days a week. The initial target volume (prostate plus draining lymph nodes) received a total dose of 44-46 Gy. The prostatic target volume was to receive a boost dose of 20-25 Gy, bringing the prescribed dose to 65-70 Gy. Among the patients who had received radical prostatectomy, the prostatic bed was to receive 60-65 Gy and irradiation of the regional lymphatics was not required if there was no histopathologic evidence of lymph node involvement. In all cases a boost target volume was designed to include the prostate with margins sufficiently wide to encompass all tumour extensions into surrounding tissues. Hormone therapy group RT/HT: 3.6 mg goserelin acetate administered subcutaneously in the anterior abdominal wall monthly starting during the last week of RT and continued indefinitely or until sign of disease progression. Hormone therapy group RT: Same as group RT/HT with the exception that treatment was initiated at recurrence.
Outcomes	Overall survival, prostate cancer specific survival, cardiovascular mortality distant metastasis-free survival, disease-free survival and locoregional control.
Notes	The groups appear to be comparable at baseline. ITT analyses appear to have been undertaken.

Study: Efstathiou (RTOG 85-31)

Bias/Quality item	Authors' judgement (Low/Unclear/ High risk of bias)	Support for judgement
Random sequence generation (selection bias)	Low	"The randomization scheme described by Zelen [reference] was used to achieve balance in treatment assignment among institutions suing the 4 [histologic differentiation, nodal status/involvement, acid phosphatase status, prior radical prostatectomy] stratification variables". Probably ok.
Allocation concealment (selection bias)	Unclear	"Patients were entered in the study by a telephone call to RTOG headquarters within the first week of RT". No further information reported.
Blinding of outcome assessment (detection bias): Objective outcomes	Unclear	No information reported.
Blinding of outcome assessment (detection bias): Subjective outcomes	Unclear	No information reported.
Incomplete outcome data (attrition bias)	Low	The data from all eligible patients are included.
Selective reporting (reporting bias)	Unclear	Adverse events not reported.

Study: Fellows

Methods	Study design: RCT Country: Britain Study period: 1980-1985 Inclusion criteria: Patients with histologically proven prostate cancer, no prior treatment with hormones or radiotherapy, no evidence of metastases on chest x-ray or isotope bone scan. Exclusion criteria: Patients with serum acid phosphatise > upper limit of normal for the local laboratory. Length of follow up (range of medians for the treatment groups): 4-5.2 years.

Participants	No. in trial arm: RT: N = 88; HT: N = 90; HT/RT: N = 99. Age (years): RT: < 65 (N = 15), 65-94 (N = 54), 75+ (N = 19); HT: < 65 (N = 18), 65-94 (N = 53), 75+ (N = 19); HT/RT: < 65 (N = 20), 65-94 (N = 50), 75+ (N = 29). T category: RT: T2 (N = 39), T3 (N = 35), T4 (N = 7), not known (N = 7); HT: T2 (N = 35), T3 (N = 36), T4 (N = 13), not known (N = 6); HT/RT: T2 (N = 45), T3 (N = 37), T4 (N = 8), unknown (N = 9). Gleason score: RT: 4-6 (N = 24), 7 (N = 19), 8-10 (N = 29), not known (N = 16); HT: 4-6 (N = 20), 7 (N = 30), 8-10 (N = 25), not known (N = 15); HT/RT: 4-6 (N = 24), 7 (N = 26), 8-10 (N = 40), unknown (N = 9). Performance status: RT: Fully active (N = 71), Restricted activity (N = 11), not known (N = 6); HT: Fully active (N = 70), Restricted activity (N = 11), not known (N = 9); HT/RT: Fully active (N = 74), Restricted activity (N = 15), not known (N = 10).
Interventions	Radiotherapy alone (RT) v hormone therapy alone (HT) v hormone-therapy + radiotherapy (***order of treatments not reported***; HT/RT) Radiotherapy: Radical course of treatment to the proastate glad (the actual technique was left to the discretion of the individual radiotherapist) Hormone therapy: Orchiectomy (total or subcapsular according to local preference).
Outcomes	Overall survival, distant metastases, adverse events.
Notes	The groups appear to be comparable at baseline. Unclear if ITT analyses undertaken.

Study: Fellows

Bias/Quality item	Authors' judgement (Low/Unclear/ High risk of bias)	Support for judgement
Random sequence generation (selection bias)	Unclear	No information reported.
Allocation concealment (selection bias)	Low	Central randomisation by telephoning the ICFR/MRC clinical trials unit.
Blinding of outcome assessment (detection bias): Objective outcomes	Unclear	No information reported.
Blinding of outcome assessment (detection bias): Subjective outcomes	Unclear	Outcome not reported.
Incomplete outcome data (at-	Low	Data from all eligible patients appear to

trition bias)		have been included in the analyses.
Selective reporting (reporting bias)	Low	The main outcomes reported for the time of the trial.

Study: Granfors

Methods	Study design: RCT Country: Sweden Study period: 1986-1991 Inclusion criteria: Patients aged < 76 years with newly cytologically or histologically diagnosed prostate cancer, negative bone scans and no clinical signs of metastases. Cases primarily represented locally advanced disease. Exclusion criteria: Patients with early stage, well or moderately well differentiated lymph node negative tumours, those with other malignancies and those unable to cooperate because of mental disorders. Length of follow up (mean, range): 9.3 years (6-11.4; time to progression), 14-19 years (overall survival).
Participants	No. in trial arm: RT: N = 46; HT/RT: N = 45. Age (mean, SD, range) at start of RT: Overall: 68.8 (5, 49.2-75.3) years. Stage: RT: T1N0 (N = 0), T2N0 (N = 21), T3N0 (N = 5), T4N0 (N = 1), T1N+ (N = 2), T2N+ (N = 11), T3N+ (N = 6), T4N+ (N = 0); HT/RT: T1N0 (N = 2), T2N0 (N = 14), T3N0 (N = 9), T4N0 (N = 0), T1N+ (N = 2), T2N+ (N = 13), T3N+ (N = 4), T4N+ (N = 1). Histopathological grade: RT: G1N0 (N = 2), G2N0 (N = 19), G3N0 (N = 6), G1N+ (N = 4), G2N+ (N = 12), G3N+ (N = 3); HT/RT: G1N0 (N = 2), G2N0 (N = 20), G3N0 (N = 3), G1N+ (N = 3), G2N+ (N = 13), G3N+ (N = 4).
Interventions	Radiotherapy alone (RT) v hormone-therapy followed by radiotherapy (HT/RT) Radiotherapy: 2 Gy/ 5 times a week/6-7 weeks. The irradiation field was bordered by the promontory upward and the bony pelvis in other directions, thus, including the lymph nodes of the minor pelvis. The irradiation dose was 50 Gy to this large field, followed by a boost to the prostate for a total mean dose of 64.9 Gy (range 59.4 to 69.0) in the HT/ RT group and 65.2 Gy (range 60.7 to 69.3) in the RT group. Radiotherapy was started 4-5 weeks after orchiectomy in the HT/RT group. Hormone therapy: Orchiectomy. At progression patients in the RT group were treated with orchiectomy or gonadotropin releasing hormone analogues in N = 4.
Outcomes	Overall survival, time to progression.

Notes	The groups were comparable at baseline in terms of T and N stage and histological grade. ITT analyses undertaken.

Study: Granfors

Bias/Quality item	Authors' judgement (Low/Unclear/ High risk of bias)	Support for judgement
Random sequence generation (selection bias)	Unclear	Random assignment with stratification for T and N stage. No further information reported.
Allocation concealment (selection bias)	Unclear	No information reported
Blinding of outcome assessment (detection bias): Objective outcomes	Unclear	No information reported.
Blinding of outcome assessment (detection bias): Subjective outcomes	Unclear	Outcome not reported
Incomplete outcome data (attrition bias)	Low	Data from all eligible patients appear to have been included in the analyses.
Selective reporting (reporting bias)	Unclear	Adverse events not reported.

Study: Jones

Methods	Study design: RCT (multicentre phase 3) Country: USA and Canada Study period: 1994-2001 Inclusion criteria: Histologically confirmed prostate adenocarcinoma, stage T1b-T2b and a PSA level ≤ 20 ng/ml, Karnofsky performance status ≥ 70, alanine aminotransferase level ≤ twice the upper limit of the normal range, no evidence of regional lymph-node involvement or distant metastases, no previous chemotherpy/radiotherapy/hormonal therapy/cryosurgery/ definitive surgery for prostate cancer. Patients with previous basal cell or squamous-cell skin carcinomas who had been disease-free for ≥ 2 years before study entry, and patients with invasive cancers who had been disease-free ≥ 5 years, were eligible

	if their participation was approved by the study cochairs Exclusion criteria: None listed Length of follow up (median, range): RT: 9.2 (0.-14.1) years; HT/RT: 9.1 (0.01-13.5) years.
Participants	No. in trial arm: RT: N = 992; HT/RT: N = 987 Age (median, range): RT: 71 (47-88) years; HT/RT: 70 (47-91) years. Karnofsky performance score: RT: 90-100 (N = 920), 70-80 (N = 72); HT/RT: 90-100 (N = 905), 70-80 (N = 82). Intercurrent disease: RT: Present (N = 712), Absent (N = 275), Unknown (N = 5); HT/RT: Present (N = 742), Absent (N = 245). Tumour stage: RT: T1 (N = 476), T2 (N = 516); HT/RT: T1 (N = 488), T2 (N = 499). Nodal stage: RT: Nx (N = 954), N0 (N = 38); HT/RT: Nx (N = 944), N0 (N = 43). Gleason score: RT: 2-6 (N = 592), 7 (N = 286), 8-10 (N = 87), Unknown (N = 27); HT/RT: 2-6 (N = 623), 7 (N = 252), 8-10 (N = 93), Unknown (N = 19). PSA (ng/ml): RT: < 4 (N = 100), 4-20 (N = 892); HT/RT: < 4 (N = 109), 4-20 (N = 8789). Risk subgroup*: RT: Low (N = 334), Intermediate (N = 544), High (N = 114); HT/RT: Low (N = 351), Intermediate (N = 524), High (N = 112). * Low-risk disease was defined as a Gleason score of 6 or less, a PSA level ≤ 10 ng/ml, and a clinical stage ≤ T2a; intermediate-risk disease as a Gleason score of 7 or a Gleason score ≤ 6 with a PSA level > 10 and < 20 ng/ml or clinical stage T2b; and high-risk disease as a Gleason score of 8-10.
Interventions	Radiotherapy alone (RT) v hormone-therapy followed by radiotherapy (HT/RT) Radiotherapy: Administered in daily 1.8-Gy fractions prescribed to the isocenter of the treatment volume, consisted of 46.8 Gy delivered to the pelvis (prostate and regional lymph nodes), followed by 19.8 Gy to the prostate, for a total dose of 66.6 Gy. Treatment of the regional lymph nodes was omitted in patients with negative lymph-node dissections or with a PSA level of less than 10 ng/ml and a Gleason score < 6. Hormone therapy: Flutamide at a dose of 250 mg orally three times a day and either monthly subcutaneous goserelin at a dose of 3.6 mg or intramuscular leuprolide at a dose of 7.5 mg for 4 months. Radiotherapy commenced after 2 months of androgen deprivation. Flutamide was discontinued if the level of alanine aminotransferase increased to more than twice the upper limit of the normal range.
Outcomes	Overall survival, disease-specific mortality, distant metastases, biochemical failure, rate of positive findings on repeat prostate biopsy at 2 years.
Notes	Unplanned post-hoc analysis comparing overall survival within risk groups defined according to baseline characteristics. The groups ap-

	pear comparable at baseline. Unclear if ITT analyses undertaken.

Study: Jones

Bias/Quality item	Authors' judgement (Low/Unclear/ High risk of bias)	Support for judgement
Random sequence generation (selection bias)	Low	Random assignment according to the permuted-block randomisation method described by Zelen.
Allocation concealment (selection bias)	Unclear	No information reported
Blinding of outcome assessment (detection bias): Objective outcomes	Unclear	No information reported
Blinding of outcome assessment (detection bias): Subjective outcomes	Unclear	No information reported
Incomplete outcome data (attrition bias)	Low	Data from all eligible patients appear to have been included in the analyses.
Selective reporting (reporting bias)	Low	All relevant outcomes appear to have been reported.

Study: Laverdiere (L 101)

Methods	Study design: RCT Country: Canada Study period: 1990-1999 Inclusion criteria: Prostatic adenocarcinoma confirmed by histological analysis, and measurable lesions on digital examination and transrectal ultrasound. All patients had T2 or T3 clinical cancer stages. Exclusion criteria: None listed Length of follow up (median): 5 years.
Participants	No. in trial arm: RT: N = 43; HT3/RT: N = 63; HT10/RT: N = 55 Age (median): RT: 68 years; HT3/RT: 69 years; HT10/RT: 69 years

	Stage: RT: T2 (72%), T3 (28%); HT3/RT: T2 (65%), T3 (35%); HT10/RT: T2 (73%), T3 (27%). Gleason score: RT: ≤ 6 (80%), 7-10 (20%); HT3/RT: ≤ 6 (71%), 7-10 (29%); HT10/RT: ≤ 6 (72%), 7-10 (28%).
Interventions	Radiotherapy alone (RT) v hormone-therapy for 3 months followed by radiotherapy (HT3/RT) v neoadjuvant, concomitant and adjuvant hormone therapy for a total of 10 months + radiotherapy (HT10/RT) Radiotherapy (both groups): All patients underwent pelvic CT for target volume delimitation as well as a retrograde urethrogram. Four orthogonal fields were used such that the 95% isodose curve included clinical tumor volume. A total dose of 64 Gy was prescribed at the 95% isodose line with a daily fraction of 2 Gy. *No further details provided.* Hormone therapy: Total androgen suppression with a luteinizing hormone-releasing hormone agonist plus an antiandrogen was used as hormonal treatment. *No further details provided.*
Outcomes	Biochemical recurrence-free survival
Notes	Unclear if the groups are comparable at baseline. Unclear if ITT analyses undertaken.

Study: Laverdiere (L 101)

Bias/Quality item	Authors' judgement (Low/Unclear/ High risk of bias)	Support for judgement
Random sequence generation (selection bias)	Unclear	No information reported
Allocation concealment (selection bias)	Unclear	No information reported
Blinding of outcome assessment (detection bias): Objective outcomes	Unclear	No information reported
Blinding of outcome assessment (detection bias): Subjective outcomes	Unclear	No information reported
Incomplete outcome data (attrition bias)	Low	All data appear to have been included in the analyses.
Selective reporting (reporting bias)	High	Only biochemical recurrence-free survival reported

Study: Mottet

Methods	Study design: RCT (multicentre) Country: France & Tunisia Study period: 2000-2008 Inclusion criteria: Patients aged < 80 years with histologically confirmed T3-4N0M0 prostate cancer. Exclusion criteria: None reported. Length of follow up (median): 67 months.
Participants	No. in trial arm: HT: N = 131; HT/RT: N = 133 Age (mean, SD): HT: 70.47 (5.64) years; HT/RT: 70.71 (5.66) years. Karnofsky (mean?, SD): HT: 96.11 (5.89); HT/RT: 96.62 (5.06). T3N0M0: HT (N = 122); HT/RT (N = 123). PSA (baseline, ng/ml; mean, SD): HT: 51.77 (129.32); HT/RT: 41.5 (45.87).
Interventions	Hormone therapy alone (HT) v hormone therapy + radiotherapy (HT/RT) Hormone therapy: Leuprorelin 11.25 mg SR, 1 sc injection every 3 months for 3 years. Radiotherapy: 48 ± 2 Gy (pelvic) and 70 ± 4 Gy (prostate) over 7 weeks starting within 3 months of HT (?).
Outcomes	5-year overall (clinical and biological) progression-free survival, overall survival, prostate cancer-specific survival.
Notes	Unclear if baseline characteristics comparable between the groups as not many reported. Unclear if ITT analyses undertaken.

Study: Mottet

Bias/Quality item	Authors' judgement (Low/Unclear/ High risk of bias)	Support for judgement
Random sequence generation (selection bias)	Unclear	No information reported
Allocation concealment (selection bias)	Low	Central randomisation

Blinding of outcome assessment (detection bias): Objective outcomes	Unclear	No information reported
Blinding of outcome assessment (detection bias): Subjective outcomes	Unclear	No information reported
Incomplete outcome data (attrition bias)	Low	264/273 included patients were randomized. The data from the 264 patients appear to have been included in the analyses
Selective reporting (reporting bias)	Low	All relevant outcomes appear to be reported

Study: Roach (RTOG 8610)

Methods	Study design: RCT (multicentre) Country: USA Study period: 1987-1991 Inclusion criteria: Patients with bulky (5 X 5 cm) primary tumours, (T2-4) with or without pelvic lymph node involvement. No further information listed. Exclusion criteria: None listed Length of follow up: 15-19 years. Median for all living patients = 13.2 years (RT) and 11.9 years (RT-HT).
Participants	No. in trial arm: RT: N = 232; HT/RT: N = 224 Age (median, range): RT: 71 (49-84) years; HT/RT: 70 (50-88) years. Karnofsky performance status: RT: 60 (N = 0), 70 (N = 0), 80 (N = 10), 90 (N = 125), 100 (N = 97); HT/RT: 60 (N = 1), 70 (N = 2), 80 (N = 15), 90 (N = 119), 100 (N = 87). PSA: RT: N = 67, median = 33.8, range = 1.9-264.6; HT/RT: N = 64, median = 22.6, range = 2.2-128. Institutional Gleason: RT: 3-6 (N = 90), 7-10 (N = 103), missing (N = 39); HT/RT: 3-6 (N = 77), 7-10 (N = 96), missing (N = 51). Central Gleason: RT: 3-6 (N = 59), 7-10 (N = 156), missing (N = 17); HT/RT: 3-6 (N = 70), 7-10 (N = 145), missing (N = 9). Group stage: RT: B2 (N = 71), C (N = 161); HT/RT: B2 (N = 64), C (N = 160).
Interventions	Radiotherapy alone (RT) v hormone therapy + radiotherapy (HT/RT) Radiotherapy: 44-46 Gy, 1.8-2 Gy/day to regional lymphatics fol-

	lowed by 20-25 Gy, 1.8-2 Gy/day to a total of 65-70 Gy to the prostate. Hormone therapy: Goserelin acetate (3.6 mg) monthly X 4, starting 2 months prior to radiation and flutamide (250 mg) po TID.
Outcomes	Overall survival, disease-specific mortality, distant metastasis, biochemical failure, local progression, disease-free survival, and fatal cardiac events.
Notes	The groups appear to be comparable at baseline. RT: 232/232 received allocated treatment; HT/RT: 221/224 received allocated treatment. ITT analyses appear to have been undertaken.

Study: Roach (RTOG 8610)

Bias/Quality item	Authors' judgement (Low/Unclear/ High risk of bias)	Support for judgement
Random sequence generation (selection bias)	Unclear	No information reported
Allocation concealment (selection bias)	Unclear	No information reported
Blinding of outcome assessment (detection bias): Objective outcomes	Unclear	No information reported
Blinding of outcome assessment (detection bias): Subjective outcomes	Unclear	No information reported
Incomplete outcome data (attrition bias)	Low	The data from all the randomized patients appear to have been included in the analyses.
Selective reporting (reporting bias)	Low	All relevant outcomes appear to be reported

Study: See (EPC trials 23, 24, 25; analysis of the patients who received RT as standard care)

Methods	Study design: RCT (multicentre) Country: International

	Study period: Ongoing Inclusion criteria: Patients aged ≥ 18 (trials 23, 24) or 18-75 (trial 25) years with clinically or pathologically confirmed T1-2N0/Nx or T3-4 any N, or any T N+ prostate cancer with no evidence of distant metastases. Exclusion criteria: Prior systemic therapy for prostate cancer. Length of follow up (median): 7.2 years.
Participants	No. in trial arm: RT: N = 671; RT/HT: N = 699 Age (mean, range): RT: 69.3 (47-82) years; RT/HT: 69.6 (48-85) years. Gleason score: RT: 2-4 (22.1%), 5-6 (52.2%), 7-10 (25.6%), not known (0.1%); RT/HT: 2-4 (23.8%), 5-6 (49.6%), 7-10 (23.7%), not known (1.4%). T stage: RT: T1-2 (79.1%), T3 (20.1%), T4 (0.8%); RT/HT: T1-2 (77.5%), T3 (21.7%), T4 (0.7%). N stage: RT: N0 (33.1%), Nx (65.9%), N+ (1%); RT/HT: N0 (30.8%), Nx (68.2%), N+ (1%). Median PSA level (ng/ml; range): RT: Prior to RT (11.2; 0.4-204), At randomisation (3.5; not quantifiable-147.2), localised disease (3.4; not quantifiable-101.3), locally advanced disease (4; not quantifiable-147.2); RT/HT: Prior to RT (11.3; 0.3-681), At randomisation (3.4; not quantifiable-119.3), localised disease (3.3; not quantifiable-69), locally advanced disease (3.8; not quantifiable-119.3) Use of neoadjuvant therapy: RT: 32.5%; RT/HT: 30%. Trial: RT: 23 (47.7%), 24 (48.4%), 25 (3.9%); RT/HT: 23 (46.5%), 24 (47.9%), 25 (5.6%).
Interventions	Radiotherapy followed by placebo once daily (RT) v radiotherapy followed by oral biccalutamide 150 mg once daily for ≥ 2 years(RT/HT) Radiotherapy (both groups): EPC program was designed to reflect current standard care worldwide, therefore radiotherapy techniques and dose fractionation schedules as well as type and duration of hormonal therapy were not specified in the protocol.
Outcomes	Objective progression-free survival, overall survival, prostate-specific antigen and tolerability.
Notes	Not sure if the baseline characteristics of RT/HT are better than those of RT. Information about the characteristics of the radiotherapy used was not collected, but the authors attempted to collect this information retrospectively in trials 24 and 25, but not 23. Some records are no longer available or incomplete. Of the 725 patients receiving radiotherapy in trials 24 and 25, information was collected for 681 patients on the type of radiotherapy given, 643 patients on the dose of radiotherapy, 619 patients on the number of fractions and 621 patients on the duration of therapy. Of these data, 93.4% of patients received external-beam radiotherapy alone (median dose 64 Gy, median fractions = 32, median duration 6.6 weeks) while 6.5% re-

	ceived external-beam radiotherapy and brachytherapy. ITT analyses undertaken.

Study: See (EPC trials 23, 24, 25; analysis of the patients who received RT as standard care)

Bias/Quality item	Authors' judgement (Low/Unclear/ High risk of bias)	Support for judgement
Random sequence generation (selection bias)	Unclear	No information reported
Allocation concealment (selection bias)	Unclear	No information reported
Blinding of outcome assessment (detection bias): Objective outcomes	Unclear	No information reported
Blinding of outcome assessment (detection bias): Subjective outcomes	Unclear	No information reported
Incomplete outcome data (attrition bias)	Low	All data appear to have been included in the analyses
Selective reporting (reporting bias)	Low	The main relevant outcomes appear to have been reported.

Study: Warde (PR07)

Methods	Study design: RCT (phase 3, multicentre) Country: International Study period: 1995-2005 Inclusion criteria: Histologically confirmed prostate adenocarcinoma, clinical T3-4, N0/NX, or M0 disease. In 1999, the entry criteria changed to include patients with clinical T2 tumours with either PSA concentration > 40 ng/mL or both T2 and PSA concentration > 20 ng/mL with a Gleason score > 8, ECOG performance status 0–2, and age < 80 years. Surgical staging was allowed, but if done pelvic nodes had to be histologically confirmed free of disease. Exclusion criteria: Previous treatment for prostate cancer was not allowed, with the exception of neoadjuvant androgen-deprivation

	therapy in the 12 weeks before randomisation. Length of follow up (median and inter-quartile range): 6 (4.4-8) years.
Participants	No. in trial arm: HT: N = 602; HT/RT: N = 603. Age (median, inter-quartile range): HT: 69.7 (65.5-73.5) years; HT/RT: 69.7 (65.5-74) years. PSA: HT: < 20 ng/mL (N = 224), 20-50 ng/mL (N = 228), > 50 ng/mL (N = 150); HT/RT: < 20 ng/mL (N = 220), 20-50 ng/mL (N = 228), > 50 ng/mL (N = 155). Clinical stage: HT: T2 (N = 76), T3 (N = 499), T4 (N = 27), missing (N = 0); HT/RT: T2 (N = 70), T3 (N = 501), T4 (N = 30); missing (N = 2). Gleason score: HT: < 8 (N = 489), 8-10 (N = 107), not available (N = 6); HT/RT: < 8 (N = 489), 8-10 (N = 111), not available (N = 3). Previous hormone therapy: HT: N = 255; HT/RT: N = 256. ECOG performance status: HT: 0 (N = 474), 1 (N = 119), 2 (N = 9); HT/RT: 0 (N = 469), 1 (N = 126), 2 (N = 8). Lymph node staging: HT: Clinical or radiological (N = 477), not done (N = 113), surgical (N = 12); HT/RT: (N = 475), not done (N = 111), surgical (N = 17).
Interventions	Hormone therapy alone (HT) v hormone therapy + radiotherapy (HT/RT) Hormone therapy: All patients received lifelong androgen-deprivation therapy before randomisation consisting of bilateral orchiectomy or luteinising hormone-relasing hormone (LHRH) agonist (initially given with 2 weeks of antiandrogens, which could be continued at the investigator's discretion). Radiotherapy: Commenced within 8 weeks of randomisation and was delivered with a four-field box technique. The pelvic target volume (45 Gy/ 25 fractions/5 weeks) included the whole pelvis, the prostate, seminal vesicles,and external and internal iliac lymph nodes. The prostate target volume (20–24 Gy/10–12 fractions/ 2–2·5 weeks, at the investigator's discretion) encompassed the prostate gland with known periprostatic tumour extension. Patients with histologically negative lymph nodes and those for whom the treating physician judged that pelvic RT was inappropriate were treated to the prostate volume (65–69 Gy).
Outcomes	Overall survival, prostate cancer-specific mortality, time to disease-progression, PSA recurrence, adverse events, health-related quality of life.
Notes	The groups appear to be comparable at baseline. 13/603 HT/RT patients did not receive RT, 560/603 received 64–69 Gy, 17/603 received < 64 Gy, 12/603 received > 69 Gy; 419/603 patients received RT to the prostate and pelvic lymph nodes, 167/603 were treated to the prostate alone. 9/602 HT patients received RT as part of their initial management

	(defined as RT more than 50 Gy to the prostate and pelvis given within 1 year of randomisation with no evidence of relapse). LHRH agonists were used as HT in 550/603 HT/RT patients and in 555/602 HT patients, and orchiectomy was done in 48/603 HT/RT patients and in 45/602 HT patients. ITT analyses undertaken.

Study: Warde (PR07)

Bias/Quality item	Authors' judgement (Low/Unclear/ High risk of bias)	Support for judgement
Random sequence generation (selection bias)	Low	All randomisation was done centrally by computer with stratification by dynamic minimisation. Patients were stratified by institution, PSA concentration at diagnosis, type of ADT (orchiectomy or luteinising hormone-releasing hormone agonist), neoadjuvant androgen-deprivation therapy, lymph node staging, and Gleason score.
Allocation concealment (selection bias)	Low	
Blinding of outcome assessment (detection bias): Objective outcomes	High	The study was not blinded and the physicians assessing the patients appear to have been aware of which study group the patient was allocated to.
Blinding of outcome assessment (detection bias): Subjective outcomes	High	
Incomplete outcome data (attrition bias)	Low	Data from all randomized participants appear to be included in the analyses, apart from for health-related QoL where there is progressively more missing data as time elapsed.
Selective reporting (reporting bias)	Low	All main outcomes appear to be reported.

Study: Widmark (SPCG-7/SFUO-3)

Methods	Study design: RCT (multicentre) Country: Scandinavia Study period: 1996-2002 Inclusion criteria: Histologically proven prostate cancer in men < 76

	years, with a good performance status, a life expectancy > 10 years, and clinical T1b–T2, G2–G3, or T3, any WHO Grade 1–3. Participants had a prostate specific antigen (PSA) ≤ 70 ng/mL, and no evidence of metastases as determined by bone scanning and pulmonary radiography. Participants with a PSA ≥ 11 ng/mL had a pelvic lymph node dissection (fossa obturatoria). Exclusion criteria: Patients with nodal disease. Length of follow up (median and range): 7.6 (0.2-11.9) years.
Participants	No. in trial arm: HT: N = 439; HT/RT: N = 436. Age (mean, SD): HT: 66.2 (5.1) years; HT/RT: 65.7 (5.5) years. PSA (ng/mL; median, inter-quartile range): HT: 16 (8.9-27); HT/RT: 16 (9-26.7). PSA level: HT: < 4 ng/mL (N = 26), 4-10 ng/mL (N = 104), 10.1-20 ng/mL (N = 132), 20.1-30 ng/mL (N = 90), > 30 ng/mL (N = 87); HT/RT: < 4 ng/mL (N = 22), 4-10 ng/mL (N = 110), 10.1-20 ng/mL (N = 132), 20.1-30 ng/mL (N = 85), > 30 ng/mL (N = 87). Stage: HT: T1b (N = 1), T1c (N = 7), T2 (N = 83), T3 (N = 347), unknown (N = 1); HT/RT: T1b (N = 2), T1c (N = 9), T2 (N = 86); T3 (N = 335), unknown (N = 4). WHO grade: HT: I (N = 66), II (N = 283), III (N = 84), unknown (N = 6); HT/RT: I (N = 65), II (N = 289), III (N = 80), unknown (N = 2). Seminal vesicle involvement: HT: N = 107; HT/RT: N = 96.
Interventions	Hormone therapy alone (HT) v hormone therapy followed by radiotherapy (HT/RT) Hormone therapy: Leuprorelin (Procren depot; Abbott, 3.75 mg a month or 11.25 mg every 3 months), for 3 months and were simultaneously treated with 250 mg oral flutamide 3 times a day. After 3 months of HT, patients continued using flutamide until progression or death. Radiotherapy: Commenced after 3 months of HT. Central dose of 50 Gy was given to the prostate and the seminal vesicles. A sequential boost of at least 20 Gy was added to the prostate, which received a total dose of minimum 70 Gy. When invasion to the seminal vesicles was detected using palpation or TRUS-guided biopsy, 70 Gy was given. If more than half of the rectal cross-section received an accumulated dose higher than 50 Gy, the posterior margin was reduced. Pelvic lymph nodes were not intentionally irradiated, but some of the obturatorious nodes were included in the standard target volume. When antiandrogen treatment side-effects were evident, flutamide was stopped and then reinstituted with stepwise increased dose to at least 500 mg. If this treatment failed, antiandrogen was changed to bicalutamide (150 mg once a day). 80% of all patients received breast irradiation to prevent gynecomastia. Initially, castration was

	recommended at time of appearance of clinical symptoms related to progression. No change of treatment was recommended in the event of PSA increase only. After the first publication of the SPCG-6 data in 2002, the addition of leuprorelin was allowed before clinical progress when the PSA level was > 10 µg/mL.
Outcomes	Overall survival, prostate cancer-specific mortality, PSA recurrence, adverse events, quality of life.
Notes	The groups appear to be comparable at baseline. 35/439 HT patients and 58/436 HT/RT patients had their dose of flutamide reduced; 77/439 HT patients and 88/436 HT/RT patients had their treatment changed to bicalutamide. ITT analyses undertaken.

Study: Widmark (SPCG-7/SFUO-3)

Bias/Quality item	Authors' judgement (Low/Unclear/ High risk of bias)	Support for judgement
Random sequence generation (selection bias)	Low	Patients were randomly assigned with stratification according to study centre, T stage, and grade. Randomisation was by computer with a block size of four through a telephone service at the Oncology Centre at Umea University.
Allocation concealment (selection bias)	Low	
Blinding of outcome assessment (detection bias): Objective outcomes	High	The study was not blinded and the physicians assessing the patients were aware of which study group the patient was allocated to.
Blinding of outcome assessment (detection bias): Subjective outcomes	High	
Incomplete outcome data (attrition bias)	Low	Data from all randomized participants appear to be included in the analyses apart from Ns = 7 and 6 from the HT and HT/RT groups respectively for PSA recurrence.
Selective reporting (reporting bias)	Unclear	Disease-free survival, local and distant recurrence not reported.

Study: Zagars

Methods	Study design: RCT Country: USA Study period: 1967-1973 Inclusion criteria: Clinical stage C adenopcarcinoma of the prostate. No patient had received any prior treatment for his prostatic carcinoma, except in cases the transurethral resection (TURP) of the prostate was done. Exclusion criteria: None listed. Length of follow up: Unclear, but appear to be up to 15 years.
Participants	No. in trial arm: RT: N = 43; RT/HT: N = 39 Age: All patients: Mean and median = 64 (range 51-73) years. Prostatism: RT: N = 26; RT/HT: N = 29. TURP: RT: N = 21; RT/HT: N = 21. Grade: RT: 1 (N = 15), 2-3 (N = 11), 4 (N = 2); RT/HT: 1 (N = 11), 2-3 (N = 2), 4 (N = 2). Bladder invasion: RT: N = 2; RT/HT: N = 2. Sidewall involved: RT: N = 7; RT/HT: N = 14. Elevated serum prostatic acid phosphatase: RT: N = 6; RT/HT: N = 5. Creatine > 1.5 mg/dl: RT: N = 1; RT/HT: N = 1. Hydronephrosis: RT: N = 3; RT/HT: N = 0.
Interventions	Radiotherapy alone (RT) v radiotherapy + immediate estrogen (RT/HT) Radiotherapy: Patients were treated with high-energy (18-25 MV) photon beams via a four-field portal arrangement using app 10 X 10 cm anteroposterior and 10 X 8 cm lateral fields. The inferior margin of these fields was at or just cranial to the lower border of the ischial tuberosities, and the posterior border of the lateral fields bisected the rectal lumenh. After 50 Gy was delivered in 5 weeks at 2 Gy per fraction with this technique, a reduced volume of 8 X 8 or 9 X 9 cm was given an additional 20 Gy in 2 weeks through anteroposterior parallel-opposed fields. Hormone therapy: 5 mg daily diethylstilbestrol started immediately after completion of RT. In 1972 dose reduced to 2 mg daily. HT to continue indefinitely.
Outcomes	Clinical disease-free survival, overall survival, distant metastasis-free survival, cause-specific mortality and locoregional control. QoL was not obtained in this study.
Notes	The groups appear to be comparable at baseline. RT: 40/43 were evaluable (N = 1 did not have documented carcinoma, N = 1 refused to complete RT and N = 1 was lost to follow up); RT/HT: 38/39 were evaluable (N = 1 had bone metastasis). 4/38 did not receive HT, 20/34 patients treated with HT recived 5 mg daily, 12/34 recived 2 mg daily and 2/34 received 12 mg daily chlorotrianisene (Tace), 12/34 patients terminated HT prematurely (i.e., after relapse or death) after taking HT for 9-93 (mean = 42, median = 41)

	months. The reasons for discontinuing HT were unclear (N = 5), cardiac or cerebrovascular problems (N = 5), refusal of further treatment due to feminizing effects (N = 2) Treatment after relapse not specified in protocol: 27/40 RT patients relapsed, 14 of whom received estrogen only, 9 received orchiecyomy and estrogen, 3 had orchiectomy and 1 received non-hormonal treatment. 11/38 HT/RT patients relapsed: 6 underwent orchiectomy, 1 received higher dose of estrogen, 1 underwent TURP only, 1 received chemotherapy and 2 had no specific additional treatment. ITT and per-protocol analyses undertaken. Authors report that results did not differ between these two methods opf analysis.

Study: Zagars

Bias/Quality item	Authors' judgement (Low/Unclear/ High risk of bias)	Support for judgement
Random sequence generation (selection bias)	Unclear	No details reported.
Allocation concealment (selection bias)	Unclear	No details reported.
Blinding of outcome assessment (detection bias): Objective outcomes	Unclear	No details reported.
Blinding of outcome assessment (detection bias): Subjective outcomes	Unclear	No details reported.
Incomplete outcome data (attrition bias)	Low	The data from all the randomized patients have been analysed for all reported outcomes.
Selective reporting (reporting bias)	Unclear	No adverse events of RT reported

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What is the optimal duration of hormone therapy when combined with external beam radiotherapy?

Rationale

External beam radiotherapy (EBRT) is a standard treatment for localized non-metastatic prostate cancer. Hormone therapy which blocks androgen stimulation to the prostate cancer cells also suppresses tumour growth and may control prostate cancer for some years. Resistance to hormone therapy is inevitable and it is therefore not seen as a long-term definitive treatment in a patient whose life expectancy is likely to extend beyond the duration of response, typically 2 to 3 years. The advantage of hormone therapy however is that as a systemic treatment it will affect prostate cancer cells outside the prostate gland and will be active on micrometastases. It will also reduce the tumour burden in the prostate if given before EBRT thus potentially reducing the number of viable cells which radiotherapy has to eliminate. Combining the two treatments may therefore provide optimal local and distant tumour control, but is only relevant to those patients where EBRT alone would not encompass and eliminate the full extent of the prostate cancer.

EBRT is a defined event within a specific time frame, typically 7 to 8 weeks when EBRT is used alone. Hormone therapy may be given for a variable length of time and may precede radiotherapy (neoadjuvant treatment, NAH), be given during radiotherapy, and/or for a period following radiotherapy. The optimal timing and overall duration is uncertain; typically, patients with 'intermediate to high-risk' localized disease receive NAH for 3-6 months before EBRT, while patients with 'locally advanced' cancers might receive hormone treatment for 2 years or longer, with NAH often, but not always, being part of that treatment. Although most trials of hormone therapy used in association with EBRT have used androgen deprivation therapy (ADT), some, including the SPCG-7 study for locally advanced disease, have used anti-androgens. Which patients should receive hormone therapy, when, what type, and for how long have not been clearly defined.

In addition, as prolonged hormone therapy has significant morbidity associated with it, it can only be justified if long duration hormone therapy is clearly superior to short duration, in those patients in whom it is indicated, in terms of tumour control and survival.

PICO question

Population	Intervention	Comparator	Outcomes
Men receiving combined hormone therapy and EBRT	Less than or equal to 6 months hormone therapy	Greater than 6 months hormone therapy	• Overall survival • Disease-free survival • Metastases-free survival • Biochemical disease-free survival • Treatment-related morbidity (cardiovascular events) • Treatment-related mortality • Health-related quality of life

How the information will be searched

Sources to be searched	
Can we apply date limits to the search	These topics are updates of ones in the original 2008 guideline so we will search for studies published since.
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	A randomised trials filter will be used
List useful search terms.	

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? List subgroups here and planned statistical analyses	We will use the evidence table for randomised trials (NICE guidelines manual appendix J). The RCT checklist will be used (NICE guidelines manual appendix C). Time to events meta-analysis will be done for survival outcomes. Dichotomous outcomes will be meta-analysed using risks ratios or odds ratios. Patient subgroups are noted in the PICO (see 9a) – although we may have to rely on the original studies definition of risk group.

Methods

Selection of studies

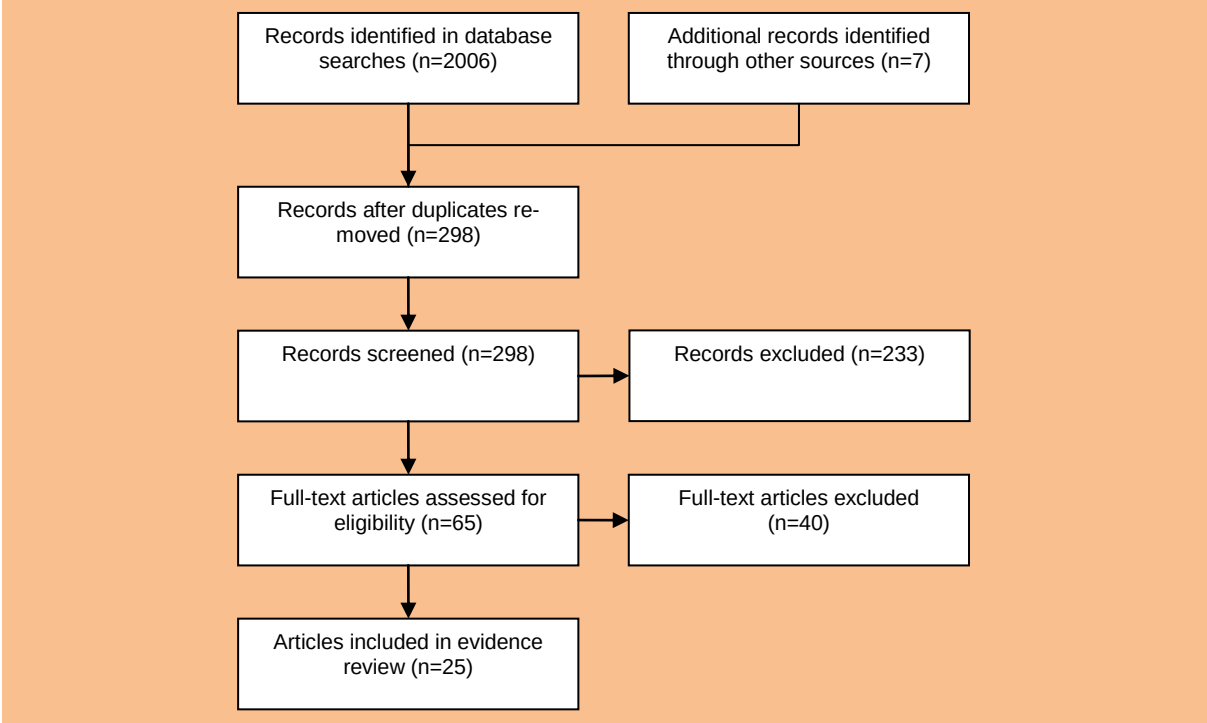
The information specialist (EH) did the first screen of the literature search results. Two reviewers (KC and JH) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO question. The full articles were then obtained for possibly eligible studies and checked against the inclusion criteria.

Analysis

For outcomes where time to the event was important (overall, disease-free, metastases-free, and biochemical disease-free survival) time to events meta-analysis was undertaken using the methods described in Tierney et al. (2007). Adverse events were treated as dichotomous outcomes and classified in the same way as in the original studies. Quality of life outcomes were reported descriptively.

Results

Results of the literature searches



The literature searches identified 298 possibly relevant articles (including seven identified from the reference lists of included articles) of which 65 were ordered in full text. Twenty-five publications referring to eight different studies were included.

Characteristics of included studies

The characteristics of included studies are summarised in Table 111. Three of the publications identified were only available in abstract form and three reported sub-group analyses within the trial results. Only seven of the 25 publications contained useful data for synthesis in the meta-analysis. For one study (GICOR DART 01) only a conference abstract was available but, as this study is ongoing, the authors will be approached for the full trial results prior to the final publication of the guideline. All included studies were of randomised and controlled design.

Two of the studies compared three treatment arms: short- or long-term hormone therapy with EBRT or EBRT alone; only the combined treatment arms were included in this analysis. The majority of the studies were of good size (>100 patients per treatment arm), with two large trials (RTOG 92-02; EORTC 22962) including > 400 patients in each treatment arm. Only one trial (Laverdiere *et al*. 2004) was considered small, with only 161 patients randomised across three treatment arms. With the exception of the ongoing trial (GICOR DART 01), all studies provided at least 5 years of patient follow-up.

Patient characteristics

Only one study included prostate cancer patients of any stage (T1-T4; Crook *et al*. 2004). One study included those with stages T1b-T3c (GICOR DART 01). One study included those with stages T2-T3 (Laverdiere *et al*. 2004), one with stages T2b-T4 (TROG 96-01), and one with stages T2c-T4 (RTOG 92-02). The ICORG 97-01 trial only included those patients with locally advanced cancer (stage ≥ T3) unless they presented with a PSA > 20 ng/mL or Gleason score ≥ 7. The TROG 03-04 trial excluded any patients with ≥ T2b and metastases or > T2a and Gleason ≥ 7 and PSA ≥ 10 ng/ml.

Five of the studies report excluding patients with lymph node involvement (TROG 96-01; TROG 03-04; RTOG 92-02; ICORG 97-01; GICOR DART 01). The EORTC 22962 trial included those patients with stages T2c-T4 with or without lymph node involvement, but also those staged T1c-T2b if there was lymph node involvement. Only one of the studies did not report exclusion of patients with distant metastases (Laverdiere *et al*. 2004).

Hormone therapy

Six of the studies compared neoadjuvant hormone therapy of differing treatment lengths. In two of these studies (Crook *et al*. 2004; ICORG 97-01) both short- and long-term hormone therapies were completed prior to the start of EBRT. In one study (Laverdiere *et al*. 2004) the short-term therapy was completed prior to EBRT whilst the long-term therapy was neoadjuvant, concurrent and ongoing. One study (TROG 96-01) provided neoadjuvant and concurrent hormone therapy, with both short- and long-term therapies ceasing one month after the start of EBRT. Two of the studies (RTOG 92-02; GICOR DART 01) treated patients with 4 months of neoadjuvant and concurrent hormone therapy, with the long-term treatment arm providing ongoing hormone therapy for 2 years following completion of EBRT. The RTOG 03-04 trial began ADT 5 months prior to EBRT in both arms. EORTC 22961 was the only trial to compare hormone therapies starting alongside EBRT and continuing beyond its completion (ceasing 6 or 30 months after completion).

Evidence statements

Overall survival

Five randomised controlled trials provided evidence on the overall survival of men receiving combined hormone therapy and external beam radiotherapy (EBRT) for prostate cancer. Four (ICORG, RTOG 92-02, TROG 96-01 and Crook *et al*. 2004) of these trials provide low quality evidence of

similar overall survival of men treated with long-term (6-28 months) compared to short-term (3-4 months) neoadjuvant and concurrent hormone therapy (hazard ratio of 0.98; 95% CI 0.87-1.11).

The fifth trial (EORTC) provides moderate quality evidence of better overall survival in men treated with long-term (36 months) concurrent and adjuvant hormone therapy compared to those treated short-term (6 months). The hazard ratio of 1.42 (95% CI 1.09-1.84) suggests that if hormone therapy were continued after 6 months for a further 30 months, there would be an absolute increase in survival of 5.7% at 5 years, increasing overall survival from 79.1% to 84.8% (based on Bolla *et al*. 2005).

Disease-free survival

Very low quality evidence from two randomised controlled trials suggests uncertainty about the duration of hormone therapy and disease-free survival. In one trial (RTOG 92-02) comparing 4 versus 28 months neoadjuvant and adjuvant hormone therapy, the risk of disease recurrence was significantly lower in those receiving short-term therapy (HR 0.82 95% CI 0.73-0.91; see Figure 56). However, the second trial (TROG 96-01), which compared 3 versus 6 months neoadjuvant and concurrent hormone therapy, found the risk of disease recurrence to be significantly lower in those receiving long-term therapy (HR 1.25 95% CI 1.02-1.54).

Metastases-free survival

Three trials (RTOG 92-02, TROG 96-01 and GICOR DART 01) provided moderate quality evidence which suggests that men receiving neoadjuvant and concomitant hormone therapy combined with EBRT are at greater risk of developing distant metastases with short-term therapy (3-4 months) than with long-term (6-28 months). Two of these studies contributed to the meta-analysis which gave a hazard ratio of 1.66 (95% CI 1.34-2.06), suggesting that if hormone therapy were continued after 3 months for a further 3 months, there would be an absolute decrease in the number of patients developing metastases of 6.5% at 10 years, decreasing the proportion who develop metastases from 17.4% to 10.9% (based on Horwitz *et al*. 2008).

Biochemical disease-free survival

Low quality evidence from six randomised controlled trials (ICORG, RTOG 92-02, TROG 96-01, GICOR DART 01, Crook *et al*. 2004, and Laverdiere *et al*. 2004) suggests that men receiving neoadjuvant & adjuvant hormone therapy combined with EBRT have a greater likelihood of biochemical recurrence with short-term therapy (3-4 months) than with long-term (6-28 months). Five of these studies were included in the meta-analysis which gave a hazard ratio of 1.20 (95% CI 1.08-1.33), suggesting that if hormone therapy were continued after 3 months for a further 3 months, there would be an absolute decrease in the number of patients with biochemical recurrence of 6.6% at 10 years, decreasing the proportion who experience biochemical recurrence from 64.8% to 58.2% (based on Horwitz *et al*. 2008).

Cardiovascular adverse events

Low quality evidence from two randomised controlled trials (RTOG 92-02 and GICOR DART 01) suggests that cardiovascular events are less likely to occur in men treated with short-term (4 months) neoadjuvant and adjuvant hormone therapy combined with EBRT, than with long-term (28 months) therapy (RR 0.42 95% CI 0.06-2.82). The evidence suggests that for every 100 men treated with short- instead of long-term neoadjuvant and adjuvant hormone therapy when combined with EBRT, there will 58 fewer cardiovascular adverse events.

Health-related quality of life

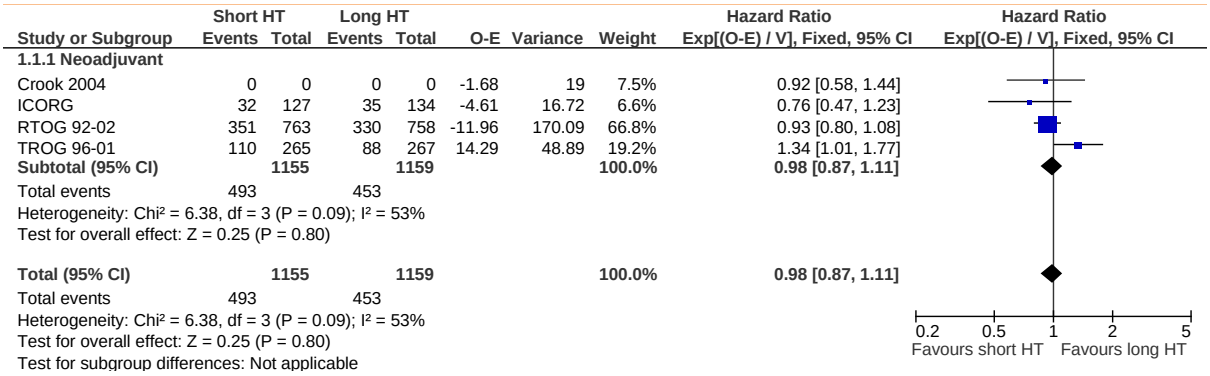
Two trials (EORTC; TROG 03-04) reported moderate-quality evidence on quality of life using the QLQ-C30 tool. The EORTC trial found no significant difference between groups treated with 6 versus 30 months of concurrent and adjuvant hormone therapy for any of the function scales: global health status and quality of life, physical functioning, cognitive functioning, emotional functioning,

role functioning, or social functioning (p≥0.1 for each). Of the symptom scales used, only insomnia (p=0.006) reached statistical significance (a significance level of p<0.01 was used to allow for multiple subgroup analyses). Appetite loss, constipation, diarrhea, dyspnea, nausea or vomiting, fatigue and pain were not found to be significantly different between treatment groups. However, the TROG 03-04 trial found all outcomes within the functional domain of the EORTC QLQ-C30 tool to be significantly different at both 18 and 36 months (global, role, cognitive, social, emotional and physical). Within the symptoms domain, dyspnea and fatigue were found to be significantly different at both 18 and 36 months.

A number of ad hoc quality of life questions were also included by the EORTC authors, all of which were scored significantly lower by those treated with short-term (6-month) hormone therapy: hot flushes, enlarged nipples or breasts, swelling of legs, problems passing urine, reduced interest in sex, and reduced sexual activity.

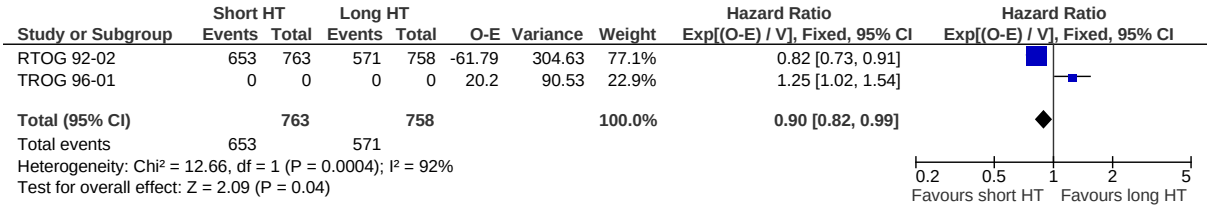
The TROG 03-04 study also provided moderate quality evidence of no significant difference between 6 months and 18 months of neoadjuvant and concurrent ADT using the overall International Prostate Symptom Score (IPSS) at 18 or 36 months (p<0.01). However, there was a significant difference in the sexual activity and hormone-treatment-related symptoms domains of the PR-25 tool at both 18 and 36 months.

Figure 55 Forest plot of overall survival in trials comparing neoadjuvant and adjuvant hormone therapies combined with EBRT*



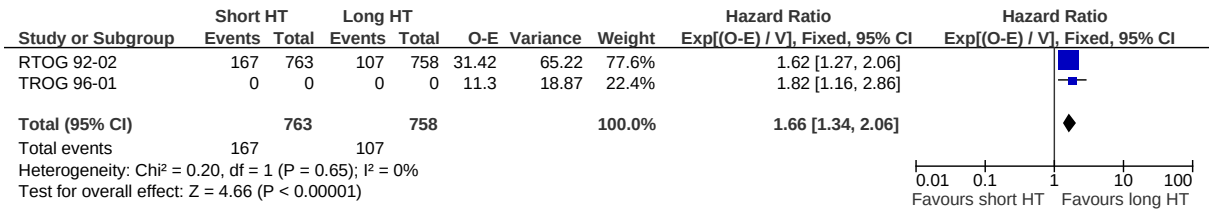
*The number of men surviving was not reported by the TROG 96-01 trial but the hazard ratio was available to allow meta-analyses.

Figure 56 Forest plot of disease-free survival in trials comparing neoadjuvant and adjuvant hormone therapies combined with EBRT*



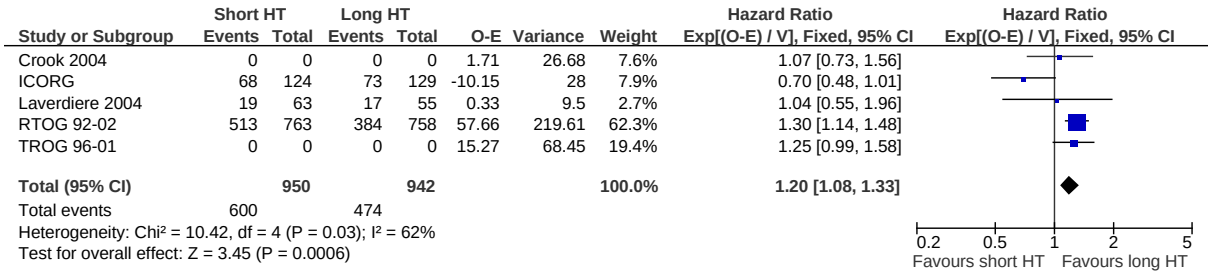
*The number of men surviving was not reported by the TROG 96-01 trial but the hazard ratio was available to allow meta-analyses.

Figure 57 Forest plot of metastases-free survival in trials comparing neoadjuvant and adjuvant hormone therapies combined with EBRT*



*The number of men surviving was not reported by the TROG 96-01 trial but the hazard ratio was available to allow meta-analyses.

Figure 58 Forest plot of biochemical disease-free survival in trials comparing neoadjuvant and adjuvant hormone therapies combined with EBRT*



*The number of men surviving was not reported by the Crook et al. (2004), Laverdiere et al. (2004), or TROG 96-01 trials but the hazard ratios were available to allow meta-analyses.

Figure 59 Forest plot of cardiovascular adverse events occurring in trials comparing hormone therapies combined with EBRT

Study or Subgroup	Short HT Events	Short HT Total	Long HT Events	Long HT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
GICOR DART 01	0	108	1	103	43.3%	0.32 [0.01, 7.72]
RTOG 92-02	1	763	2	758	56.7%	0.50 [0.05, 5.47]
Total (95% CI)		**871**		**861**	**100.0%**	**0.42 [0.06, 2.82]**
Total events	1		3			

Heterogeneity: Chi² = 0.05, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.89 (P = 0.37)

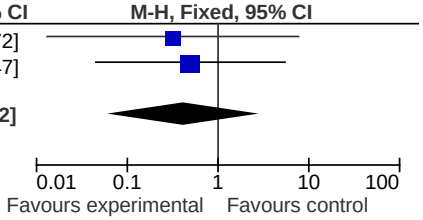


Table 111 Summary of study characteristics

Abbreviations: RCT = randomised controlled trial; EBRT = external beam radiotherapy; PCa = prostate cancer; HT = hormone therapy; LHRH = luteinising hormone-releasing agonist; NHT = neoadjuvant hormone therapy

Study	Study type	Country /ies	Study period	Number of patients	Median follow-up (range)	Inclusion criteria	Exclusion criteria	Radiotherapy	Hormone therapy	Additional comments
Crook et al. (2004)	RCT	Canada	1995 – 2001	Randomised: 378 Short-term HT: 184 Long-term HT: 194	6.6 years (1.6-10.1)	Histologically-confirmed localised Pca stage T1-T4 M0		EBRT 66 Gy within 2 weeks of NHT completion	3 vs. 8 months of NHT of flutamide 250 mg daily (orally, three times a day) & goserelin acetate every 4 weeks (subcutaneous)	
Laverdiere et al. (2004)	RCT	NR	1990 – 1999	Randomised: 161	5 years	Histologically-confirmed Pca stage T2-T3	None reported	4-field; 64 Gy in daily fractions of 2 Gy	3 months of LHRH agonist & antiandrogen prior to EBRT vs. 10 months prior, concurrent & adjuvant to EBRT	3-arm trial with EBRT alone arm
TROG 96-01	RCT	Australia & New Zealand	1996 – 2001	Randomised: 818 Short-term HT: 270 Long-term HT: 272 No HT: 276	10.6 years (0.1-13.9)	Locally advanced Pca stage T2b-T4 N0 M0	Significant medical conditions; prior malignancies or metastases	66 Gy in 2 Gy daily fractions	3 vs. 6 months of goserelin 3.6 mg once per month (subcutaneously) & flutamide 250 mg 3 times daily (orally), beginning 2 or 5 months prior to RT	3-arm trial with RT alone arm
RTOG 92-02	RCT	US	1992 – 1995	Randomised: 1521 Short-term HT: 763 Long-term HT: 758	11.3 years	Histologically-confirmed locally advanced Pca stage T2c-T4	Lymph node involvement; PSA≥ 150 ng/mL; prior therapy	EBRT to whole pelvis & boost to prostate of 4-field 65-70 Gy	4 months goserelin 3.6 mg subcutaneously monthly + flutamide 250 mg 3 times daily before & during RT (starting 2 months before RT). No further HT vs. 24 further months of goserelin	
TROG 03-04 RADAR	RCT	Australia & New Zealand	2003 - 2007	Randomised: 1071 Short-term: 268 Long-term: 268	NR	Histologically-confirmed PCa	Lymph node involvement; systemic metastases & ≥ T2b; Gleason ≥ 7 & T2a & PSA ≥ 10 ng/ml	5 months RT to prostate & seminal vesicles (but not pelvic lymph nodes)	6 months leuprorelin (22.5 mg im 3 monthly) OR 18 months leuprorelin (22.5 mg im 3 monthly)	
EORTC 22961	RCT	NR	1997 – 2001	Randomised: 970 Short-term HT: 483 Long-term HT: 487	6.4 years	Histologically-confirmed PCa stage T1c-T2b N1-2 M0 or T2c-T4 N0-2 M0		3D conformal EBRT 70 Gy	6 months of LHRH (triptorelin) starting on first day of RT & antiandrogen (flutamide 750 mg daily or bicalutamide 50 mg daily) starting 1 week prior to LHRH & RT. No further HT vs. further 2.5 years of LHRH.	
ICORG 97-01	RCT	Ireland	1997 - 2001	Randomised: 276 Short-term HT: 137 Long-term HT: 139	8.5 years (1.0-11.4)	PCa M0 with at least one of the following: stage ≥ T3; PSA > 20 ng/mL; Gleason ≥ 7	Lymph node involvement; previous therapy or malignancy; bilateral orchiectomy; severe medical illness	3D conformal EBRT; 70 Gy in 35 fractions	4 vs. 8 months of LHRH agonist (triptorelin) 3.75 mg per month & flutamide 250 mg 3 times daily, prior to RT	
GICOR DART 01	RCT	Spain	Ongoing	Randomised: 361 Short-term HT:	NR	Histologically-proven PCa stage	Concomitant chemotherapy; serious psy-	3D conformal EBRT; minimum	4 months of neoadjuvant & concomitant androgen deprivation.	Only poster available

				180 Long-term HT: 181		T1b-T3c N0 M0; PSA < 100 ng/mL; intermediate or high risk patients	chiatric or medical conditions; current synchronic malignan-cies	dose of 76 Gy	No further HT vs. adjuvant goserelin for 2 years.	

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In men with prostate cancer receiving hormone therapy, are bisphosphonates effective at preventing bone metastases?

Short Summary

A good quality placebo controlled randomised trial (Mason *et al.* 2007) examined clodronate for the prevention of bone metastasis in men with localised or locally advanced prostate cancer. There was no significant difference in overall survival, symptomatic bone metastases or prostate cancer death between the treatment arms. Dose modifying adverse events were more likely in the clodronate group.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOMES
Men who have localised or locally advanced disease (T2 – T4) • Undergoing hormonal therapy • No evidence of bone metastases • With no prior or concomitant use of bisphosphonates	• Bisphosphonate	▪ Placebo ▪ Same bisphosphonate (different duration of therapy or route of administration) ▪ Other bisphosphonate treatment	• Time till development of symptomatic bone metastases • Skeletal related events – all associated events including symptomatic fractures and SCC • Overall Survival • Toxicity • Type of progressive disease (bone vs. non malignant bone events) • Analgesic consumption • Quality of life • Need for palliative RT

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

Evidence Summary

Prevention of bone metastasis

The PR04 trial examined the effect of clodronate on the time to bone metastasis in men with localised or locally advanced prostate cancer (Mason *et al.* 2007). At a median follow up of 7 years, there was no significant difference between clodronate and placebo arms in terms of symptomatic bone metastases or prostate cancer death (clodronate vs. placebo: HR=1.22 [95% C.I. 0.88 to 1.68]). There was no significant difference between overall survival in the two arms (clodronate vs. placebo: HR = 1.03 [95%CI 0.76 to 1.39]).

The Zometa 704 trial (Smith et al. 2005) examined the use of zoledronic acid for the prevention of bone metastasis in men with rising PSA despite ADT. The trial was closed prematurely due to a lower than expected rate of bone metastasis. While results were published from the 201 patients in the control arm (Smith et al. 2005), literature searches did not find any published data about the 188 patients who received zoledronic acid.

Adverse effects

In the PR04 trial, there were 202 adverse events in the clodronate arm and 181 in the placebo arm. More detail is required to interpret these figures, for example, it is unclear whether some patients experienced multiple adverse events.

Evidence Tables

Randomized controlled trials

Mason, Sydes, Glaholm, Langley, Huddart, Sokal, Stott, Robinson, James, Parmar, Dearnaley & Medical Research Council. Oral sodium clodronate for nonmetastatic prostate cancer--results of a randomized double-blind placebo-controlled trial: Medical Research Council PR04 (ISRCTN61384873). J Natl Cancer Inst 99[10]. 2007.

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

Country: International, setting: Tertiary care

Inclusion criteria Men receiving standard treatment for T2 to T4 prostate cancer, with no evidence of metastases a WHO performance status of 0-2. Patients were recruited between 1994 and 1997.

Exclusion criteria Previous bisphosphonate treatment or long term hormonal therapy.

Population number of patients = 508.

Interventions Men were randomised to receive 4 tablets per day of either oral sodium clodronate (Loron 520mg) or matching placebo. Patients were encouraged to stay on this medication for 5 years or until one of the primary endpoints was reached.

Outcomes Primary outcome was symptomatic bone metastasis free survival. Overall survival, toxicity, rate of events affecting bone and type of progressive disease (bone or soft tissue).

Follow up Minimum follow up was at least 5 years. 38% of patients in the clodronate group completed 5 years of medication, compared to 48% in the placebo group.

Results -

COMPARISON IN MEN WITH PROSTATE CANCER AND NO BONE METASTASES	SODIUM CLODRONATE	PLACEBO	OVERALL RESULT
Symptomatic bone metastases or prostate cancer death	80/254	68/254	Favours placebo but not statistically significant, HR=1.22 (95% C.I. 0.88 to 1.68; p=0.23, log rank test)
Overall survival	5 year survival was 78% (95% C.I. 73 to 83%)	5 year survival was 79% (95% C.I. 73 to 83%)	No sig. diff. in overall survival, HR=1.02, 95% C.I. 0.80 to 1.30, p= 0.90 (log rank test)
Adverse events	132/254 experienced one or more adverse events	117/254 experienced one or more adverse events	Tended to favour placebo, p=0.18
Dose modifying ad-	105/254 experienced	71/254 experienced	Favoured placebo,

verse events	one or more dose modifying adverse events	one or more dose modifying adverse events	p=0.002

General comments Potency of oral clodronate is less than latest generation bisphosphonates (e.g. zoledronic acid).

Smith, Kabbinavar, Saad, Hussain, Gittelman, Bilhartz, Wynne, Murray, Zinner, Schulman, Linnartz, Zheng, Goessl, Hei, Small, Cook & Higano. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 23. 2005.

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

Country: unclear, setting: Tertiary care

Inclusion criteria Men with prostate cancer, no radiographic evidence of bone metastases, and rising PSA despite androgen deprivation therapy.

Exclusion criteria Patients with disease related symptoms, KPS of less than 90, life expectancy less than 6 months

Population number of patients = 389.

Interventions All patients were receiving ADT, either bilateral orchietomy or treatment with a gonadotropin-releasing hormone agonist. Patients were randomly assigned to receive either zoledronic acid or placebo intravenously every 4 weeks for 49 treatments. Patients were also prescribed daily calcium (500 mg) and vitamin D (400 to 500 IU).

Outcomes Time to first bone metastasis (as detected on bone scan or radiograph). Serum PSA.

Follow up Patients were evaluated every month for 48 months, when symptoms were assessed. Serum PSA was measured at baseline and then every 4 months.

Results The Data safety Monitoring Board terminated the study before the target accrual of 991 patients because the rate of bone metastasis was lower than predicted.

For the placebo group (n=201): at 2 years, 33% of patients had developed bone metastases. Median bone metastasis-free survival was 30 months. Median time to first bone metastases and overall survival were not reached.

-

General comments No results reported from the bisphosphonate treatment arm, not even adverse effects data.

Health Economic Short Summary

The literature search on the use of bisphosphonates for the prevention of skeletal-related events (SREs) identified 153 potentially relevant papers. Thirteen of these papers were obtained for appraisal, of which 1 full economic evaluation was identified and reviewed (Reed et al. 2004). It examined 4 mg zoledronic acid (versus placebo), every 3 weeks, in men with advanced-stage prostate cancer and a history of metastatic bone disease as a method of preventing SREs. It was a non-UK based cost-utility analysis that was performed from a health services perspective. Results were presented in 2000-2002 US$. The evaluation was considered to be a good quality analysis.

The analysis was based on a single RCT of 15-months duration; treatment costs and benefits were not extrapolated past this period. Approximately 650 patients were entered into the RCT, however only information relating to 360 was included in the economic evaluation (for which baseline details were not provided). Utility scores were calculated using the EQ-5D questionnaire, which were recorded every 3-months as part of the trial design. Resource use was also collected prospectively alongside the RCT.

The results from the analysis showed that patients receiving zoledronic acid experienced fewer hospital days than people receiving placebo, although this difference was not statistically significant at conventional levels (mean of 5.6 vs 8.0 days respectively; p = 0.20). The additional healthcare costs of providing zoledronic acid plus its administration was approximately $5,700. The baseline incremental cost-effectiveness ratio per additional QALY was approximately $160,000, although this varied considerably during the sensitivity analysis. Using $2=£1, translates to an ICER of approximately £80,000 per additional QALY. The authors concluded that the use of zoledronic acid for the prevention of SREs for people with metastatic prostate cancer was unlikely to be cost-effective, which appears to be a reasonable conclusion given the quality of the evidence.

Health Economics Summary

Overview

The objective of this topic is to estimate the cost-effectiveness of bisphosphonates in relief of metastastic bone symptoms and control of metastatic bone disease in men with prostate cancer.

The analysis by Reed et al., identified from the evidence review, estimates the cost-effectiveness of zoledronic acid versus placebo in men with prostate cancer for decreasing skeletal complications.

Overall, this is a well balanced, recent paper where intervention was clearly stated and sensitivity analysis was thoroughly carried out, which supports the robustness of conclusions. The methodology of obtaining preference and applying them to clinical data was clearly stated and justified. However, the multinational nature of the population sample has limited relevancy to the UK health system. The analysis is based on a single randomized control trial. These conclusions provide a valuable guide, but are not conclusive to the UK setting. More economic evidence on this topic is necessary.

Comparison(s)

The analysis by Reed et al. (2004) compared patients with prostate cancer receiving 4 mg of zoledronic acid versus patients receiving placebo.

Population Sample

The analysis was based on a multinational, double-blind, placebo controlled randomized trial of 643 men with advance stage prostate cancer conducted by Saad et al. (Saad *et al*. 2002).

Costs

The following cost components were included in the analysis: direct medical costs, which included hospitalization, outpatient and institutionalization costs. All costs are reported in US dollars ($). Unit costs in countries other than the USA were converted to year 2000 dollars using purchasing power parities.

Clinical Effectiveness

The authors state that zoledronic acid decreased the incidence of skeletal related events relative to placebo. This result consistent with the conclusions of several other cited studies investigating the efficacy of zoledronic acid in the prevention of skeletal related events.

Results

The cost per patient receiving zoledronic acid was $5,365, while the cost per patient receiving placebo was $5,689. The difference of $324 was insignificant (95% CI: $1,781, $1,146), and the authors concluded that the incremental cost of the intervention could be calculated as the cost of zoledronic acid and its administration at $5,677 +/-3,809.

Incremental cost-effectiveness ratios (ICERs) and cost-utility ratio were calculated. The ICERs were $12,300 per skeletal related event avoided (95% CI: $6,900, $48,700) and $51,400 per additional patient free of skeletal related events during the trial (95% CI: $26,900, $243,700). The incremental cost per QALY was $159,200 (95% CI: $88,500, $786,600)

Sensitivity Analysis

The authors conducted sensitivity analyses by considering following: (a) change in the price of zoledronic acid, (b) community-based utility weights derived from the EQ-5D and (c) the number of days that patient experienced lower quality of life due to skeletal related event.

Reviewer Comments

The analysis was based on a randomised controlled clinical trial, which was appropriate for this topic. The authors conducted a cost study with thorough sensitivity analysis and reported results in an incremental format.

Although the analysis was conducted using patient level data that was collected during the trial, the authors acknowledge some of its limitation with respect to resource use data and EQ-5D measure. The authors further stress the need for future research of this topic.

Health Economics Evidence Table

Question: How cost-effective are bisphosphonates for relief of metastatic bone symptoms and control of metastatic bone disease?

By: Eugenia Priedane, Pat Linck, Dyfrig Hughes and Rhiannon Tudor Edwards
Date: 30/03/2006

Bibliographic reference	Reed, S. D., J. I. Radeva, et al. (2004). "Cost-effectiveness of zoledronic acid for the prevention of skeletal complications in patients with prostate cancer." Journal of Urology 171(4): 1537-1542
Source of funding	Novartis Pharmaceuticals Corporation, NJ, USA
Economic study type	Cost-effectiveness analysis; Cost utility analysis
Population, country & perspective	The study included a population sample from a multinational, double-blind, placebo controlled randomized trial of 643 men with advance stage prostate cancer (Saad et al. 2002). 214 patients were randomized to zoledronic acid and 208 to placebo. Excluding patients without resource use data, 181 and 179 were randomized to the zoledronic acid and placebo arms, respectively. The median age of all patients included in the economic evaluation was 73 years. Ethnicity composition of the sample was split as follows – 85.3% white, 9.7% black, 1.1% Asian and 3.9% 'other'. Majority of patients came from the USA (59.9%), followed by Canada (21.1%) and Australia (10.6%). The economic analysis adopted a societal perspective.
Comparison(s)	Patients receiving 4mg zoledronic acid were compared to those who received placebo.
Source of effectiveness data	Effectiveness data were derived from a single study by Saad et al.(2002)
Cost components included and health care resource utilization (HCRU)	The following cost components were included in the study: Direct medical costs, which included hospitalization, outpatient and institutionalization costs. The cost of zoledronic acid in the US was based on the 2002 federal supply schedule from the Department of Veterans Affairs National Formulary. Costs of zoledronic acid outside of the US were based on 2002 ex-factory prices (excluding VAT). In conjunction with the clinical trial resource use data was collected and included information on hospitalization, outpatient visits, treatment, procedures, concomitant medication and institutionalized care.
Time horizon, discount rate	Time horizon: 15 months. Discount rate was not applied.
Results – cost per patient per alternative	The cost per patient receiving zoledronic acid was $5,365 and the cost per patient receiving placebo was $5,689. The difference of $324 was insignificant (95% CI: $1,781, $1,146), and the authors concluded that the incremental cost of the intervention could be calculated as the cost of zoledronic acid and its administration at $5,677 +/- $3,809. Incremental cost-effectiveness ratios (ICERs) and cost-utility ratio were calculated. The ICERs were $12,300 per skeletal related event avoided (95% CI: $6,900, $48,700) and $51,400 per additional patient free of skeletal related events during the trial (95% CI: $26,900, $243,700). The incremental cost per QALY was $159,200 (95% CI: $88,500, $786,600)
Results – effectiveness per patient per alternative	During the trial, 33.2% of patients receiving zoledronic acid and 44.2% of patients receiving placebo experienced skeletal related events. The mean number of skeletal related events per patient was 0.78 in the zoledronic acid group and 1.24 in the placebo group. Confidence intervals and detailed results were not reported.
Results-uncertainty	A sensitivity analysis was performed by varying the following: change in the price of zoledronic acid, community-based utility weights derived from the EQ-5D and the number of days that patient experienced lower quality of life due to

	skeletal related event. The results of variation the within-trial cost of zoledronic acid from $1,000 to $8,000 ($80 to $635 per dose) were reported. The authors reported relatively small differences in incremental cost per QALY when community-based utility weights derived from the EQ-5D was applied. Cost per QALY was about $50,000 when patients were adversely affected for at least 120 days by each skeletal related event and the cost of each dose of $300 and less than $75,000/QALY when the cost per dose was less than $450.
Comments	The analysis was based on a randomized controlled clinical trial, which was appropriate for the study question. The authors conducted a cost study with thorough sensitivity analysis and reported results in an incremental format. Although the study was conducted using patient level data that was collected during the trial, the authors acknowledge study some of its limitation with respect to resource use data and EQ-5D measure. It is reported that resource use data was not collected for about 17% of patients and at the individual study visits 9%-16% of EQ-5D measures were missing. The authors further stress the need for future research of this topic.

Health Economic Quality Checklist

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

Scoring - yes, no, not clear and not appropriate	Study ID	Reed et al. (2004)
	Checklist completed by	EP
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?	Not clear
	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)	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

	Was the primary outcome measure/s for the economic evaluation clearly stated?	Yes
	Were the methods to value health states and other benefits stated?	Yes
	Were the details of the subjects from whom valuations were obtained given?	Yes
	Were any productivity changes (if included) reported separately?	Not applicable
	Was the relevance of any productivity changes to the study questions discussed?	Not applicable
	Were the quantities of resources reported separately from their unit costs?	Yes
	Were the methods for estimation of quantities and unit costs described?	Yes
	Was the currency and price data recorded?	Yes
	Were the details of currency of price adjustments for inflation or currency conversion given?	Yes
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
Analysis and interpretation of results	Was the time horizon of costs and benefits stated?	Yes
	Was the discount rate stated?	No
	Was the choice of discount rate justified?	No
	Was an explanations given if costs or benefits were not discounted?	Yes
	Were the details of statistical tests and confidence rates given for stochastic data?	Yes
	Was the approach to sensitivity analysis given?	Yes
	Was the choice of variables for sensitivity analysis justified?	Yes
	Were the ranges over which the variables are varied stated?	Yes
	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 caveats?	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)?	No
	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	How well was the study conducted? *Code ++, + or –*	++

THE STUDY		
	Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes

Reference List

Mason, M. D., Sydes, M. R., Glaholm, J., Langley, R. E., Huddart, R. A., Sokal, M., Stott, M., Robinson, A. C., James, N. D., Parmar, M. K., Dearnaley, D. P. & Medical Research Council, P. R. (2007) Oral sodium clodronate for nonmetastatic prostate cancer--results of a randomized double-blind placebo-controlled trial: Medical Research Council PR04 (ISRCTN61384873). *J Natl Cancer Inst,* 99: 765-776.

Reed, S. D., J. I. Radeva, et al. (2004). "Cost-effectiveness of zoledronic acid for the prevention of skeletal complications in patients with prostate cancer." *Journal of Urology* 171(4): 1537-1542.

Smith, M. R., Kabbinavar, F., Saad, F., Hussain, A., Gittelman, M. C., Bilhartz, D. L., Wynne, C., Murray, R., Zinner, N. R., Schulman, C., Linnartz, R., Zheng, M., Goessl, C., Hei, Y. L., Small, E. J., Cook, R. & Higano, C. S. (2005) Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. *Journal of Clinical Oncology,* 23: 2918-2925.

What is the clinical and cost-effectiveness of pelvic radiotherapy in patients receiving radical radiotherapy for prostate cancer?

Short Summary

The evidence comprises one large randomised trial (Lawton *et al.* 2005). This trial shows acceptable toxicity and a benefit in biochemical control, which might translate into a more clinically meaningful benefit with longer follow-up.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Patients who are to receive radical radiotherapy	• Prostate + pelvic radiotherapy • field, dose-fractionation and technique	Radiotherapy to prostate alone	• overall survival • biochemical failure free survival • freedom from salvage treatment • side effects • quality of life

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

Evidence Summary

The search identified three RCTs comparing whole pelvic radiotherapy plus prostate boost (WPRT) with prostate only radiotherapy (PORT).The trials differed in their eligibility criteria and use of hormonal therapy. Of these trials RTOG-9413 and GETUG-01 are the most relevant to the clinical question. However, only preliminary results from GETUG-01 are available.

RTOG 7706 This pre-PSA era trial included patients with relatively good prognosis (no evidence of lymph node involvement, by lymphangiogram or surgical staging). Only 5% of the patients received neoadjuvant hormonal therapy.

RTOG 9413 This trial included patients with a predicted risk of lymph node involvement of more than 15%. Patients were randomised to either neoadjuvant (NHT) or adjuvant hormonal therapy (AHT).

GETUG 01 This trial included patients without clinical evidence of lymph node involvement. Neoadjuvant or adjuvant hormonal therapy was limited to patients at high risk of lymph node involvement.

Overall survival (OS)

In RTOG 7706 there was no significant difference between the 12 year OS of the WPRT and PORT groups at median follow up of 12 years (Asbell *et al.* 1998). In RTOG 9413 there was no significant difference between the 5 year OS of the WPRT and PORT groups at median follow up of 5.9 years (Lawton *et al.* 2005). In a preliminary report of GETUG 01, at median follow up of 3.3 years, no significance in 5 year OS was observed (Pommier *et al.* 2005).

Progression free survival (PFS)

In RTOG 9413 WPRT was associated with a 4 year PFS of 54% compared to 47% in the PORT group (p=0.02) (Roach, III *et al.* 2003a). In an update of RTOG 9413 (Lawton *et al.* 2005) 5 year PFS in the group treated with WPRT+NHT (48%) was significantly better in those treated with

PORT+NHT (37%) and WPRT+AHT (38%), but not significantly better than PORT+AHT (40%). Similar results were reported at a median follow-up of 7 years (Lawton *et al.* 2007). The simple comparison between WPRT and PORT was not reported in this update (Lawton *et al.* 2005).

No significant difference in progression free survival was reported in the preliminary report of GETUG 01 (Pommier *et al.* 2005). 5 year PFS was 68% for the WPRT group compared to 64% in the PORT group.

Treatment related toxicity

Meta-analysis of the toxicity reported in RTOG 7706 (Pilepich *et al.* 1987) and RTOG 9413 (Roach, III *et al.* 2003b) suggests that, compared to PORT, WPRT is associated with an increased risk of gastrointestinal toxicity [relative risk = 2.79; 95% CI 1.31 – 5.94], but no increased risk of genitourinary toxicity [relative risk = 0.96; 95% CI 0.61 – 1.48]. The absolute difference in risk, however, is small: 54 patients would need to be treated with WPRT (instead of PORT) to cause on additional patient to experience grade 3 or 4 gastrointestinal toxicity.

The investigators in GETUG 01 did not find a statistical difference between the rates of grade 2 to 4 toxicity in the two treatment arms, but their data were not reported in sufficient detail to be included in the meta-analysis.

Figure 60 meta-analysis of gastrointestinal toxicity

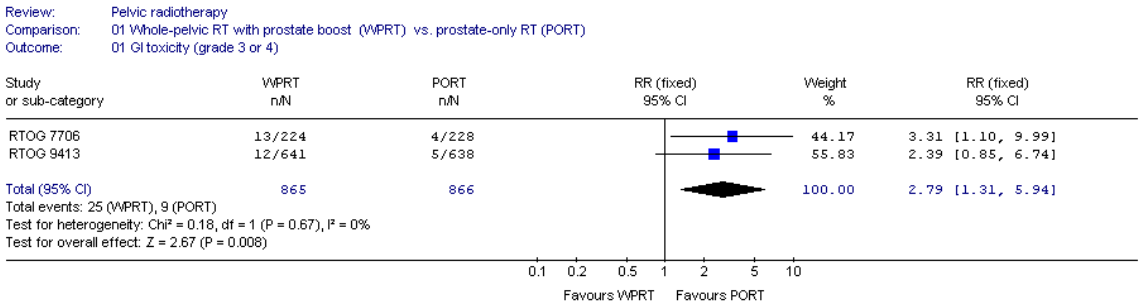
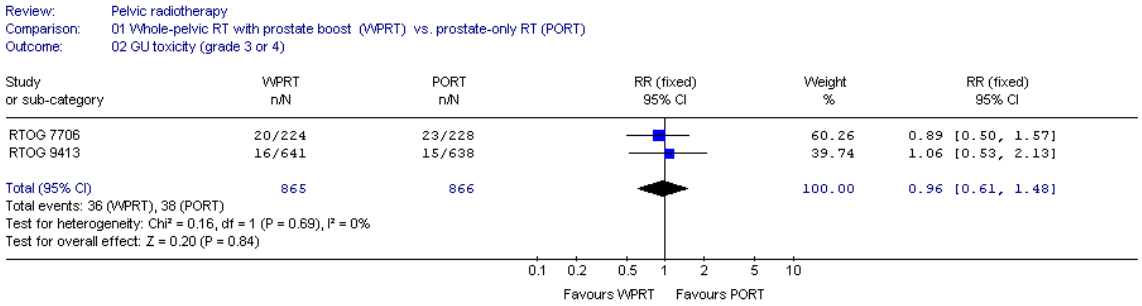


Figure 61 meta-analysis of genitourinary toxicity



Evidence tables

(Asbell *et al.* 1998)

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

Country: United States, setting: Tertiary care

Inclusion criteria Patients with stage A2 (T1bN0M0) or B (T2N0M0) prostate cancer, according to Jewett-Whitmore staging (i.e. no evidence of nodal involvement by lymphangiogram or surgical staging). Patients were entered into the trial (RTOG 77-06) between 1978 and 1983. Randomization was stratified by histological grade, hormonal therapy and method of node evaluation (lymphangiogram or staging laporotomy).

Exclusion criteria Previous radiation therapy or potentially curative surgery. Other cancer (apart from skin cancer).

Population number of patients = 449, age range 46 to 47 years, mean age = 68 years.

Interventions After lymphangiogram (LAG) or staging lymphadenectomy (SL) patients were randomized between prophylactic radiation to the pelvic lymph nodes and prostatic bed vs. prostatic bed alone.

For those randomized to receive prophylactic pelvic lymph nodal irradiation, 45 Gy of megavoltage RT was delivered via multiple portals in 4.5 to 5 weeks, while all patients received 65 Gy in 6.5 to 8 weeks to the prostatic bed.

Outcomes Overall survival, recurrence free survival, distant-metastasis free survival and no-evidence-of-disease (NED) survival. Local or regional failure was defined as either progression of measurable disease at any time, or histological verification of tumour 2 years after radiotherapy. Progression of tumour was defined as at least a 25% increase in the palpable tumour mass dimensions.

Morbidity outcomes for this trial are reported in Pilepich et al (1983,1984,and 1987).

Follow up Follow-up was a median of 12 years and a maximum of 16 years.

Results 117 patients had had staging lymphadenectomy (SL), the remaining 332 had staging lymphangiogram (LAG).

There was no significant difference in survival, NED survival, local control or time to distant metastases, whether treatment was administered to the prostate or prostate and pelvic lymph nodes. Median survival was 10.7 years for the prostate-only group and 10.5 years for the pelvis+prostate group. 12 year survival was 43% and 38% for the two groups respectively [p not significant using the log rank test].

The SL group had greater 12-year overall survival than the LAG group (48% vs. 38%, p = 0.02, log rank test), the LAG group , however, had a greater proportion of older patients

Numeric results

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General comments Pre PSA era study. Multivariate analysis was not done, but would have

been useful for the SL vs. LAG comparison. The authors comment that the accuracy of LAG for staging is questionable, the observed survival difference may be due to this inaccuracy.

(Lawton *et al.* 2005)

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

Country: United States, setting: Tertiary care

Inclusion criteria patients enrolled in RTOG trial 94-13 between 1995 and 1999. All men had histologically confirmed, clinically localised prostate cancer. PSA 100 ng/ml or less. Randomisation was stratified by T stage, PSA and Gleason score. Patients were required to have a predicted risk of lymph node involvement of more than 15% (using Roach's equation derived from the Partin tables). Karnofsky performance status of 70% or more. Liver function tests less than 1.2 times the upper limits of normal.

Exclusion criteria Patients who were surgically staged. Patients with metastatic disease. Prior hormonal therapy, radiotherapy or chemotherapy.

Population number of patients = 1292.

Interventions treatment interventions included: neoadjuvant and concurrent hormonal therapy (NCHT), adjuvant hormonal therapy (AHT), whole-pelvic radiotherapy followed by a boost to the prostate (WPRT), and prostate only radiotherapy (PORT).

Patients were randomised to 1 of 4 treatment arms: WPRT + NCHT, PORT + NCHT, WPRT + AHT or PORT + AHT.

All patients received combined androgen suppression, goserelin acetate 3.6 mg subcutaneously or leuprolide acetate 7.5 mg intramuscularly (both monthly), and flutamide 250 mg orally (daily) for 4 months. Patients receiving NCHT started hormonal therapy 2 months before radiotherapy (RT), and continued it during RT. Patients receiving AHT started hormonal therapy 2 months after completing RT.

RT was given at 1.8 Gy per fraction to a total dose of 70.2 Gy. WPRT used a conventional four field technique (minimum size 16cm X 16 cm) to a maximum central dose of 50.4 Gy followed by an additional 19.8 Gy to the prostate using a cone-down boost technique. PORT was limited to the prostate and seminal vesicles (minimum size 11cm X 11 cm) to a total of 70.2 Gy.

Outcomes Primary endpoint was progression free survival. Progression (treatment failure) was defined as the first occurrence of local, regional or distant disease; PSA failure or death from any cause.

Secondary endpoints were overall survival, local failure, distant metastases and PSA failure. PSA failure was defined using the ASTRO consensus definition of consecutive and significant PSA rises separated by a month. Toxicity was recorded using the RTOG toxicity scoring scale.

Follow up Median follow up of 5.9 years since study entry.

Results Five year PFS for patients treated with WPRT+ NHT, PORT+ NHT, WPRT+ AHT and PORT+ AHT was 48.3%, 36.8%, 38.1%, and 40.4% respectively. Patients treated with WPRT+ NHT, in pair wise comparison analysis, showed better PFS than those treated with PORT+ NHT (p=0.0041) and a statistically significant improvement over WPRT+ AHT (p=0.0045). WPRT+ NHT showed a trend in progression free survival over PORT+ AHT (p= 0.0656).

Five year overall survival for patients treated with WPRT+ NHT, PORT+ NHT, WPRT+ AHT and PORT+ AHT was 81.6%, 77.8%, 75.5%, and 81.2% respectively. There was no significant difference in overall survival between the treatment arms.

(Lawton *et al.* 2007)

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

Country: United States, setting: Tertiary care

Inclusion criteria patients enrolled in RTOG trial 94-13 between 1995 and 1999. All men had histologically confirmed clinically localised prostate cancer. PSA 100 ng/ml or less. Randomisation was stratified by T stage, PSA and Gleason score. Patients were required to have a predicted risk of lymph node involvement of more than 15% (using Roach's equation derived from the Partin tables). Karnofsky performance status of 70% or more. Liver function tests less than 1.2 times the upper limits of normal.

Exclusion criteria Patients staged surgically. Patients with metastatic disease. Prior hormonal therapy, radiotherapy or chemotherapy.

Population number of patients = 1292, age range 44 to 87 years, median age = 70 years.

Interventions treatment interventions included: neoadjuvant and concurrent hormone therapy (NCHT), adjuvant hormone therapy (AHT), whole-pelvic radiotherapy followed by a boost to the prostate (WPRT), and prostate only radiotherapy (PORT).

Patients were randomised to 1 of 4 treatment arms: WPRT + NCHT, PORT + NCHT, WPRT + AHT or PORT + AHT.

All patients received combined androgen suppression, goserelin acetate 3.6 mg subcutaneously or leuprolide acetate 7.5 mg intramuscularly (both monthly), and flutamide 250 mg orally (daily) for 4 months. Patients receiving NCHT started hormone therapy 2 months before radiotherapy (RT), and continued it during RT. Patients receiving AHT started hormone therapy 2 months after completing RT.

RT was given at 1.8 Gy per fraction to a total dose of 70.2 Gy. WPRT used a conventional four field technique (minimum size 16cm X 16 cm) to a maximum central dose of 50.4 Gy followed by an additional 19.8 Gy to the prostate using a cone-down boost technique. PORT was limited to the prostate and seminal vesicles (minimum size 11cm X 11 cm) to a total of 70.2 Gy.

Outcomes Primary endpoint was progression free survival. Progression (treatment failure) was defined as the first occurrence of local, regional or distant disease; PSA failure or death

from any cause.

Secondary endpoints were overall survival, local failure, distant metastases and PSA failure. PSA failure was defined using the ASTRO consensus definition of consecutive and significant PSA rises separated by a month. Toxicity was recorded using the RTOG toxicity scoring scale.

Follow up Median follow-up for patients alive at analysis was 7.0 years (range 2 to 10.4 years).

Results Only toxicity of grade 3 or worse was included in the analysis.

Pairwise comparison of the 4 treatment arms suggested a trend towards improved progression free survival in the WPRT+NHT arm when compared to the WPRT+AHT (p=0.022) and PORT+NHT (p=0.066) arms, but not the PORT+AHT arm (p=0.75).

COMPARISON IN MEN AFTER EBRT FOR PCA	WPRT+NHT	PORT+NHT	WPRT+AHT	PORT+AHT	OVERALL RESULT
Disease progression	198/320	210/316	220/319	199/320	overall there was no significant difference (log rank test, p=0.065)
Death due to any cause	104/320	99/316	130/319	101/320	survival was significantly worse in the WPRT+AHT group (log rank test, p=0.027)
Late GI toxicity	5%	1%	2%	2%	more late GI toxicity with WPRT+NHT (p=0.002)
Late GU toxicity	not reported	not reported	not reported	not reported	no significant group differences (p=0.16)
Acute radiation toxicity	not reported	not reported	not reported	not reported	no significant group differences (p not reported)
Acute hormone toxicity	8%	5%	3%	3%	more acute hormone toxicity with NHT (p=0.003)

General comments The study was not designed to test the interaction between field size and timing of hormone therapy, and was underpowered to detect such an interaction.

(Pilepich *et al.* 1987)

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

Country: United States, setting: Tertiary care

Inclusion criteria Patients with stage A2 (T1bN0M0) or B (T2N0M0) prostate cancer, according to Jewett-Whitmore staging (i.e. no evidence of nodal involvement by lymphangiogram or surgical staging). Patients were entered into the trial (RTOG 77-06) between 1978 and 1983. Randomization was stratified by histological grade, hormonal therapy and method of node evaluation (lymphangiogram or staging laporotomy).

Exclusion criteria Previous radiation therapy or potentially curative surgery. Other cancer (apart from skin cancer).

Population number of patients = 453.

Interventions After lymphangiogram (LAG) or staging lymphadenectomy (SL) patients were randomized between prophylactic radiation to the pelvic lymph nodes and prostatic bed vs. prostatic bed alone.

For those randomized to receive prophylactic pelvic lymph nodal irradiation, 45 Gy of megavoltage RT was delivered via multiple portals in 4.5 to 5 weeks, while all patients received a minimum 65 Gy (maximum 72 Gy) in 6.5 to 8 weeks to the prostatic bed.

Outcomes Treatment related morbidity. Morbidity was classified using a grading system (RTOG scale?), ranging from grade 1 (minor symptoms requiring no treatment) to grade 5 (fatal complications). Treatment related reactions occurring during the radiotherapy course were not labelled as complications unless they persisted beyond the first month after treatment completion or were classified as grade 3 or higher.

Follow up The minimum follow up was 2 years, median was 5 years.

Results Pelvic irradiation (WPRT), compared to prostate irradiation only, (PORT) was not associated with a significantly increased incidence of treatment related morbidity.

Bowel morbidity rates (any grade, WPRT vs. PORT) : diarrhoea (14% vs. 9%), proctitis (10% vs. 11%), rectal/anal stricture (5% vs. 1%), rectal bleeding (10% vs. 13%) and rectal ulcer (2% vs. 0%).

Genitourinary morbidity rates (any grade, WPRT vs. PORT) : cystitis (11% vs. 12%), haematuria (6% vs. 11%), and urethral stricture (7% vs. 7%).

In general a significant effect of prostate radiation dose on morbidity was not observed. Total doses to the prostate of more than 70 Gy, however, were associated with an increased risk of rectal bleeding ($p<0.01$, Mantel-Haenszel test stratified by grade).

Numeric results

Comparison: Whole pelvic radiotherapy plus prostate boost versus prostate-only radiotherapy

	WPRT	PORT
GI toxicity (grade 3 or higher)	13/224	4/228
	WPRT	PORT
GU toxicity (grade 3 or higher)	20/224	23/228

(Roach, III *et al.* 2003c)

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

Country: United Kingdom, setting: Tertiary care

Inclusion criteria Patients enrolled in RTOG trial 94-13 between 1995 and 1999. All men had histologically confirmed, clinically localised prostate cancer. PSA 100 ng/ml or less. Randomisation was stratified by T stage, PSA and Gleason score. Patients were required to have a predicted risk of lymph node involvement of more than 15% (using Roach's equation derived from the Partin tables). Karnofsky performance status of 70% or more. Liver function tests less than 1.2 times the upper limits of normal.

Exclusion criteria Patients who were surgically staged. Patients with metastatic disease. Prior hormonal therapy, radiotherapy or chemotherapy. Liver function tests 1.2 times the upper limits of normal.

Population number of patients = 1292, median age = 70 years.

Interventions Treatment interventions included: neoadjuvant and concurrent hormonal therapy (NCHT), adjuvant hormonal therapy (AHT), whole-pelvic radiotherapy followed by a boost to the prostate (WPRT), and prostate only radiotherapy (PORT).

Patients were randomised to 1 of 4 treatment arms: WPRT + NCHT, PORT + NCHT, WPRT + AHT or PORT + AHT.

All patients received combined androgen suppression, goserelin acetate 3.6 mg subcutaneously or leuprolide acetate 7.5 mg intramuscularly (both monthly), and flutamide 250 mg orally (daily) for 4 months. Patients receiving NCHT started hormonal therapy 2 months before radiotherapy (RT), and continued it during RT. Patients receiving AHT started hormonal therapy 2 months after completing RT.

RT was given at 1.8 Gy per fraction to a total dose of 70.2 Gy. WPRT used a conventional four field technique (minimum size 16cm X 16 cm) to a maximum central dose of 50.4 Gy followed by an additional 19.8 Gy to the prostate using a cone-down boost technique. PORT was limited to the prostate and seminal vesicles (minimum size 11cm X 11 cm) to a total of 70.2 Gy.

Outcomes Primary endpoint was progression free survival. Progression (treatment failure) was defined as the first occurrence of local, regional or distant disease; PSA failure or death from any cause.

Secondary endpoints were overall survival, local failure, distant metastases and PSA failure. PSA failure was defined using the ASTRO consensus definition of consecutive and significant PSA rises separated by a month. Toxicity was recorded using the RTOG toxicity scoring

scale.

Follow up Median follow up was 5 years

Results WPRT was associated with a 4-year PFS of 54% compared with 47% in patients treated with PORT (p =0.02). Patients treated with NCHT experienced a 4-year PFS of 52% versus 49% for AHT (p =0.56). When comparing all four arms, there was a progression-free difference among WPRT + NCHT, PORT + NCHT, WPRT + AHT, and PORT + AHT (60% vs. 44% vs. 49% vs. 50%, respectively; p =.008).

There was no grade 5 (fatal) toxicity. The 2 year rates of late grade 3 or 4 gastrointestinal toxicity were 1.7% and 0.6% the WPRT and PORT arms respectively (p=0.09). The corresponding rate of genitourinary toxicity was 2% in both groups (p=0.85).

For acute grade 3 or 4 toxicity: there was a tendency towards more GI toxicity with WPRT than PORT (2% vs. 1%, p=0.06), but not much difference in GU toxicity (3% vs. 4%. p=0.39).

(Pommier *et al.* 2005)

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

Country: France, setting: Tertiary care

Inclusion criteria Histologically proven PCa, clinical stage T1b, N0, and M0 to T3, N0, and M0. No metastases by bone scan or chest x-ray. At least one month since prior transurethral resection. At least 2 to 6 months since prior hormonal therapy. Age 75 or younger. Life expectancy of 10 years or more. Karnofsky performance status of 70 or more. Randomisation was stratified into high and low risk groups, using Gleason score, clinical stage and PSA level.

Exclusion criteria Concurrent LHRH agonists, anti-androgen or hormonal therapy (short term (6 months) concurrent or neoadjuvant hormonal therapy was allowed for high risk patients). Prior pelvic radiotherapy. Prior lymphadenectomy, prostatectomy or surgical castration. Other malignancy (except basal cell carcinoma). Adenopathy.

Population number of patients = 444, age range 50 to 75 years, median age = 70 years.

Interventions One arm (group A) of the trial received pelvis and prostate radiotherapy (RT), the other arm (group B) received prostate-only radiotherapy.

The median pelvis RT dose was 46 Gy in group A. The total dose recommended to the prostate changed from 66 Gy (first 3 years) to 70 Gy. The median dose to the prostate was 68.4 Gy in both groups.

Outcomes Study was planned with 5 year progression free survival (PFS) as the primary endpoint. Progression was defined as PSA recurrence (RTOG criteria) or clinical evidence of local or distant recurrence. Acute and late toxicities were recorded according to the RTOG and LENT-SOMA scales. Quality of life was recorded using the EORTC QLQ-C30, IPSS and SFI scales.

Follow up Median follow up for this preliminary report is 3.3 years.

Results Progression rates were 18% in group A and 17% in group B. Using the Kaplan-Meier method, 5-year PFS was 67.8% [95%CI, 59.5-76.2] and 63.6% [95%CI, 54.2-72.9] in groups A and B respectively.

Acute toxicity (grade 3 or 4) rates were 1.8% and 2.4% for the digestive tract in groups A and B respectively (p=0.70). For the urinary tract the corresponding rates were 3.2% and 8.1% (p=0.02).

Late toxicity (grade 2,3 or 4) rates were 27.8% and 24.6% for the digestive tract in groups A and B respectively (p=0.50). For the urinary tract the corresponding rates were 36.6% and 41.2% (p=0.30).

The authors report that there was no significant change in quality of life 1 year after treatment in either group.

General comments This preliminary analysis reports progression free survival at a median follow up of 3.3 years, too early to comment on the primary endpoint of progression free survival. The number of patients in each treatment arm is not reported, cannot use this study for meta-analysis.

Health Economic Summary

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

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Roach, M., III, DeSilvio, M., Lawton, C., Uhl, V., Machtay, M., Seider, M. J., Rotman, M., Jones, C., Asbell, S. O., Valicenti, R. K., Han, S., Thomas, C. R., Jr., Shipley, W. S. & Radiation Therapy Oncology Group (2003a) Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413.[see comment]. *Journal of Clinical Oncology,* 21: 1904-1911.

6 Hormone therapy

6.1 Hormone therapy in metastatic disease

Is intermittent hormone therapy as effective as continuous hormone therapy in men receiving long-term hormonal therapy for prostate cancer?

Rationale

The function of hormone therapy is to stop testosterone feeding prostate cancer and encouraging growth. The reason for the question is because men on hormonal therapy are generally kept on treatment long-term ie other treatments are added but hormone therapy remains constant. There are reported side-effects of treatment and other believed (metabolic) problems of androgen suppression and mainly with long-term treatment. What we don't know is if stopping treatment at an agreed positive response(ie PSA/symptomatic –not yet agreed) and re-starting at a PSA or symptom concern level (not yet agreed) equally controls cancer progression (overall survival, cancer specific survival, symptoms; disease progression) and by being off treatment are the side-effects improved. Bearing in mind that testosterone is not automatically back to normal immediately and usually takes 6 months, maybe a year, or even longer or perhaps not at all. Therefore, once treatment is stopped how long does it take for the PSA/symptoms to necessitate re-starting treatment and within this time have the side-effects improved? Basically can we safely stop then re-start hormone therapy under parameters and does the duration off treatment allow for improvement of side-effects?

In addition prostate cancer becomes 'resistant' to hormone therapy after a period of typically 2 to 3 years. It may be that intermittent use reduces the drive for the cancer cells to develop resistance and thereby prolongs the overall duration of response. The parallel concern is that by allowing the cancer cell to regenerate and proliferate during periods without hormone therapy it may have an opportunity to develop further than if continually suppressed by hormone therapy.

There is also a cost-implication if not requiring constant treatment.

PICO question

Population	Intervention	Comparison	Outcomes
Men receiving long-term hormonal therapy for prostate cancer	Intermittent hormone therapy	Continuous hormone therapy	• Overall survival • Progression free survival (not biochemical) • Treatment-related morbidity • Treatment-related mortality • Adverse events • Patient acceptability • Health-related quality of life

How the information will be searched

Sources to be searched	
Can we apply date limits to the search	This topic is an update of one in the original 2008 guideline so we will search for studies published since.

Are there any study design filters to be used (RCT, systematic review, diagnostic test).	A randomised trials filter will be used
List useful search terms.	

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results?	We will use the evidence table for randomised trials (NICE guidelines manual appendix J).
Which quality checklist will we use for appraisal?	The RCT checklist will be used (NICE guidelines manual appendix C).
List subgroups here and planned statistical analyses	Time to events meta-analysis will be done for survival outcomes. Dichotomous outcomes will be meta-analysed using risks ratios or odds ratios.

Methods

Search strategy

The full strategy will be available in the full guideline. We restricted the search to randomized trials and systematic reviews of such trials.

Selection of studies

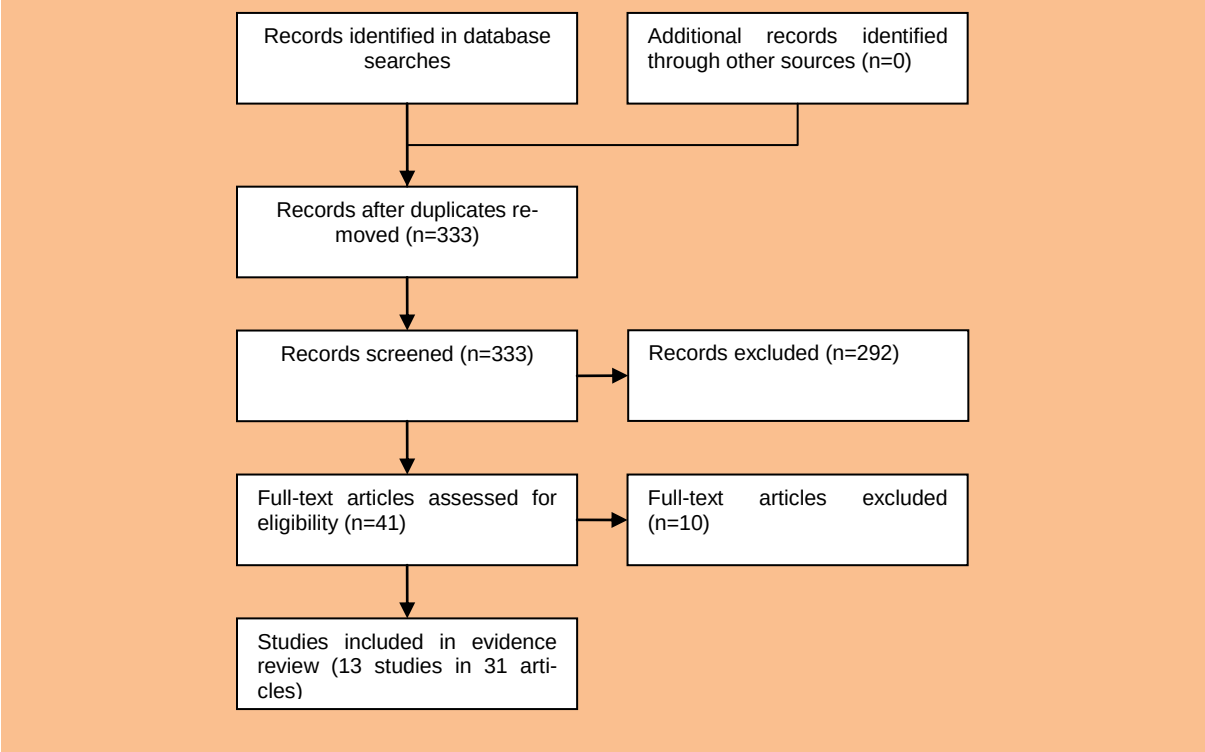
The information specialist (EH) did the first screen of the literature search results. One reviewer (NB) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO question. The full articles were then obtained for possibly eligible studies and checked against the inclusion criteria.

Analysis

For outcome where time to the event was important (overall and progression free survival) time to events meta-analysis was done using methods described in Tierney et al (2007). Adverse events were treated as dichotomous outcomes for meta-analysis using whatever classification was used in the original studies.

Results

Results of the literature searches



The literature searches identified 333 possibly relevant publications of which 37 were ordered as full text articles and 31 included which referred to 13 studies.

Characteristics of included studies

The characteristics of included studies are summarised in Table 112. Three of the 21 included studies were only available as abstracts and three of the studies did not report any useful results. (Schasfoot 2003; Tunn 2003; Yamanaka 2005).

Types of patients

Five studies were in men with advanced or locally advanced disease (Calais da Silva 2009; De Leval 2002; Miller 2007; Schasfoort 2002). Five studies included only men with bone metastases (Mottet 2009; Hering 2000; Verhagen 2008; Dutkiewicz 2012; Hussain 2013). Two studies included men with biochemical relapse after prostatectomy (Tunn 2003) or radiotherapy (Crook 2011).

Hormone therapies

Most studies used complete androgen blockade with an LHRH agonist and anti-androgen. Two studies, in men with bone metastases, used cyproterone acetate only (Verhagen 2008; Hering 2000). One study used an LHRH agonist alone (Yamanaka 2005).

Criteria for stopping and starting intermittent hormone therapy

Serum PSA < 4 ng/ml was the typical criteria for stopping treatment in men receiving intermittent hormone therapy. Serum PSA > 10 ng/ml or symptomatic progression were typical criteria for restarting hormone therapy.

Evidence statements

Overall survival

Moderate quality evidence from five randomized trials (Crook 2011; Calais da Silva 2009; Hussain 2013; Salonen 2013; Mottet 2009) (see Figure 62) shows no significant difference in overall survival between men treated with intermittent hormone therapy and those treated with continuous hormone therapy (p=0.17).

Miller et al (2007) reported no significant difference between intermittent and continuous therapy groups in overall survival, but did not supply sufficient information to be included in the effect size estimate.

Progression free survival

Low quality evidence from two randomized trials (Calais da Silva 2009; Hussain 2013) found no significant difference in progression-free survival between intermittent and continuous therapy (see Figure 63). However, both trials included both clinical and biochemical progression in their definition of disease progression.

Two studies (Dutkiewicz 2012; Mottet 2009) provided very low quality evidence of no significant difference between intermittent and continuous treatment groups for clinical progression. One other randomised trial (Miller 2007) found no significant difference between the progression-free survival of the treatment groups, but did not supply sufficient information to estimate effect size.

Crook et al (2011) and De Leval et al (2002) both reported better hormone resistance-free survival with intermittent than with continuous therapy (see Figure 64). However their results were heterogeneous and could not be pooled.

Treatment-related mortality

This outcome was not reported in any of the studies.

Adverse events

Any adverse events

One moderate quality study (Mottet 2009) found the incidence of treatment-emergent adverse events to be borderline significantly higher in the continuous treatment group (p=0.042). However, two studies (Miller 2007; Salonen 2013) provided low quality evidence of no significant difference in the rates of adverse events between intermittent and continuous treatment arms (but no figures given). Crook et al (2011) reported no significant difference between treatment arms in the rate of cardiovascular events or osteoporotic fractures (but did not provide figures).

Hering et al (2000) observed fewer mild adverse events (gastrointestinal, gynaecomastia and fatigue) and severe adverse events (severe nausea/vomiting and oedema of the lower limb) with intermittent than with continuous therapy (RR 0.29 and 0.15 respectively).

Hot flushes

Low quality evidence from two randomized trials (Crook et al 2011 and Calais da Silva et al 2009) suggests that hot flushes are significantly less likely with intermittent than with continuous hormone therapy. While both studies reported fewer hot flushes with intermittent therapy (RR 0.66 and 0.97 respectively) there is uncertainty about the size of the effect due to heterogeneity (see Figure 65).

Gynaecomastia

Moderate quality evidence from one randomized trial (Calais da Silva et al 2009) shows gynaecomastia is less likely in men treated with intermittent than with continuous hormone therapy (RR 0.64 [95% CI 0.43, 0.93]). The evidence suggests that for every 100 men treated with intermittent instead of continuous therapy there would be seven fewer cases of gynaecomastia.

Crook et al (2011) reported patients receiving intermittent had significantly less gynaecomastia than those receiving continuous therapy (p<0.001 but no effect size was reported).

Sexual function

Low quality evidence from one randomized trial (Calais da Silva et al 2009) suggests sexual activity within the previous month was more likely during intermittent therapy than during continuous therapy (RR 2.90 [95% CI 1.52 to 5.53]). The evidence suggests for every 100 men treated with intermittent instead of continuous therapy there would be an additional 18 reporting sexual activity within the previous month.

Low quality evidence from one randomized trial (Hering et al,2000) found impotence was much less likely in men receiving intermittent than in those on continuous therapy (RR 0.06 [95% CI 0.01 to 0.28]).

Crook et al (2011) reported patients receiving intermittent had significantly greater desire for sexual activity and better erectile function than those receiving continuous therapy (p<0.001 but no effect sizes reported). Miller et al (2007) self assessed sexual activity better with intermittent therapy (but no effect sizes were reported).

Patient acceptability

This outcome was not reported in any of the studies

Health-related quality of life

Very low quality evidence from five randomized trials (Crook 2011; Miller 2007; Verhagen 2008; Hussain 2013; Salonen 2013) suggests better quality of life with intermittent than with continuous therapy. Crook et al (2011) reported patients receiving intermittent had significantly better physical function than those receiving continuous therapy (p<0.001 but no other figures reported). Miller et al (2007) self assessed overall health better with intermittent therapy (but no figures given). Verhagen et al (2008) scores on physical and emotional domains of the EORTC QLQ C30 were better in the intermittent than continuous therapy groups (but no figures were provided). There was no significant difference between groups in role and social function domains. Cognitive function was reduced from its baseline value in the intermittent group but not in the continuous group.

Hussain et al. (2013) found that those in the intermittent group were significantly less likely to report impotence (p<0.001) or poor mental health (p=0.003) at 3 months. At 9 months patients in the intermittent group were more likely to report high libido (p=0.01) and less likely to report impotence (p<0.001). However, at 15 months there remained no significant difference between groups in any of the quality of life outcomes.

Salonen et al. (2013) found significant differences in sexual functioning but not activity limitation or physical capacity, favouring intermittent treatment at a median follow-up of 65 months, but did not report individual scores or outcomes of other domains.

One moderate quality study (Mottet 2009) did not find any significant difference between the treatment groups using the QLQ-C30 but did not provide figures.

Figure 62 Forest plot of overall survival

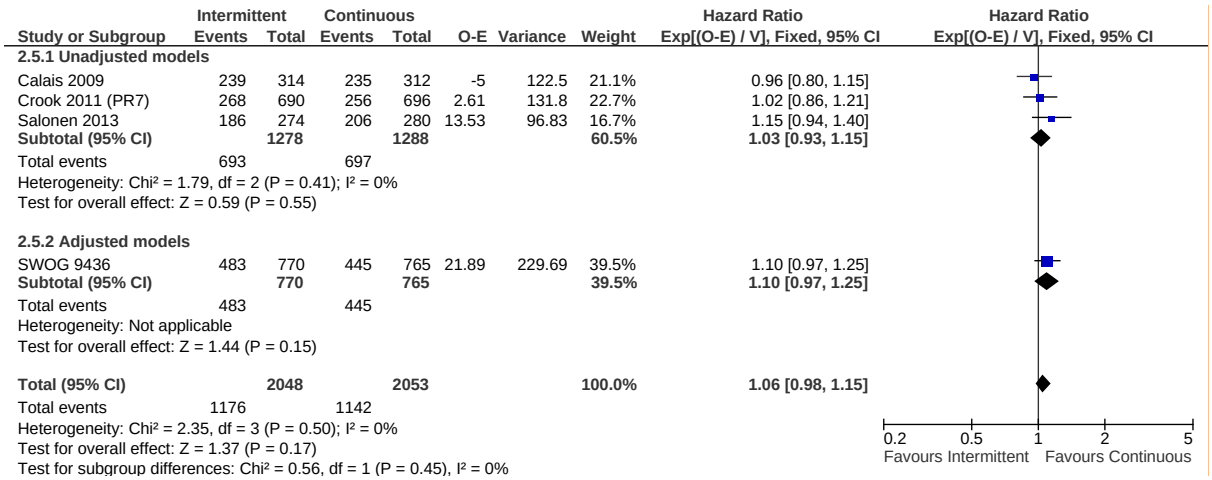
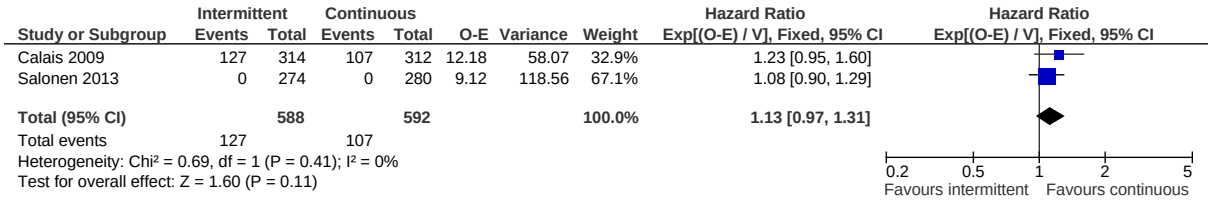
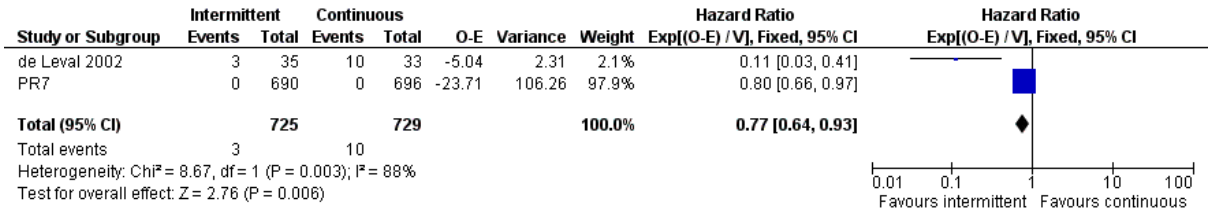


Figure 63 Forest plot of progression-free survival



*The number of men experiencing disease progression was not reported in Salonen (2013) – but the hazard ratio was available.

Figure 64 Forest plot of hormone resistance free survival*



*The number of men experiencing hormone resistance was not reported in PR7 (Crook et al, 2011) – but the hazard ratio was available.

Figure 65 Forest plot of hot flushes

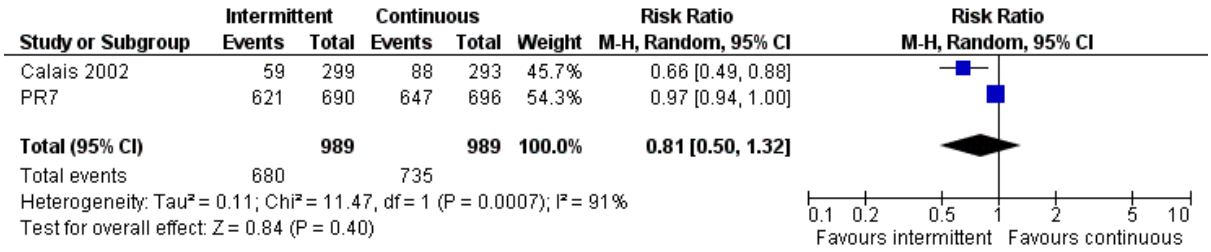


Table 112 Summary of study characteristics

Abbreviations: CPA, cyproterone acetate; RCT, randomised controlled trial; LHRH, luteinizing hormone-releasing hormone.

Study	Study type	Study period	Number of patients	Prostate cancer characteristics	Hormone therapy	Intermittent arm: stop treatment PSA criteria	Intermittent arm: resume treatment PSA criteria	Additional comments
Calais da Silva et al (2009; 2011) (SEUG)	RCT	Not reported	Enrolled 766 Randomised 626 Intermittent 314 Continuous 312	Locally advanced or advanced	LHRH agonist + CPA 200 mg/day	< 4ng/ml < 80% of baseline (if nadir > 4ng/ml)	≥ 10 ng/ml with symptoms ≥ 20 ng/ml in asymptomatic men. ≥ 20% above nadir (if nadir > 4ng/ml).	Also included survival and QOL data from 2011 abstracts
Crook et al (2011) (PR7)	RCT	1999-2006	Enrolled 1386 Randomised 1386 Intermittent 690 Continuous 696	Biochemical relapse after primary or salvage radiotherapy, non-metastatic disease	Any commercially available LHRH agonist + anti-androgen.	Normal PSA level	≥ 10 ng/ml	
De Leval et al (2002)	RCT	1995-2000	Enrolled 77 Randomised 68 Intermittent 35 Continuous 33	Locally advanced, advanced or recurrent	Goserelin acetate 3.6 mg/month + flutamide 250 mg 3 times a day	< 4ng/ml	≥ 10 ng/ml	
Dutkiewicz et al. (2012)	RCT	Not reported	Enrolled 63 Randomised 63 Intermittent 31 Continuous 32	Metastatic (T3NxM1b); Gleason 6-7; intolerance to flutamide	Goserelin acetate LA + bicalutamide 50 mg intermittently +/- finasteride continuously	<0.2 ng/ml	> 0.2 ng/ml	Continuous group also adhered to PSA criteria but continued finasteride
Hering et al (2000)	RCT	1994-1996	Enrolled ? Randomised 43 Intermittent 25 Continuous 18	Bone metastases	CPA 200 mg/day	Unclear	> 10 ng/ml (if nadir PSA <20 ng/ml) >50% above nadir (if nadir > 20ng/ml).	Portuguese language
Hussain et al. (2013)	RCT	1995-2009	Enrolled 3040 Randomised **1749** Intermittent 770 Continuous 765	Metastatic; PSA ≥ 5 ng/ml falling to ≤ 4 ng/ml after 7 months induction	LHRH + antiandrogen (usually goserelin + bicalutamide)	≤ 4 ng/ml	≥ 20 ng/ml	
Miller et al (2007)	RCT	Not reported	Enrolled? Randomised 355 Intermittent ? Continuous ?	Locally advanced or advanced	Goserelin + bicalutamide	Not reported	Not reported	Abstract only
Mottet et al (2009 & 2012)	RCT	Not reported	Enrolled 383 Randomised 173 Intermittent 86 Continuous 83	Bone metastases & PSA >20 ng/ml	Leuproreline 3.75 mg/month + flutamide 750 mg/day	< 4ng/ml	≥ 10 ng/ml Or symptomatic progression	
Salonen et al. (2013)	RCT	1997-2010	Enrolled 852 Randomised 554	Locally advanced; PSA > 20 ng/ml or metastatic; PSA < 10	Goserelin acetate (3.6 mg every 28 days) or bilateral	< 10 ng/ml or by at least 50% of baseline	> 20 ng/ml or above baseline	

Study	Study type	Study period	Number of patients	Prostate cancer characteristics	Hormone therapy	Intermittent arm: stop treatment PSA criteria	Intermittent arm: resume treatment PSA criteria	Additional comments
			Intermittent **274** Continuous **280**	ng/ml or < 50% after 24 weeks ADT	orchidectomy (in continuous only)			
Schasfoort et al, 2002. (TULP)	RCT	1998 - 2001	Enrolled 290 Randomised 193 Intermittent 97 Continuous 96	Locally advanced or advanced	Buserelin depot + nilutamide	< 4ng/ml	>10 ng/ml (for N0-3M0) >20 ng/ml (for N0-3M1)	Abstract only
Tunn et al (2003) & Tunn et al. (2012)	RCT	1998 - 2005	Enrolled 244 Randomised 201 Intermittent 109 Continuous 92	Biochemical relapse (PSA ≥ 1 ng/ml) within 3 months of prostatectomy	Leuproreline depot (11.25 mg 3-month depot) + cyproterone acetate (200 mg/day) for first 4 weeks	<0.5 ng/ml	≥ 3 ng/ml on two consecutive months	
Verhagen et al (2008)	RCT	Not reported	Enrolled 366 Randomised ? Intermittent ? Continuous ?	Bone metastases	CPA 100 mg twice daily	Not reported	Not reported	Abstract only
Yamanaka et al (2005)	RCT	2001-2003	Enrolled 215 Randomised 162 Intermittent 80 Continuous 82	Locally advanced	Leuoporelin or goserelin	<1.0 ng/ml	≥ 10 ng/ml Or clinical recurrence of disease	

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Excluded studies

Intervention not in PICO

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Expert review

Boccon-Gibod, L., Hammerer, P., Madersbacher, S., Mottet, N., Prayer-Galetti, T., & Tunn, U. (2007). The role of intermittent androgen deprivation in prostate cancer. [Review] [40 refs]. BJU International, 100, 738-743.

Buchan, N. C. & Goldenberg, S. L. (2010). Intermittent androgen suppression for prostate cancer. [Review]. Nature Reviews Urology, 7, 552-560.

Sharifi, N., Gulley, J. L., & Dahut, W. L. (2010). An update on androgen deprivation therapy for prostate cancer. [Review]. Endocrine-Related Cancer, 17, R305-R315.

Tsai, H-T. Comparative efficacy of intermittent vs. continuous androgen deprivation therapy in advanced prostate cancer: A meta-analysis. Pharmacoepidemiology and Drug Safety 2012; Conference(var.pagings): 239-240.

Zhu, J. Intermittent androgen blockade or continuous androgen blockade in advanced prostate cancer: A meta-analysis of efficacy, qualityof life and side effects. Journal of B 2012; 17(2): 350-356.

Duplicate

Calais Da, SF. Phase III study of intermittent mab vs continuos mab. Journal of Urology 2011; Conference(var.pagings): 4

Study type – non-RCT

Calais Da Silva, FM. Pooled analysis of two protocols of intermittent hormonal therapy in advanced prostatic cancer. Journal of Urology 2012; 187(4): E317-E317.

Outcomes

Moinpour, C. Preliminary quality-of-life outcomes for SWOG-9346: Intermittent androgen deprivation in patients with hormone-sensitive metastatic prostate cancer (HSM1PC)-Phase III. Journal of Clinical Oncology 2012; Conference(var.pagings): 15

6.2 Managing the complications of hormone therapy

6.2.1 Cardiovascular effects

What are the adverse cardiovascular effects of long-term androgen deprivation and how prevalent are they?

Rationale

NICE clinical guidelines for prostate cancer recommend hormone therapy as a treatment option for men with locally advanced and advanced (metastatic) prostate cancer, although it can also be offered to men with high risk localised prostate cancer. Androgen suppression blocks the production of androgens including testosterone, with the aim of slowing the growth of prostate cancer cells. The resulting decrease in testosterone levels over a long term can lead to adverse effects, which may include cardiovascular effects. The prevalence of cardiovascular effects is unclear, for androgen suppression therapies as a whole, as well as for the different types of therapies.

PICO question

Population	Intervention	Comparator	Outcomes
Men with prostate cancer	Androgen deprivation therapy	No androgen deprivation therapy	• Cardiovascular mortality • Cardiovascular morbidity • Cerebrovascular accident mortality • Cerebrovascular accident morbidity • Thromboembolic events

How the information will be searched

Sources to be searched	
Can we apply date limits to the search	No date limits
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	No study design filter – although it may be appropriate to limit the evidence to large cohort studies.
List useful search terms.	

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? List subgroups here and planned statistical analyses	We will use the evidence table for cohort studies (NICE guidelines manual appendix J). The cohort studies checklist will be used (NICE guidelines manual). Subgroup analyses according to type of hormone therapy. 1) Surgical Orchiectomy (orchidectomy) - castration 2) LHRH agonists – medical castration 3) LHRH antagonists – medical castration 4) Androgen receptor blockade (Casodex [bicalutamide], Flutamide, cyproterone acetate) 5) Oestrogens (Stilboesterol) 6) Novel AR blockers or drugs that block androgen synthesis – Abiraterone; MDV3100)

Methods

Selection of studies

The information specialist (EH) did the first screen of the literature search results. Two reviewers (NB and KC) then selected possibly eligible studies by comparing their title and abstract to the inclu-

sion criteria in the PICO question. The full articles were then obtained for possibly eligible studies and checked against the inclusion criteria. Conference abstracts of non-RCT studies were excluded.

Analysis

Outcomes were summarised into five groups: cardiovascular mortality, cerebrovascular accident mortality, cardiovascular morbidity, cerebrovascular accident morbidity, and thromboembolic events. The following events were included in these outcomes:

Cardiovascular

Included: coronary heart disease, cardiac event, cardiac arrest, heart failure, arrhythmia, myocardial infarction

Thromboembolic

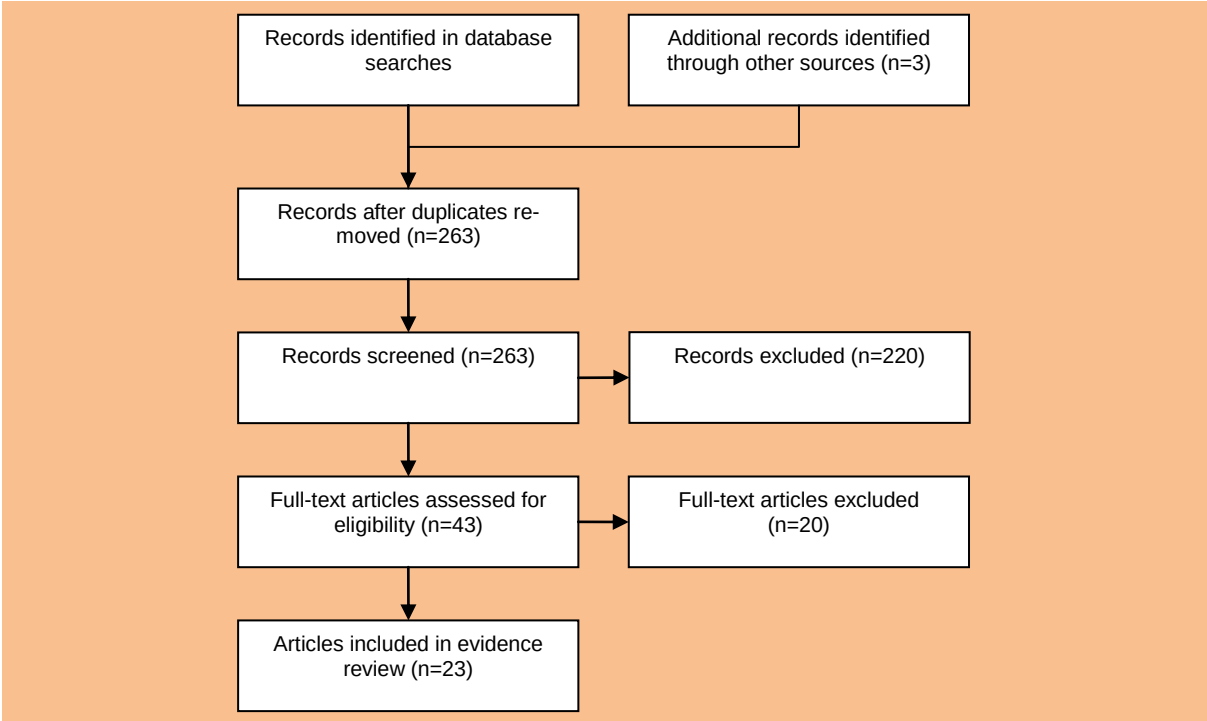
Included: deep venous thrombosis, pulmonary embolism

Excluded: arterial embolism, peripheral arterial disease

All outcomes were dichotomous. Any information relating to the incidence of these events was summarised e.g. raw incidence rate, incidence per 1,000 person-years, hazard ratios, standardised mortality/incidence ratios. Where the number of cases/deaths was reported, data were pooled into a meta-analysis and risk ratios calculated. Where available, data for different types of hormone therapy were summarised in sub-group analyses.

Results

Results of the literature searches



The literature searches identified 263 possibly relevant articles (including three identified from the reference list of an identified systematic review and 12 from the update search) of which 43 were ordered in full text. Twenty-three articles referring to 19 different studies were included.

Characteristics of included studies

The characteristics of included studies are summarised in Table 116. Three of the studies were randomised controlled trials (RCTs) and one was a pooled analysis of the results of multiple RCTs. The remaining 15 were cohort studies, of which three were prospective and eleven were retrospective analyses. For one retrospective cohort study, only an abstract was available (Blood 2010).

Seven (37%) of the studies reported a median length of follow-up greater than 5 years (Alibhai 2009; D'Amico 2007; Efstathiou 2009; Hu 2012; Kim 2011; McLeod 2006; Merrick 2006). Length of follow-up was not reported by seven (37%) of the studies (Blood 2010; Chung 2012; Punnen 2011; Roach 2008; Saigal 2007; Wilcox 2012; Jespersen 2013).

One abstract reporting the outcome of a systematic review and meta-analysis was also found.

Definition of outcome

Five studies reported cardiovascular mortality as an outcome (see Table 113); Blood et al. (2010) simply defined this as death from any cardiac or vascular diseases, or stroke. Of the remaining four studies, all included deaths from myocardial infarction, sudden cardiac death, coronary artery disease, and arrhythmia. Three of the studies included death from stroke as cardiovascular mortality (Blood 2010; Kim 2011; Tsai 2007) and three specified death from cardiac ischemia to be included (Punnen 2011; Tsai 2007; Kim 2011). One study (Kim 2011) included deaths from diabetes mellitus as cardiovascular mortality; this outcome has not been extracted individually from studies included in this review. Only one study (Saigal 2007) reported cardiovascular morbidity as an outcome and no definition was provided.

Two studies reported the incidence of thromboembolic events; Ehdaie et al. (2012) defined these as a primary diagnosis of deep venous thrombosis, pulmonary embolism, or arterial embolism. However, van Hemelrijck et al. (2012) defined these as a primary diagnosis of deep venous thrombosis only.

Table 113 Definitions of outcomes used in studies

Outcome	Definition	Study
Cardiovascular mortality	Death from cardiac or vascular disease, or stroke	Blood et al. (2010)
	Death from acute myocardial infarction, sudden cardiac arrest or death, coronary artery disease, cardiac ischemia, or malignant arrhythmia	Punnen et al. (2011)
	Death from acute myocardial infarction, sudden cardiac death, fatal arrhythmia, atherosclerosis, coronary artery disease, ischemic heart disease, cerebrovascular accident, congestive heart failure, or diabetes mellitus.	Kim et al. (2011)
	Death from acute myocardial infarction, sudden cardiac arrest or death, coronary artery disease, cardiac ischemia, malignant arrhythmia, or thromboembolic disease (e.g. pulmonary embolism or cerebrovascular accident).	Tsai et al. (2007)
	Death from coronary artery disease, cardiovascular disease, congestive heart failure, cardiac arrest, cardiomyopathy, cardiovascular arrhythmia, myocardial infarction, or sudden death.	Efstathiou et al. (2009)
Cardiovascular morbidity	Not defined.	Saigal et al. (2007)
Thromboembolic event	Deep venous thrombosis, pulmonary embolism, or arterial embolism.	Ehdaie et al. (2012)
	Deep venous thrombosis.	van Hemelrijck et al. (2012)

Population

Of the studies reporting this information, nine were based in the US, three in Canada, one in China, one in Denmark, and one in Sweden. The three remaining studies were based across multiple countries and, in two cases, multiple continents.

The majority (74%) did not specify the clinical stage for inclusion but nine (47%) of the studies report excluding metastatic disease. Three studies included only patients with stage T1-T3a disease (Merrick 2006; Punnen 2011; Tsai 2007). One study (Roach 2008) included only men with stages T2-T4 and one study (Efstathiou 2009) included only men with stage T3 disease or regional lymphatic involvement.

Treatment

Ten (53%) studies included both medical and surgical treatment in the hormone therapy group studied. The remaining nine studies included medical hormone therapy, with or without local treatment, only. Eight of these included patients treated with LHRH agonists with (six studies) or without (three studies) anti-androgens. Only one study (McLeod 2006) included only patients treated with anti-androgens and standard care in the hormone therapy group. At least ten (53%) of the studies included patients treated with local therapy in addition to hormone therapy in the hormone therapy treatment group.

Though all studies included patients receiving medical hormone therapy, only two reported the median duration of medical hormone therapy given; this was 4.1 months in combination with local therapy (Tsai 2007) and 4.2 years in combination with radiotherapy (Efstathiou 2009). Two RCTs report that patients received 2 months (Roach 2008) or 6 months (Wilcox 2012) of medical hormone therapy. Alibhai et al. (2009) also report that they excluded patients receiving less than 6 months of medical hormone therapy. Six of the studies (Hu 2012; Alibhai 2009; Merrick 2006; Kim 2011; Ehdaie 2012; D'Amico 2007) undertook sub-group analyses, where patients were categorised by duration of hormone therapy.

Evidence statements

Cardiovascular mortality

Eleven studies provided low quality evidence on cardiovascular mortality in patients receiving hormone therapy. Five of these studies reported cardiovascular disease (CVD) as an outcome and varied in their inclusion of types of event. The reported raw incidences of death from cardiovascular disease ranged from 1% to 14% in those receiving hormone therapy (alone or combined with local therapy), compared to between 1% and 11% in those not receiving hormone therapy.

The adjusted hazard ratio of receiving any hormone therapy compared to a control without hormone therapy ranged from 0.96 to 1.70. Adjusted hazard ratios for receiving hormone therapy and radiotherapy compared to radiotherapy alone ranged from 0.7 to 1.2. These suggest that studies results varied over whether hormone therapy resulted in greater or less risk. While adjusted hazard ratios for receiving both hormone therapy and prostatectomy compared to prostatectomy alone ranged from 1.3 to 2.6, all reporting a higher risk for those receiving hormone therapy.

The standardised mortality ratio (SMR) for patients receiving any form of hormone therapy ranged from 0.38 to 1.29, with study results varying in whether more or less deaths were observed that had been expected. The number of cases was given in seven of the studies which enabled a meta-analysis of the relative risk; however, this was not statistically significant at 1.37 (95%CI 0.90 – 2.07).

Cerebrovascular accident mortality

Two studies (McLeod 2006; van Hemelrijck 2010) provided very low quality evidence of no significant increase in deaths from stroke in patients treated with hormone therapy. A randomised controlled trial by McLeod et al. (2006) found a raw incidence of 1% in both the hormone therapy and no hormone therapy treatment groups. A cohort study by van Hemelrijck et al. (2010a) found the SMR

to range between 0.81 and 1.24 for different hormone therapies, compared to 0.99 and 1.01 for the curative therapy and surveillance control groups.

Cardiovascular morbidity

Six studies provided very low quality evidence of cardiovascular morbidity in patients receiving hormone therapy. One study (Saigal 2007) included any cardiovascular event as an outcome; five studies (Keating 2006; Keating 2010; van Hemelrijck 2010a; Alibhai 2009; Jespersen 2013) reported the incidence of myocardial infarction events; three (Keating 2006; Keating 2010; van Hemelrijck 2010a & 2012) reported the incidence of coronary heart disease; two (Alibhai 2009; van Hemelrijck 2010a) reported on the incidence of heart failure; and one study (van Hemelrijck 2010a) reported the incidence of arrhythmia.

The reported raw incidence ranged from 5% to 18% in patients receiving hormone therapy, this compares to between 1% and 20% in the no hormone therapy control groups. The incidence rate ranged widely between studies; between 10.2 and 61.3 cases per 1,000 person-years in those receiving hormone therapy, compared to between 7.4 and 29.7 per 1,000 person-years in the no-hormone therapy group. Studies also varied in whether the risk of cardiovascular disease was found to be lower in the hormone therapy or no-hormone therapy group, with the hazard ratio varying between 0.92 and 1.98.

Only one study (van Hemelrijck 2010a and 2010b) reported the standardised incidence rate (SIR) which was found to range between 1.12 and 1.47. Only two studies (Alibhai 2009; van Hemelrijck 2010) provided the number of cases to allow incorporation into the meta-analysis. These resulted in a non-significant relative risk of 1.30 (95CI 0.64 – 2.66) for cardiovascular events in those receiving hormone therapy.

Cerebrovascular accident morbidity

Five studies (van Hemelrijck 2010a and 2012; Keating 2010; Alibhai 2009; Chung 2012; Jespersen 2013) provided very low quality evidence on incidence of stroke in patients treated with hormone therapy. The raw incidences of stroke reported in the hormone therapy group ranged from 6% to 17%, compared with 5% to 19% in the no-hormone therapy group. The incidence rate ranged widely between studies; between 14.7 and 34.7 cases per 1,000 person-years in those receiving hormone therapy, compared to between 11.3 and 12 per 1,000 person-years in the no-hormone therapy group. The adjusted hazard ratios reported for the hormone therapy group varied between 0.88 and 1.81 with studies results varying as to whether the risk was higher or lower in those treated with hormone therapy.

Van Hemelrijck et al. (2010a) found the SIRs to range from 1.19 to 1.36 for the different hormone therapies, compared to 0.98 and 1.19 for the curative therapy and surveillance groups. Three of the studies could be incorporated into a meta-analysis; the resulting relative risk of 1.02 (95% CI 0.70 – 1.47) was not statistically significant.

Thromboembolic events

Three studies provided very low quality evidence of the incidence of thromboembolic events in patients receiving hormone therapy. Two of these studies (Ehdaie 2012; van Hemelrijck 2012) included any thromboembolic event, however their definitions varied. Ehdaie et al. (2012) included any deep venous thrombosis, pulmonary embolism, or arterial embolism as a thromboembolic event, while van Hemelricjk et al. (2012) only included cases of deep venous thrombosis. The third study (Hu 2012) reported only the number of cases of deep venous thrombosis seen.

The reported raw incidence in patients receiving hormone therapy ranged from 2% to 15%, compared with between 2% and 11% in the no-hormone therapy group. The reported incidence rate ranged from 13.2 to 14.7 per 1,000 person years for patients receiving hormone therapy (where reported); only one study reported this for the no-hormone therapy group which was found to be 10.1 cases per 1,000 person-years. The adjusted hazard ratio ranged from 1.10 to 1.56, suggesting an increased risk in patients receiving hormone therapy. The SIRs ranged from 1.56 to 2.81, also suggesting more cases than would be expected. However, where surveillance or curative therapy was

used as a comparator, the SIRs ranged from 1.27 to 1.57 and from 1.73 to 2.03 respectively suggesting that these groups also saw more cases than expected.

Subgroup analyses

Type of hormone therapy

Seven studies limited included patients to those receiving a particular type of medical ADT. Only one study (van Hemelrijck 2010) allowed comparison of the number of cases by hormone therapy type. The hormone therapy subgroups in this study were pooled into two: anti-androgen monotherapy and any other ADT. Cardiovascular and thromboembolic event outcomes were not pooled as these were from the same study (this would have resulted in double-counting of patients) and are reported separately. Several other studies reported the incidence rate, hazard ratio, or SIR/SMRs by hormone therapy type but these measures could not be combined.

Cardiovascular disease and cerebrovascular accident mortality

Of the studies which restricted included patients by type of ADT received, five reported the number of deaths due to cardiovascular disease. There was no significant difference between patients receiving LHRH agonists alone or with anti-androgens and those receiving no ADT ($p > 0.05$) (see Figure 71). In three of these four studies ADT was given alongside radiotherapy. One study (McLeod 2006) showed a borderline significant difference between those receiving anti-androgens and standard care (radical therapy or watchful waiting) compared to those receiving standard care alone (RR 1.3 95% CI 1.0-1.6).

One study (Van Hemelrijck 2010a) provided very low quality evidence of significantly fewer deaths due to myocardial infarction, arrthymia, ischemic heart disease (IHD), heart failure, and stroke in patients receiving anti-androgen monotherapy compared to other medical ADT (RRs: 0.57, 0.36, 0.54, 0.26 and 0.56 respectively). The results suggest that for every 1,000 patients treated with anti-androgen monotherapy instead of another type or combined ADT, there would be 17 fewer deaths from myocardial infarction, four fewer from arrthymia, 32 fewer from IHD, 10 fewer from heart failure, and eight fewer from stroke.

Following restriction of the meta-analysis to anti-androgen monotherapy versus no hormone therapy there remained no statistically significant difference in the incidence of stroke or deaths due to stroke. No combined measure of cardiovascular mortality was reported by the only study reporting cases following anti-androgen monotherapy.

Cardiovascular disease morbidity

Van Hemelrijck et al. (2010a) also provided very low quality evidence of significantly fewer overall cases of myocardial infarction, ischemic heart disease (IHD), heart failure, and stroke (ORs: 0.79, 0.85, 0.54, and 0.85 respectively). The results suggest that for every 1,000 patients treated with anti-androgen monotherapy instead of another or combined type of ADT, there would be 14 fewer cases of myocardial infarction, 15 fewer cases of IHD, 33 fewer cases of heart failure, and 12 fewer cases of stroke. There was no significant difference in the risk of developing arrthymia for patients receiving anti-androgen monotherapy compared with any other type of ADT.

Thromboembolic events

The study by van Hemelrijck et al. (2010b) also provided very low quality evidence of significantly fewer overall cases of deep venous thrombosis and pulmonary embolism (RRs: 0.54 and 0.67 respectively). The results suggest that for every 1,000 patients treated with anti-androgen monotherapy instead of another or combined type of ADT, there would be seven fewer cases of DVT and four fewer cases of pulmonary embolism.

Duration of ADT ≥ 6 months

Though all studies included patients receiving medical hormone therapy, only two reported the median duration of medical hormone therapy given; this was 4.1 months in combination with local therapy (Tsai 2007) and 4.2 years in combination with radiotherapy (Efstathiou 2009). Six of the studies (Hu 2012; Alibhai 2009; Merrick 2006; Kim 2011; Ehdaie 2012; D'Amico 2007) undertook sub-group analyses, where patients were categorised by duration of hormone therapy.

Two studies which reported including only patients receiving ≥ 6 months of medical ADT or surgical ADT (Alibhai 2009; Wilcox 2012), the study with a median treatment duration of 4.2 years (Efstathiou 2009), and one study which reported appropriate subgroup analysis by ADT duration (Merrick 2006) were included in the subgroup meta-analysis looking at ADT duration of ≥ 6 months.

Cardiovascular disease and cerebrovascular accident mortality

Following restriction of the meta-analysis to studies involving ≥ 6 months ADT, there remained no significant increase in the incidence of cardiovascular deaths or deaths due to stroke between patients treated with ≥ 6 months of ADT and patients receiving no ADT (see Figure 72 and Figure 73), based on very low quality evidence from two studies (Merrick 2006; Efstathiou 2009).

In a very low quality study not included in the meta-analysis Kim et al. (2011) found that incidence of cardiovascular death at 7 years was significantly higher at 1.4% in patients receiving > 6 months of ADT alongside EBRT, compared to 2.6% in patients receiving EBRT alone (p=0.001). Another low quality study by Alibhai et al. (2009) found that patients receiving > 24 months of ADT had a significantly lower risk of sudden cardiac death compared to patients receiving < 3 months (RR 0.81 95% CI 0.69-0.96), but patients receiving 3-6 months or 6-24 months ADT did not. In a moderate quality study D'Amico et al. (2007) reported that men aged ≥ 65 years who received 6 months of ADT experienced a shorter time to fatal myocardial infarction than men of the same age group who did not receive ADT (p=0.017). However, in their second study no significant difference in time to fatal myocardial infarction was found between patients aged ≥ 65 years receiving 6-8 months of ADT compared to patients receiving 3 months.

Cardiovascular disease morbidity

One study (Alibhai 2009) provided low quality evidence of a borderline significant difference in the incidence of myocardial infarction between patients receiving ≥ 6 months ADT and patients receiving no ADT. The relative risk of 0.87 (95% CI 0.80-0.95) suggests that for every 1,000 patients treated with ≥ 6 months ADT there will be seven fewer myocardial infarctions. However, in their multivariate model Alibhai et al. (2009) found no significant difference in the risk of myocardial infarction for patients receiving 3-6 months, 6-24 months, or > 24 months ADT compared to patients receiving < 3 months.

Alibhai et al. (2009) did find a significant difference in the incidence of congestive heart failure between patients treated with ≥ 6 months of ADT compared to patients receiving no ADT. The relative risk of 0.92 (95% CI 0.87-0.97) suggests that for every 1,000 patients 10 fewer would develop congestive heart failure if treated with ≥ 6 months of ADT. The multivariate model suggests that this different was only significant for the subgroup receiving > 24 months ADT (HR 0.81 95% CI 0.69-0.96) and not for the 3-6 or 6-24 month-subgroups.

Cerebrovascular accident morbidity

When the meta-analysis was restricted to studies comparing ≥ 6 months ADT with no ADT, only one study (Alibhai 2009) providing low quality evidence was included. Unlike the previous meta-analysis, this study found a significant difference in the incidence of stroke between patients treated with ≥ 6 months of ADT compared to patients receiving no ADT (see Figure 74). The relative risk of 0.84 (95% CI 0.78-0.91) suggests that for every 1,000 patients 10 fewer would have a stroke if treated with ≥ 6 months of ADT.

Thromboembolic events

No studies provided the number of thromboembolic events for inclusion in the meta-analysis. However, a very low quality study by Ehdaie et al. (2012) found that risk of thromboembolic event was increased by 40% (95% CI 1.33-1.45) in patients receiving < 1 year of ADT, by 66% (95% CI 1.57-1.75) in patients receiving 1-3 years of ADT, and doubled in patients receiving > 3 years of ADT (95% CI 1.90-2.19) compared to patients receiving no ADT. One low quality study (Hu 2012) undertook subgroup analyses and found incidence of DVT to be significantly higher in patients receiving > 12 months of ADT compared to no ADT (HR 1.23 95% CI 1.11-1.36 for 13-24 months and HR 1.15 95% CI 1.04-1.27 for >25 months duration) but not for patients receiving ≤ 12 months of ADT. These subgroup analyses are in contrast to the results of the previous meta-analysis.

Exclusion of comorbid conditions

Of the 18 studies included in this review, only six reported excluding patients on the basis of comorbid conditions. Three studies (Keating 2006 & 2010; Tsai 2007) excluded patients with prevalent coronary heart disease or diabetes. Tsai et al. (2007) also excluded patients with prevalent hypertension. Saigal et al. (2007) excluded patients with a cardiovascular event within 12 months of prostate cancer diagnosis. Chung et al. (2012) excluded patients with a diagnosis of stroke within the previous 5 years. Finally, Hu et al. (2012) excluded patients with a diagnosis of DVT within 3 months of undergoing surgery. None of the studies reporting the outcomes stroke mortality, cardiovascular morbidity, or thromboembolic events reported restricting their patients by comorbidities criteria.

Cardiovascular disease mortality

Of the seven studies included in the meta-analysis for cardiovascular mortality, only one reported excluding patients with comorbidities (Tsai 2007). Upon exclusion of this study from the meta-analysis, there remained no significant difference in cardiovascular mortality between patients receiving ADT and those not (see Figure 75).

The very low quality study excluded found a significant increase in cardiovascular mortality in patients receiving ADT compared to patients not receiving ADT. The relative risk of 2.44 (95% CI 1.73-3.44) suggests that for every 1,000 patients treated with ADT there would be 28 more cardiovascular deaths.

Cerebrovascular accident morbidity

Of the four studies included in the meta-analysis for stroke morbidity, only one reported excluding patients with comorbidities (Chung 2012). Upon exclusion of this study from the meta-analysis, there remained no significant difference in the incidence of stroke between patients receiving ADT and those not (see Figure 76). The very low quality excluded study also found no significant difference in the incidence of stroke between patients receiving ADT and those not receiving ADT.

Randomised controlled trials (RCTs)

Of the seven studies included in the meta-analysis for cardiovascular mortality, four were RCTs or analyses of multiple RCTs (McLeod 2006; D'Amico 2007; Roach 2008; Efstathiou 2009). Upon restriction of the meta-analysis to RCTs only, there remained no significant difference in incidence of cardiovascular mortality between patients receiving ADT and those not (see Figure 77).

However, a meta-analysis of the cohort studies (Merrick 2006; Tsai 2007; Punnen 2011) provided very low quality evidence of a significant increase in risk in patients receiving ADT. The relative risk of 2.15 (95% CI 1.33-3.46) suggests that for every 1,000 patients there are 23 more cardiovascular deaths in patients treated with ADT.

Only one RCT (McLeod 2006) reported the incidence of deaths due to stroke and found no significant difference between patients treated with ADT and those not. Three and four cohort studies (Alibhai 2009; van Hemelrijck 2010; Chung 2012; Jespersen 2013) reported on the incidence of cardiovascular events and strokes respectively and found no significant difference. Two cohort studies (van Hemelrijck 2010; Ehdaie 2012) reported on the incidence of thromboembolic events and found no significant difference between patients treated with ADT and those not.

Table 114 Incidence of cardiovascular effects in men who have received hormone therapy for prostate cancer (range reported)

Abbreviations: SIR = standardised incidence ratio; SMR = standardised mortality ratio; HR = hazard ratio; HT = hormone therapy; RT = radiotherapy; RP = radical prostatectomy

Outcome	Overall follow-up (median)	Hormone therapy group						No hormone therapy group					Difference between groups	
		Treatment	No. of studies	Raw incidence	Incidence (per 1,000 person-years)	Absolute risk	SIR/SMR	Treatment	Raw incidence	Incidence (per 1,000 person-years)	Absolute risk	SIR/SMR	Unadjusted HR	Adjusted HR
Death from cardio-vascular disease	2.6 - 7.4 years	Any HT	7[6,7,8,9,15,18,20]	1% - 7%	8.3 – 15.1	-	0.38 – 1.29	No HT	2% - 6%	5.3 - 9.0	-	-	-	0.96 – 1.70
								Any curative	1%	-	-	0.73 – 1.05	-	1.94
								Surveillance	6%	-	-	0.83 – 0.97	-	-
	3.8 – 13.2 years	HT + RT	7[2,12,13,14,,16,17,19]	1% - 14%	-	-	-	RT	3% - 11%	-	-	-	0.8 – 1.3	0.73 – 1.2
	3.8 years	HT + RP	2[2,12]	6%	-	-	-	RP	2%	-	-	-	2.9	1.34 – 2.6
Death from cerebro-vascular accident	4† – 7.4 years	Any HT	2[6,18]	1%	-	-	0.81 – 1.24	No HT	1%	-	-	-	-	-
								Surveillance	-	-	-	1.01	-	-
								Any curative	-	-	-	0.99	-	-
Cardio-vascular disease	2.6 – 6.5 years	Any HT	6[1,5,6,7,8,9,21]	5% - 18%	10.2 – 61.3	-	1.12 – 1.47	No HT	4% - 20%	7.4 – 29.7	-	-	1.42	0.92 – 1.98
								RT	2%	-	-	-	-	-
								RP	1%	-	-	-	-	-
								Surveillance	17%	-	-	-	-	-
								Any curative	-	-	-	0.81 - 1.12	-	-
Cerebro-vascular accident	2.6 – 6.5 years	Any HT	5[5,6,8,9,10,21]	6% - 17%	14.7 – 34.7	-	1.19 – 1.36	No HT	5% - 19%	11.3 - 12	-	-	1.03 – 1.30	0.88 – 1.81
								RT	4%	-	-	-	-	-
								RP	3%	-	-	-	-	-
								Surveillance	9%	-	-	1.19	-	-
								Any curative	-	-	-	0.98	-	-
Thrombo-embolic event	4† – 5.1 years	Any HT	3[3,4,5,11]	2% - 15%	13.2 – 14.7	3.55 - 4.08	1.56 – 2.81	No HT	7%	10.1	-	-	-	1.10 – 1.56
								RT	11%	-	-	-	-	-
								RP	7%	-	-	-	-	-
								Surveillance	2%	-	1.89 – 2.70	1.27 – 1.57	-	-
								Any curative	-	-	1.40 – 2.17	1.73 – 2.03	-	-

[1]Saigal et al. (2007); [2]Blood et al. (2010); [3]Ehdaie et al. (2012); [4]Hemelrijck et al. (2010b); [5]Hemelrijck et al. (2012); [6]Hemelrijck et al. (2010a); [7]Keating et al. (2006); [8]Keating et al. (2010); [9]Alibhai et al. (2009); [10]Chung et al. (2012); [11]Hu et al. (2012); [12]Tsai et al. (2007); [13]Efstathiou et al. (2009); [14]Kim et al. (2011); [15]Punnen et al. (2011); [16]Roach et al. (2008); [17]Wilcox et al. (2012); [18]McLeod et al. (2006); [19]Merrick et al. 2006; [20]D'Amico et al. (2007); [21]Jespersen et al. (2013).

†Mean given where median follow-up not available.

Table 115 Incidence of cardiovascular effects in men who have received hormone therapy for prostate cancer, by type of hormone therapy

Abbreviations: SIR = standardised incidence ratio; SMR = standardised mortality ratio; HR = hazard ratio; DVT = deep venous thrombosis

Outcome measure	No. of studies	Orchidect-omy	GnRH ago-nist	Anti-androgen	GnRH + anti-androgen combined
Cardiovascular disease mortality					
Raw incidence: cardiac event	1	-	-	-	6%
Incidence rate*: sudden cardiac death	2	12.5 – 23.3	12.9 – 21.6	18.8	20.1
Adjusted HR: sudden cardiac death	2	1.01 – 1.29	1.16 – 1.35	1.06	1.22
SMR: myocardial infarction	1	1.29	1.28	0.98	1.23
SMR: arrhythmia	1	0.75	0.64	0.38	0.62
SMR: ischemic heart disease	1	1.05	1.01	0.79	1.01
SMR: heart failure	1	1.19	1.23	0.53	0.92
Cerebrovascular accident mortality					
SMR	1	0.90	1.01	0.81	0.97
Cardiovascular (morbidity)					
Raw incidence: heart disease	1	16%	18%	14%	15%
Raw incidence: myocardial infarction	1	5%	-	-	5%
Incidence rate*: coronary heart disease	2	63.3 – 210.5	72.3 – 144.0	143.2	157.7
Incidence rate*: myocardial infarction	3	13.2 – 24.3	12.8 – 13.5	11.2	10.2 - 14
Adjusted HR: coronary heart disease	2	0.99 – 1.40	1.16 – 1.29	1.10	1.27
Adjusted HR: myocardial infarction	2	0.94 – 2.11	1.11 – 1.28	1.05	1.03
SIR: myocardial infarction	1	1.20	1.28	1.12	1.19
SIR: arrhythmia	1	1.34	1.27	1.38	1.38
SIR: ischemic heart disease	1	1.27	1.30	1.13	1.24
SIR: heart failure	1	1.42	1.46	1.15	1.47
Cerebrovascular accident (morbidity)					
Raw incidence	2	7%	8%	7%	6% - 7%
Incidence rate*	2	24 - 26.2	18.5	14.9	14.8 - 15
Hazard ratio	1	1.49	1.21	0.86	0.93
SIR	1	1.19	1.27	1.19	1.36
Thromboembolic events					
Raw incidence: DVT	1	3%	3%	2%	2%
Incidence rate*: DVT	1	14.7	13.2	-	-
Adjusted HR: DVT	1	1.27	1.10	-	-
Adjusted HR: any thromboembolic event	1	1.97	1.54	-	-

*Incidence rate per 1,000 person-years

Figure 66 Forest plot of cardiovascular mortality occurring in studies comparing hormone therapies with no hormone therapy

Study or Subgroup	Androgen deprivation Events	Total	No androgen deprivation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
McLeod 2006	167	4022	134	4031	15.8%	1.25 [1.00, 1.56]	2006
Merrick 2006	21	382	27	556	12.8%	1.13 [0.65, 1.97]	2006
D'Amico 2007	42	950	16	277	12.7%	0.77 [0.44, 1.34]	2007
Tsai 2007	51	1015	80	3877	14.9%	2.44 [1.73, 3.44]	2007
Roach 2008	31	224	26	232	13.5%	1.23 [0.76, 2.01]	2008
Efstathiou 2009	52	477	65	468	14.9%	0.78 [0.56, 1.10]	2009
Punnen 2011	89	1572	106	5676	15.4%	3.03 [2.30, 4.00]	2011
Total (95% CI)		**8642**		**15117**	**100.0%**	**1.37 [0.90, 2.07]**	
Total events	453		454				

Heterogeneity: Tau² = 0.27; Chi² = 56.24, df = 6 (P < 0.00001); I² = 89%
Test for overall effect: Z = 1.48 (P = 0.14)

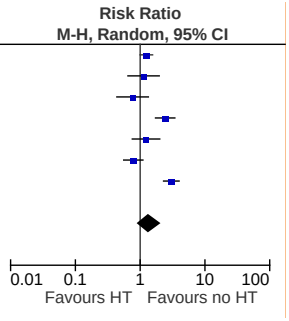


Figure 67 Forest plot of mortality due to cerebrovascular accident occurring in studies comparing hormone therapies with no hormone therapy

Study or Subgroup	Androgen deprivation Events	Total	No androgen deprivation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
McLeod 2006	47	4022	45	4031	44.7%	1.05 [0.70, 1.57]	2006
van Hemelrijck 2010	546	30642	426	45958	55.3%	1.92 [1.69, 2.18]	2010
Total (95% CI)		**34664**		**49989**	**100.0%**	**1.46 [0.81, 2.65]**	
Total events	593		471				

Heterogeneity: Tau² = 0.16; Chi² = 7.84, df = 1 (P = 0.005); I² = 87%
Test for overall effect: Z = 1.26 (P = 0.21)

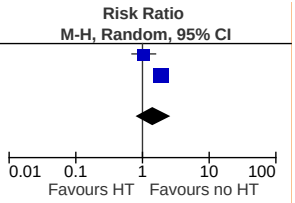


Figure 68 Forest plot of cardiovascular events occurring in studies comparing hormone therapies with no hormone therapy

Study or Subgroup	Androgen deprivation Events	Total	No androgen deprivation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Alibhai 2009	2496	19079	2715	19079	33.4%	0.92 [0.87, 0.97]	2009
van Hemelrijck 2010	4957	30642	3634	42170	33.5%	1.88 [1.80, 1.95]	2010
Jespersen 2013	573	11264	824	20307	33.1%	1.25 [1.13, 1.39]	2013
Total (95% CI)		**60985**		**81556**	**100.0%**	**1.29 [0.78, 2.16]**	
Total events	8026		7173				

Heterogeneity: Tau² = 0.20; Chi² = 475.11, df = 2 (P < 0.00001); I² = 100%
Test for overall effect: Z = 0.99 (P = 0.32)

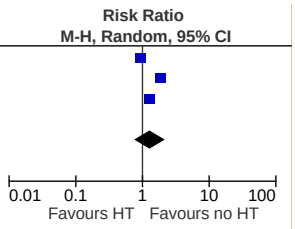


Figure 69 Forest plot of cerebrovascular events occurring in studies comparing hormone therapies with no hormone therapy

Study or Subgroup	Androgen deprivation Events	Total	No androgen deprivation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Alibhai 2009	1057	19079	1251	19079	29.3%	0.84 [0.78, 0.91]	2009
van Hemelrijck 2010	2281	30642	2420	42170	29.8%	1.30 [1.23, 1.37]	2010
Chung 2012	11	64	57	301	11.9%	0.91 [0.50, 1.63]	2012
Jespersen 2013	663	11264	922	20307	29.0%	1.30 [1.18, 1.43]	2013
Total (95% CI)		**61049**		**81857**	**100.0%**	**1.10 [0.84, 1.42]**	
Total events	4012		4650				

Heterogeneity: Tau² = 0.06; Chi² = 82.60, df = 3 (P < 0.00001); I² = 96%
Test for overall effect: Z = 0.69 (P = 0.49)

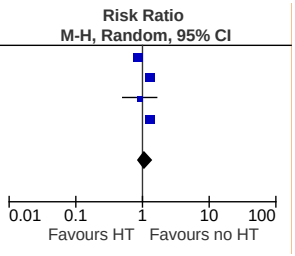


Figure 70 Forest plot of thromboembolic events occurring in studies comparing hormone therapies with no hormone therapy

Study or Subgroup	Androgen deprivation Events	Total	No androgen deprivation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
van Hemelrijck 2010	791	30642	2282	42170	50.0%	0.48 [0.44, 0.52]	2010
Ehdaie 2012	8829	58466	7121	96145	50.0%	2.04 [1.98, 2.10]	2012
Total (95% CI)		**89108**		**138315**	**100.0%**	**0.99 [0.24, 4.13]**	
Total events	9620		9403				

Heterogeneity: Tau² = 1.07; Chi² = 1139.22, df = 1 (P < 0.00001); I² = 100%
Test for overall effect: Z = 0.02 (P = 0.99)

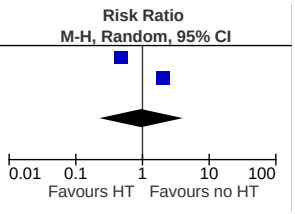


Figure 71 Forest plot of cardiovascular mortality occurring in studies comparing ADT with no ADT, where type of ADT is specified

Study or Subgroup	ADT Events	Total	No ADT Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
6.1.1 LHRH agonist & anti-androgen							
Merrick 2006	21	382	27	556	13.0%	1.13 [0.65, 1.97]	2006
Roach 2008	31	224	26	232	15.6%	1.23 [0.76, 2.01]	2008
Subtotal (95% CI)		**606**		**788**	**28.6%**	**1.19 [0.82, 1.72]**	
Total events	52		53				
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%							
Test for overall effect: Z = 0.93 (P = 0.35)							
6.1.2 Anti-androgen alone							
McLeod 2006	167	4022	134	4031	34.5%	1.25 [1.00, 1.56]	2006
Subtotal (95% CI)		**4022**		**4031**	**34.5%**	**1.25 [1.00, 1.56]**	
Total events	167		134				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.95 (P = 0.05)							
6.1.4 LHRH agonist alone							
D'Amico 2007	42	950	16	277	12.8%	0.77 [0.44, 1.34]	2007
Efstathiou 2009	52	477	65	468	24.1%	0.78 [0.56, 1.10]	2009
Subtotal (95% CI)		**1427**		**745**	**36.9%**	**0.78 [0.58, 1.04]**	
Total events	94		81				
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%							
Test for overall effect: Z = 1.67 (P = 0.09)							
Total (95% CI)		**6055**		**5564**	**100.0%**	**1.03 [0.82, 1.30]**	
Total events	313		268				
Heterogeneity: Tau² = 0.03; Chi² = 6.76, df = 4 (P = 0.15); I² = 41%							
Test for overall effect: Z = 0.28 (P = 0.78)							
Test for subgroup differences: Chi² = 6.69, df = 2 (P = 0.04), I² = 70.1%							

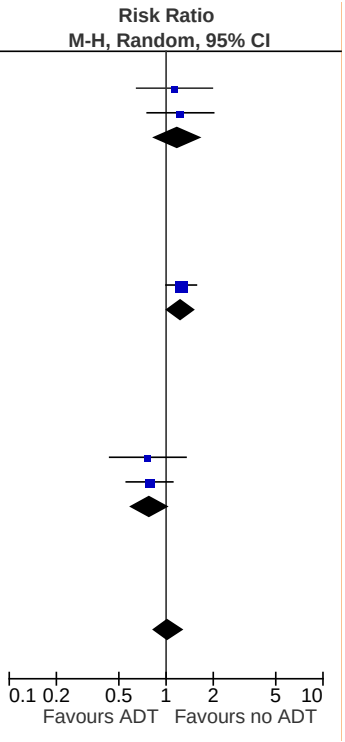


Figure 72 Forest plot of cardiovascular mortality occurring in studies comparing ≥ 6 months ADT with no ADT (ADT duration unknown subgroup shown for reference)

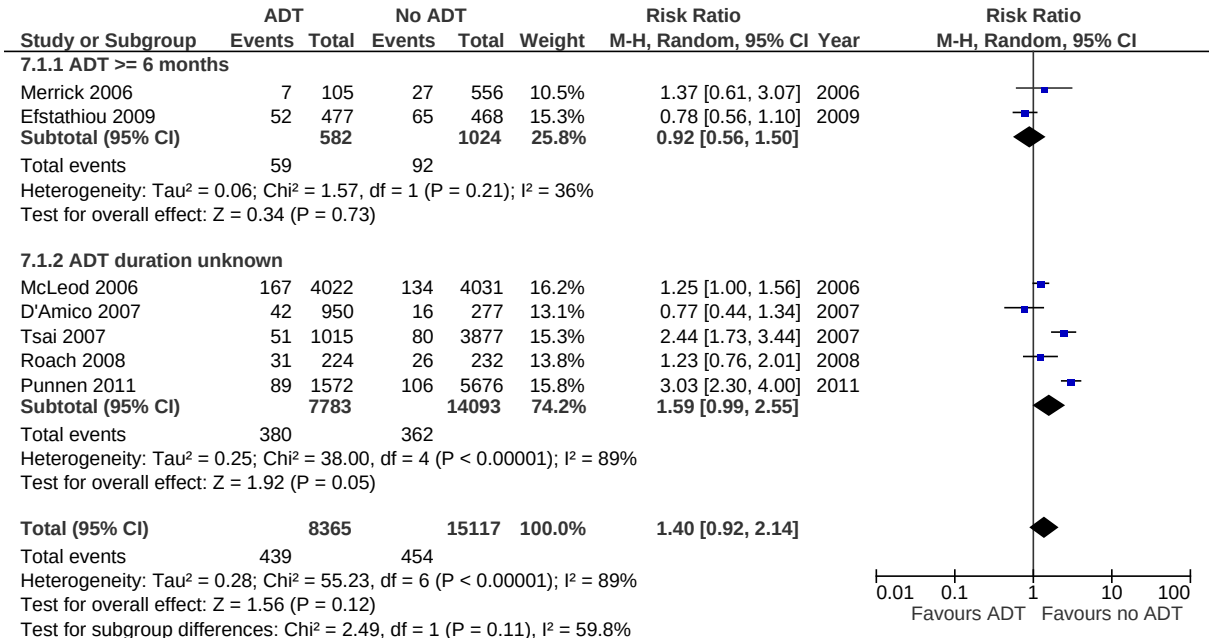


Figure 73 Forest plot of cerebrovascular accident mortality occurring in studies comparing ≥ 6 months ADT with no ADT (ADT duration unknown subgroup shown for reference)

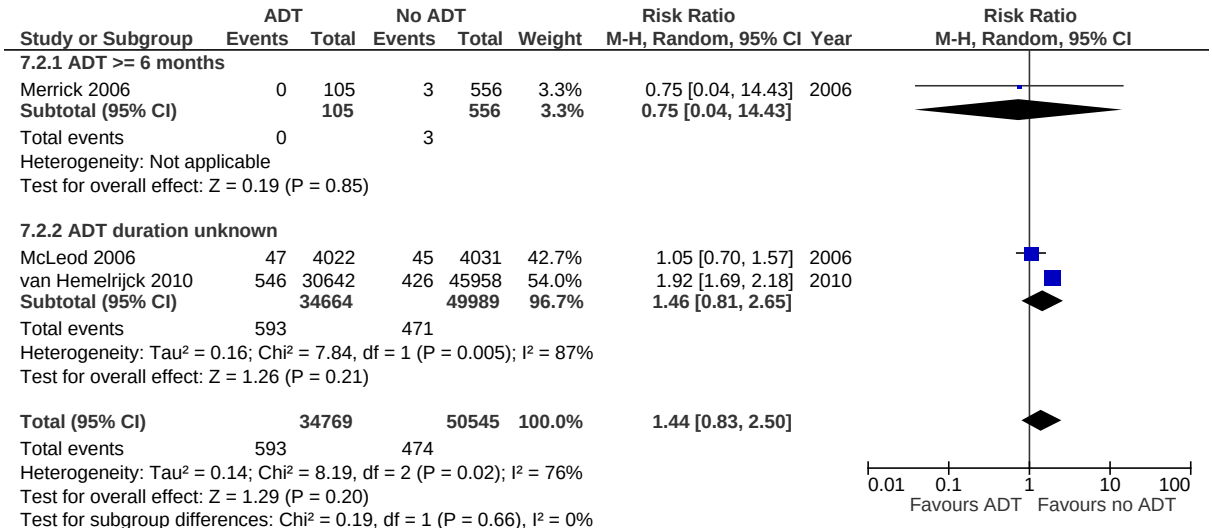


Figure 74 Forest plot of cerebrovascular accident morbidity occurring in studies comparing ≥ 6 months ADT with no ADT (ADT duration unknown subgroup shown for reference)

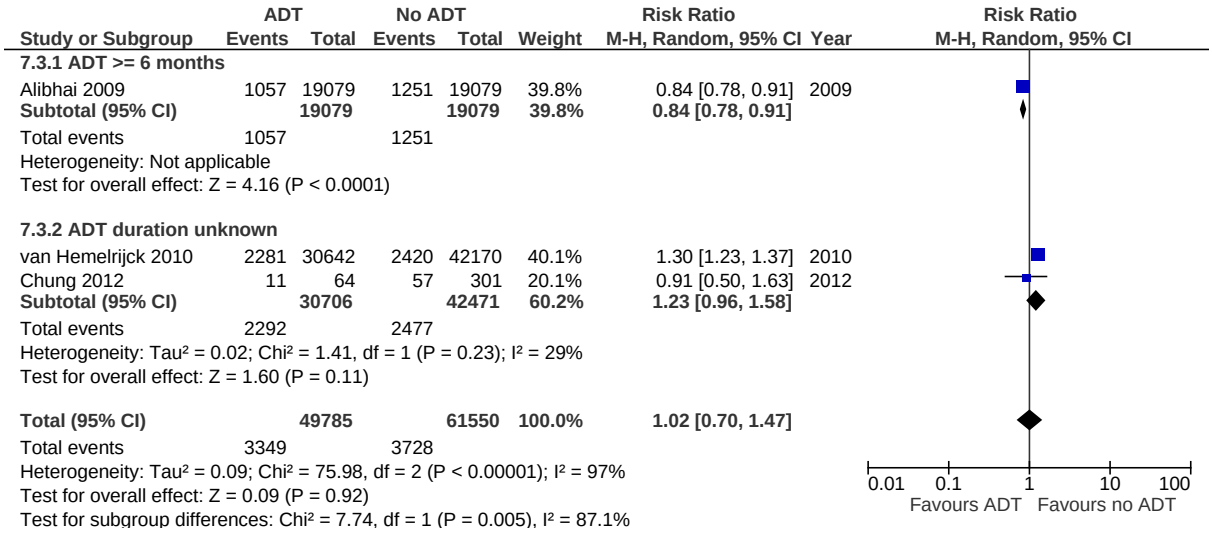


Figure 75 Forest plot of cardiovascular mortality occurring in studies comparing hormone therapies with no hormone therapy; studies which excluded patients with comorbidities versus those that did not

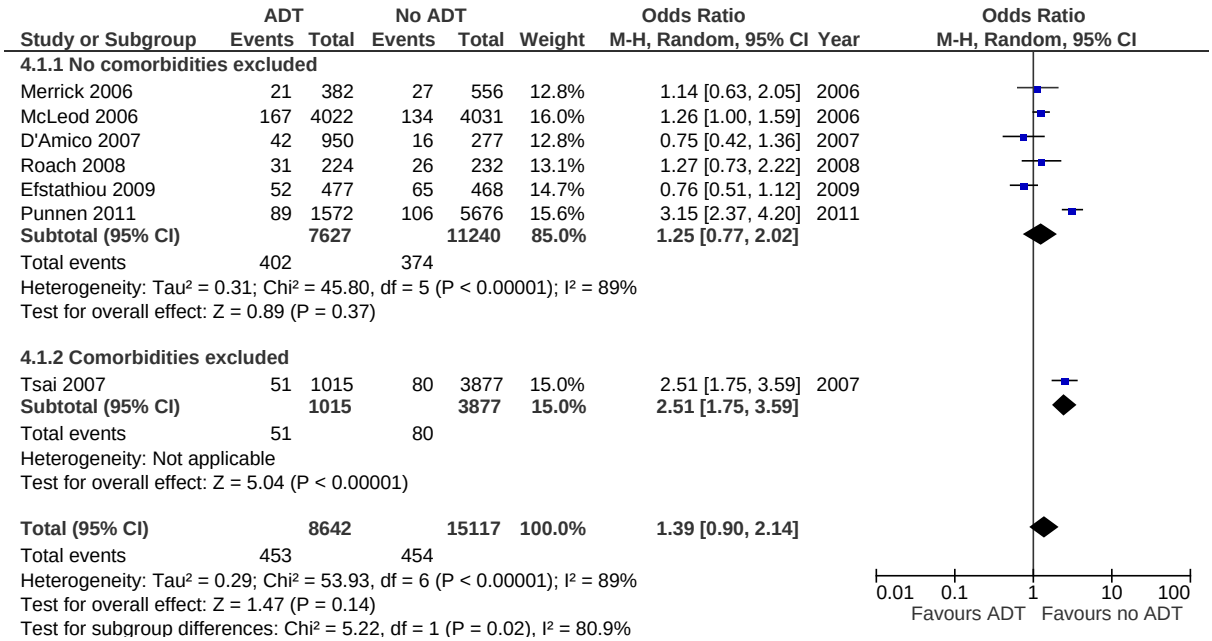


Figure 76 Forest plot of stroke events occurring in studies comparing hormone therapies with no hormone therapy; studies which excluded patients with comorbidities versus those that did not

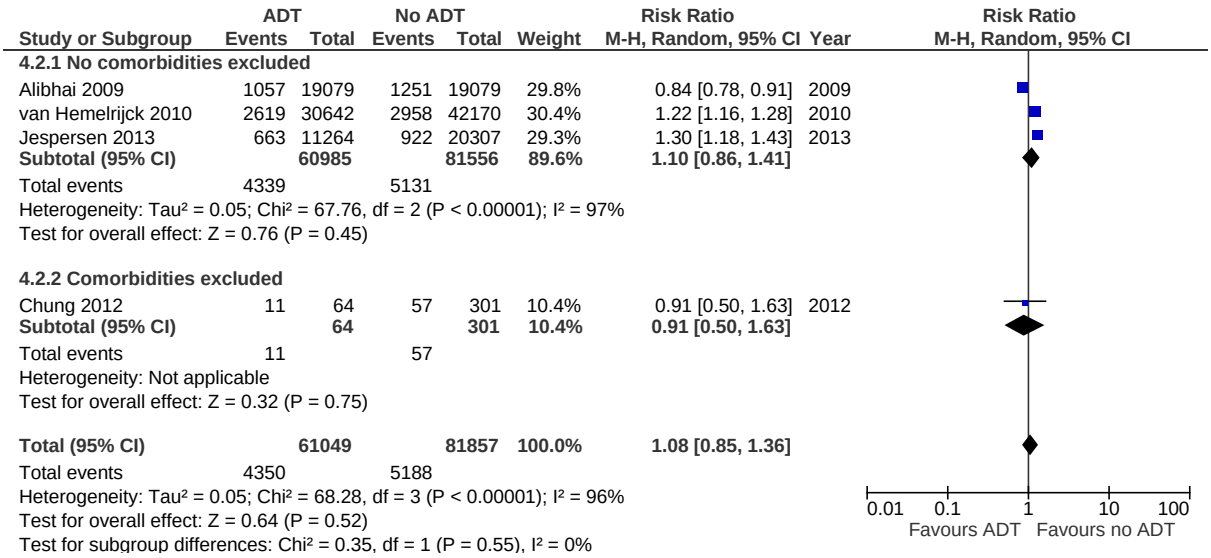


Figure 77 Forest plot of cardiovascular mortality occurring in studies comparing hormone therapies with no hormone therapy; RCTs versus cohort studies

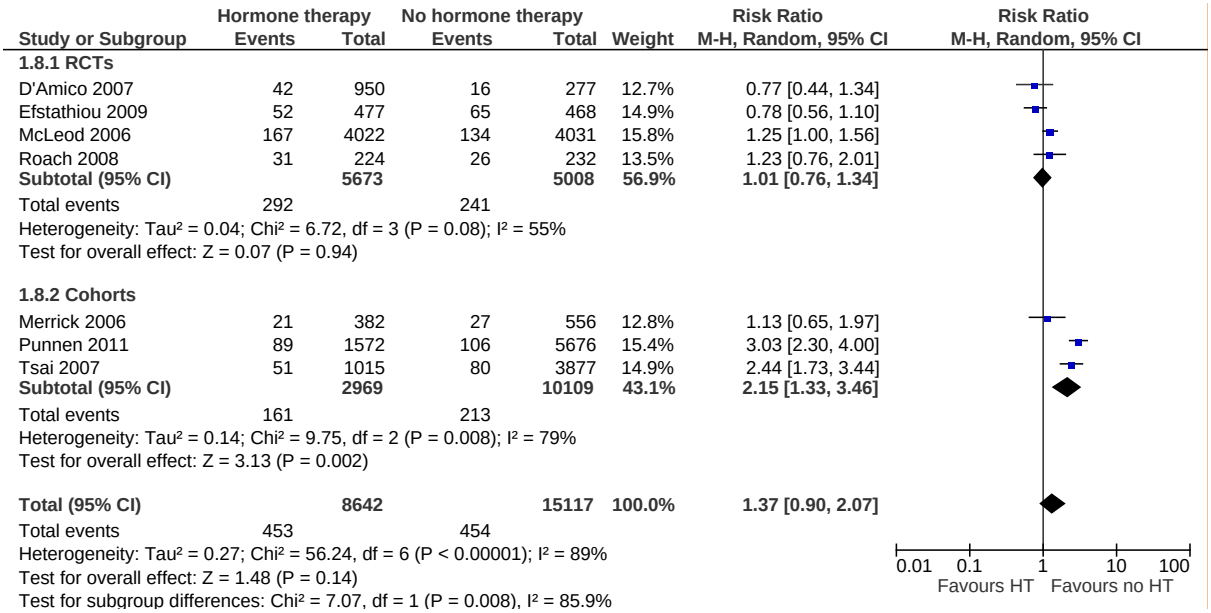


Table 116 Summary of study characteristics

Abbreviations: HT = hormone therapy; GnRH = gonadotropin-releasing hormone; AA = anti-androgen; NR = none/not reported; RT = radiotherapy; RP = radical prostatectomy

Study	Study type	Country/ies	Study period	No. of HT patients	Median follow-up	Inclusion/exclusion criteria	Hormone therapy treatment group (HT)	Comparator group
Alibhai et al. (2009)	Prospective cohort	Canada	1995-2005	19,079	6.5 years	Included: Men with PCa aged > 65 years Excluded: prior bone metastates	Continuous ADT (LHRH agonist or anti-androgen or both) for ≥ 6 months or bilateral orchiectomy	No ADT treatment
Blood et al. (2010)	Retrospective cohort	Canada	1995-2000	2,037	NR	Included: Men with PCa treated with RT or RP	With RT (69%): neoadjuvant & continuous LHRH injections ending within 3 years of end of RT With RP (31%): neoadjuvant LHRH injections ending within 3 months of RP	RT = ≥ 50 Gy in 20 fractions
Chung et al. (2012)	Prospective cohort	China	2001-2008	64	NR	Included: new-onset PCa diagnoses Excluded: history of stroke; received orchidectomy during follow-up	Any HT treatment	No HT treatment
D'Amico et al. (2007)	Pooled RCTs	Australia, New Zealand, US & Canada	1995-2001	NR	4.8 – 6.7 years	Included: PCa patients with life expectancy ≥ 5 years	RT + LHRH agonist (leuprolide acetate or goserelin or goserelin with flutamide) (3, 6 or 8 months duration)	RT alone
Efstathiou et al. (2009)	RCT	NR	1987-	477	8.1 years	Included: men with histologically-confirmed PCa, either stage T3 or evidence of regional lymphatic involvement	RT + adjuvant goserelin acetate, beginning during last week of RT	RT alone
Ehdaie et al. (2012)	Retrospective cohort	US	1999-2005	58,466	4.3 years	Included: Men aged > 65 years with non-metastatic PCa	98% received medical HT; 2% received surgical HT	No HT treatment
Hu et al. (2012)	Retrospective cohort	US	1992-2007	90,059	5.1 years	Included: Non-metastatic PCa patients ≥ 66 years-old Excluded: T-stage unknown; received abarelix during follow-up; chemotherapy within 6 months of diagnosis	96% received GNRH agonist; 4% received orchiectomy	No HT treatment
Jespersen et al. (2013)	Retrospective cohort	Denmark	2002-2010	11,264	20,307	Included: PCa patients registered for GnRH agonists, anti-androgens or orchiectomy Excluded: PCa patients treated with both GnRH agonists & orchiectomy	82% medical endocrine therapy & 18% orchiectomy	No ADT treatment
Keating et al. (2006)	Retrospective cohort	US	1992-2001	31,621	4.6 years	Included: Men with non-metastatic first diagnosis of PCa aged > 65 years Excluded: T-stage unknown	GnRH agonist or orchiectomy	No ADT treatment

Keating et al. (2010)	Retro-spective cohort	US	2001-2005	13,620	2.6 years	Included: invasive non-metastatic PCa Excluded: T-stage unknown	GNRH agnoists (96%) or oral anti-androgens (8%) or combination of both (13%), or orchidectomy (2%)	No ADT treatment
Kim et al. (2011)	Retro-spective cohort	Canada	1998-2005	4,015	5.5 years	Included: Patients receiving EBRT for PCa	EBRT(60-78 Gy) + LHRH analogues with or without non-steroidal anti-androgens	EBRT (60-78 Gy) without ADT
McLeod et al. (2006)	Pooled RCTs	Multiple countries across 5 continents	NR	4,052	7.4 years	Included: non-metastatic localised (T1-T2 N0/Nx) or locally-advanced (T3-T4, any N or any T, N+) PCa	Bicalutamide daily + standard care (RT, RP or WW)	Standard care alone (RT, RP or WW)
Merrick et al. (2006)	Pros-pective cohort	US	1995-2002	382	5.4 years	Included: Stage T1b-T3a PCa patients who underwent brachytherapy > 3 years prior to analysis	73% received ≤ 6 months ADT; 27% received > 6 months ADT. LHRH agonist + anti-androgen initiated 3 months before implantation.	Brachytherapy alone (125 Gy ^{103}Pd or 145 Gy ^{125}I)
Punnen et al. (2011)	Retro-spective cohort	US	1995-2007	1,572	NR	Included: non-metastatic localised PCa T1-T3a Excluded: primary treatment unknown or anti-androgen alone	Any ADT treatment or local (RP or RT) + ADT	Local therapy (RT or RP) or watchful waiting/active surveillance
Roach et al. (2008)	RCT	US	1987-2006	224	NR	Included: patients with bulky (5x5 cm) T2-T4 tumours with or without lymph node involvement	Goserelin + flutamide neoadjuvant & concurrent with EBRT (65-70 Gy)	EBRT (65-70 Gy) alone
Saigal et al. (2007)	Retro-spective cohort	US	1992-1996	4,810	NR	Included: men diagnosed with PCa surviving ≥ 12 months after diagnosis Excluded: in situ carcinoma; underwent bilateral orchidectomy; cardiovascular event within 12 months of diagnosis	Any ADT treatment	No HT treatment
Tsai et al. (2007)	Retro-spective cohort	US	1995-2004	1,015	3.8 years	Included: localised PCa T1-T3a Nx/N0 Mx/M0 treated with definitive local therapy, HT, chemotherapy or transurethral microwave therapy	GnRH agonist and/or anti-androgen, neoadjuvant or adjuvant, in conjunction with local therapy	No HT treatment
Van Hemelrijck et al. (2010a)	Retro-spective cohort	Sweden	1997-2007	30,642	4 years*	Included: Men with PCa who received either curative treatment, surveillance or endocrine treatment as primary treatment	11% AA; 17% orchidectomy; 30% GnRH agonists; 38% GnRH agonists combined with short-time AA; 4% other combinations	Curative treatment or surveillance
Van Hemelrijck et al. (2010b)								
Van Hemelrijck et al. (2012)								Surveillance or RP or RT
Wilcox et al. (2012)	RCT	Australia & New Zealand	1996-2000	NR	NR	Included: men with locally-advanced PCa	RT + 6 months neoadjuvant ADT (goserelin + flutamide), starting 5 months prior to RT	RT alone

*Mean given where median not available

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Duplicate

Erratum: Diabetes and cardiovascular disease during androgen deprivation therapy: Observational study of veterans with prostate cancer (Journal of the National Cancer Institute (2009) 102: 1 (39-46)). Journal of the National Cancer Institute 2012; 104(19): 1518-1523.

6.2.2 Hot flushes

What is the most effective intervention for hot flushes as a result of long-term androgen suppression for prostate cancer?

Rationale

NICE clinical guidelines for prostate cancer recommend hormone therapy as a treatment option for men with locally advanced and advanced (metastatic) prostate cancer, although it can also be offered to men with high risk localised prostate cancer. Androgen suppression blocks the production of androgens including testosterone, with the aim of slowing the growth of prostate cancer cells.

The resulting decrease in testosterone levels over a long term can lead to adverse effects, including hot flushes. One study has estimated that between 55 and 80% of men on androgen suppression therapy will experience hot flushes[9], although the prevalence is still unclear (see PICO 12a).

Hot flushes can be treated with anti-depressants, the α adrenergic agonist clonidine and hormone therapies such as medroxyprogesterone acetate, cyproterone acetate and diethylstilbestrol). Self-management (such as diet and lifestyle changes) may also be effective, as may complementary therapies.

How the information will be searched

Sources to be searched	
Can we apply date limits to the search	This topic is an update of one in the original 2008 guideline – but includes more interventions so a date limit will not be used.
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	A randomised trials filter will be used
List useful search terms.	

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? List subgroups here and planned statistical analyses	We will use the evidence table for randomised trials (NICE guidelines manual appendix J). The RCT checklist will be used (NICE guidelines manual appendix C).

Methods

Selection of studies

The information specialist (EH) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing the title and abstract to the inclusion criteria in the PICO question. The full articles were then obtained for possibly eligible studies and checked against the inclusion criteria.

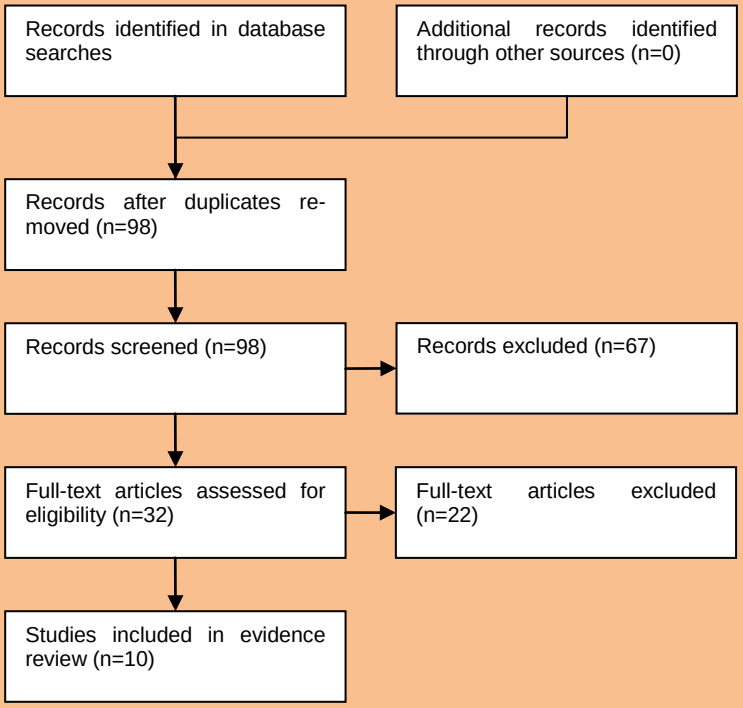
Analysis

Where possible, data were pooled into a meta-analysis.

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

Results

Results of the literature searches



The literature searches identified 98 possibly relevant studies (four from the update searches) of which 32 were ordered as full text articles and 10 were included in the evidence review.

Evidence statements

Hormone therapies

Oestrogens: Two RCTs identified in the previous guideline evidence review examined the effect of diethylstilbestrol (Atala et al., 1992) and oestrogen patches (Gerber et al., 2000) on hot flushes. No further evidence was found. Very low quality evidence showed a complete resolution of hot flushes in 86% (12/14) of men treated with diethylstilbestrol compared with 0% (0/14) of those receiving placebo (RR 25, CI 1.62 to 385.09). Full analysis and data were not presented (Atala et al., 1992). Diethylstilbestrol was associated with gynacomastia and breast tenderness, but the rates of adverse events were not reported. Low quality evidence from Gerber et al (2000) compared the effect of low dose (0.05mg) and high dose (0.10mg) estradiol patches on hot flushes in 12 men with advanced prostate cancer receiving leuprolide injections. A moderate or major improvement in hot flushes was seen in 25% of the low dose estradiol group compared with 67% of the high dose group (RR in favour of high dose 2.67, CI 0.93 to 7.69). Painless breast swelling was reported by 4/12 men on high dose estradiol and 1/12 men on low dose estradiol (RR 4.00, CI 0.52 to 30.76).

Progesterone analogues: One RCT (Loprinzi, 1994a) of low quality examined the effect of 20mg megestrol acetate on hot flushes in 66 men who had undergone surgical or medical androgen suppression. A significant reduction in both frequency and severity of hot flushes was found in favour of megestrol acetate. 79% of men in the megestrol acetate group and 12% of men in the placebo group reported at least 50% reduction in daily frequency of hot flushes (RR 6.50, CI 2.55 to 16.57). No adverse events were reported. One high quality RCT involving men with ADT associated hot flushes compared medroxyprogesterone, venlafaxine and cyproterone acetate (Irani et al., 2010).

Greater hot flush reduction was seen in the medroxyprogesterone and cyproterone acetate arm than was seen in the venlafaxine arm. Complete regression of hot flush symptoms was reported in 8% of the venlafaxine group, 37% of the cyproterone group, and 25% of the medroxyprogesterone group. Adverse event rate was higher in the cyproterone group (25%) compared to the medroxyprogesterone group (12%) and the venlafaxine group (20%). Health-related quality of life scores were high in all groups over time (mean 85, out of 100). Venlafaxine had the highest scores at 4 week and 8 week follow-up.

Cyproterone acetate

Eaton & McGuire (1983) reported a low quality RCT of cyproterone acetate versus placebo. The mean number of hot flushes per day was around 2 during the treatment period compared to 10 during the placebo phase. The authors reported a significant reduction in incidence of hot flushes with cyproterone acetate. However, it is not specified whether this is versus baseline or placebo. 5 out of 12 men complained of lethargy, severe enough to reduce dosage in one case.

Clonidine

From one RCT (Loprinzi et al., 1994b), there was no significant difference between clonidine and placebo arms in terms of frequency or severity of hot flushes. Clonidine was associated with increased dry mouth and redness under the patch.

Antidepressants

Venlafaxine: In the RCT by Irani et al (2010) venlafaxine showed a 47% reduction in hot flush score. However, hormonal therapy with medroxyprogesterone and cyproterone had a significantly larger benefit than did venlafaxine.

An unpublished study by Vitolins et al (2011) compared 4 groups of treatment for hot flushes in androgen-deprived men: placebo pill plus casein protein, soy protein plus placebo pill, venlafaxine plus casein protein, or soy plus venlafaxine. All groups showed a reduction in hot flush score over time but there were no significant differences between groups.

Complementary therapies

Soy isoflavones: One moderate quality placebo-controlled trial found no improvement in hot flushes or quality of life for high dose isoflavones compared to placebo (Sharma et al., 2009). No adverse events were reported.

Dong Quai: One RCT found no significant changes in the severity, frequency or duration of hot flashes among men receiving placebo or Dong Quai (a Chinese herbal compound) (Al-Bareeq et al., 2010). No adverse events were reported.

Acupuncture: One trial (Frisk et al., 2009) of moderate quality compared electrostimulated acupuncture (EA) and traditional acupuncture (TA) in castrated men (via surgery or GnRH analogue). 8 patients completed 6 weeks of observation before treatment and showed no changes in number of hot flushes per day and distress caused by flushes. Both groups demonstrated a significant reduction in frequency and severity of hot flushes after 12 weeks acupuncture. A decrease of hot flush frequency larger than 50% was reported in 57% of the EA group and 47% of the TA group at 12 weeks [RR 1.22, CI 0.60 to 2.48]. At 12 months follow-up 18% of the EA group and 46% of the TA group still experienced a decrease in number of hot flushes of 50% or more [RR 0.26, CI 0.04 to 1.70]. This study reported a 78% reduction of hot flush scores in the EA group and a 73% reduction in the TA group, without any statistical analysis. However, there was no placebo control group as there is no accepted placebo for acupuncture. 3 patients reported adverse events (1 distress, 1 fatigue, 1 hematoma).

Diet and lifestyle changes

No evidence was identified

Table 117 Study characteristics

HF=hot flushes; ADT=androgen deprivation therapy; FACT-P= Functional Assessment of Cancer Therapy-Prostate; EORTC QLQ=Quality of Life Questionnaire

Reference	Participants (n)	Sample	Intervention	Trial duration	Outcome measures	Adverse events	Comments
Eaton, 1983 UK	12 (I:8, C:4) Mean age=67	Patients with troublesome post-orchidectomy HF	Cyproterone acetate, 100mg, 3x/daily versus placebo.	3 week treatment before crossover (1 week washout)	Mean no. of daily HF over treatment period, recorded on daily charts	5 lassitude, 1 severe asthenia	Methods unclear, baseline characteristics not provided. No analysis of results
Loprinzi, 1994a USA	166 - 100 women, 66 men. (I:81, C:82) Mean age=NR	Men with bothersome HF for at least 1 month post-surgical (84%) or medical (16%) castration	Megastrol acetate, 20mg, 2x/daily versus placebo	4 week treatment before crossover (no washout)	Mean no. of HF daily; mean daily HF score after 4 weeks of treatment; patient preference after treatment	None reported in men. 6 dropouts for unreported reasons	
Loprinzi, 1994b USA	77 (I: 38, C: 39) Median age = 68	Men who had medical or surgical castration with HF for more than 1 month, >7 flushes/week	Transdermal clonidine 0.1mg equivalent daily dose versus placebo. Patches changed weekly.	4 week treatment before crossover (no washout)	Median no. of HF; median HF severity: median HF score	Dry mouth, redness under patch	Full efficacy data not presented
Atala, 1992 USA	14 randomised Mean age=NR	Men with post-surgical castration (no additional ADT)	Diethylstilbestrol 1mg/day versus placebo	12 week treatment before crossover (no washout)	Mean no. of HF; mean severity of HF; mean duration of HF	Gynecomastia, breast tenderness (no numbers reported)	Methods unclear, baseline data not provided. No analysis of results
Gerber, 2000 USA	12 randomised Mean age =71	Men with advanced PCa receiving leuprolide injections every 1 or 3 months with >3months HF. All men receiving leuprolide for > 1 year.	Estrogen patch low dose (0.05mg) versus high dose (0.10mg) 2x/week.	4 week treatment before crossover (4 week washout)	Mean no. of HF daily; mean severity of HF; Mean duration of HF; Improvement in symptoms	1 painless breast swelling with low dose. 4 painless breast swelling with high dose.	No control group.
Irani, 2010 France	311 (Venaflaxine: 102, Cyproterone acetate: 101, Medroxyprogesterone acetate: 108) Mean age=72	Men with >14 HF per week after 6 months ADT treatment (GnRH analogues)	Venaflaxine delayed release 75mg/day, versus Medroxyprogesterone 20mg/day, versus Cyproterone 100mg/day	10 weeks	Mayo clinic hot flush diary – No. of HF x severity = daily HF score. Quality of life: EORTC-QLQ	7, 8 and 9 patients had 1 or more adverse event leading to discontinuation in the V, C and MA groups respectively. 1 dyspnoea caused by CA, 1 urticaria caused by MA	No control group.
Vitolins, 2011 USA	120 (Placebo + casein protein: 30, Placebo + soy protein: 30: Venaflaxine + casein protein: 30, Soy + venaflaxine: 30) Median age=69	Androgen-deprived men (no inclusion criteria reported)	4 daily regimens: Placebo + casein protein, Placebo + soy protein, Venaflaxine + casein protein, Soy + venaflaxine	12 weeks	No. of HF x severity = HF severity score; Quality of Life: FACT-P	"Minimal toxicity" 88% treatment compliance	Abstract only
Sharma, 2009 USA	33 (I:17; C:16) Mean age=69	Men undergoing medical or surgical ADT for ≥3months. Mean ADT duration =	20gm Revival soy protein – 160mg total isoflavones as powder to be mixed with beverages 1x/day versus	12 weeks	Vasomotor symptoms: Blatt-Kupperman questionnaire; Quality of life: SF-36	No safety issues. 1 man withdrew due to dislike of powder. Overall compliance =80%	

		2 years	placebo whole milk protein and similar nutrients				
Al-Bareeq, 2010 Canada	22 (I: 11, C: 11) Mean age= 73	Men undergoing ADT. Mean ADT duration =17months (range:2-51)	500mg Dong Quai (derived from Angelica sinensis root) 1x/day for 12 weeks versus placebo	12 weeks	HF frequency, severity, duration and bother; partial thromoblastin time; international normalised ration of prothrombin time	5 patients withdrew (3 placebo, 2 intervention) due to gastrointestinal upset, headache, no perceived benefits, unrelated head injury and scheduling conflicts	Baseline HF data collected after randomisation. Placebo group sig fewer HF episodes per day at baseline.
Frisk et al, 2009 Sweden	31 (TA: 16, EA: 15) Mean age = 69	Men with surgical (n=2) or medical (GnRH, n=29) castration and >20 HF per week.	30min 2x/week for 2 weeks, then 1x/week for 10 weeks. Electrostimulated acupuncture (2 Hz in 4 points) versus traditional acupuncture (8 points)	12 weeks	No. of hot flushes x distress caused = Hot Flush Score	No serious side effects reported. 1 dropout due to treatment distress, 1 fatigue, 1 hematoma	No control/placebo for acupuncture

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Included

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*Gerber, G. S., Zagaja, G. P., Ray, P. S., Rukstalis, D. B. (2000). Transdermal estrogen in the treatment of hot flushes in men with prostate cancer. *Urology, 55(1),* 97-101.

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Vitolins, M. (2011). Phase III randomized, double-blind, placebo-controlled trial of soy protein and venlafaxine for treatment of hot flashes in men with prostate cancer. *Journal of Clinical Oncology, Conference(var.pagings),* 15.

Al-Bareeq, R. J., Ray, A. A., Nott, L., Pautler, S. E., Razvi, H. (2010). Dong Quai (angelica sinensis) in the treatment of hot flashes for men on androgen deprivation therapy: results of a randomized double-blind placebo controlled trial. *Canadian Urological Association Journal, 4(1),* 49-53.

Frisk, J., Spetz, A. C., Hjertberg, H., Petersson, B., Hammar, M. (2009). Two modes of acupuncture as a treatment for hot flushes in men with prostate cancer--a prospective multicenter study with long-term follow-up. *European Urology, 55(1),* 156-163.

Excluded studies

Reason: non-English language

Gonzalez, S. V., Puig, F. M., Martos, M. A., Sanchez, M. V. V., Capellan, M. D. S., Marti, S. S. (2009). Review of current treatment for hot flushes induced by androgen deprivation in prostate carcinoma. *Actas Urologicas Espanolas, 33(4),* 337-343.

Reason: not RCT

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Hayes, M., Reeder, C., Beer, T. M. (2009). Acupuncture for hot flashes for prostate cancer patients. *Journal of Clinical Oncology, 27(15),*

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Jones, J. M., Kohli, M., Loprinzi, C. L. (2012). Androgen deprivation therapy-associated vasomotor symptoms. *Asian Journal of Andrology, 14(2),* 193-197.

Morrow, P. K., Mattair, D. N., Hortobagyi, G. N. (2011). Hot flashes: a review of pathophysiology and treatment modalities. [Review]. *The Oncologist, 16(11),* 1658-1664.

Stearns, V. (2004). Management of hot flashes in breast cancer survivors and men with prostate cancer. [Review] [60 refs]. *Current Oncology Reports, 6(4),* 285-290.

Reason: duplicate

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Reason: population not relevant

Linde, K., Niemann, K., Schneider, A., Meissner, K. (2010). How large are the nonspecific effects of acupuncture? A meta-analysis of randomized controlled trials. *BMC Med, 8(* 75.

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Reason: outcomes not relevant

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6.2.3 Sexual function

Which are the most effective interventions (singly or in combination) for sexual dysfunction as a result of long term androgen suppression for prostate cancer?

Rationale:

Long term androgen suppression is often offered to men with non-localised disease. It functions to keep the disease under control by shrinking it, reducing its symptoms, or delaying its growth. In locally advanced and advanced cancer it can extend over months or years, or indefinitely. A range of methods for administering the treatment are used (injections, implants, tablets) on a regular, intermittent or 'maximal blockage' basis, and all act by stopping testosterone from reaching (prostate cancer cells.

Loss of sex drive (libido – total or reduced) and erectile problems (erectile dysfunction – ED) are very common side effects of long term androgen suppression. Such changes in sexual functioning can lead to a number of interrelated consequences:

- Physical difficulties:
- Difficulties in getting/sustaining an erection
- Inability to have penetrative sex
- Inability to ejaculate/reach orgasm
- Dry orgasm/infertility
- Psycho-emotional and relationship difficulties:
- How the man feels about sex (lack of interest, lack of confidence, and anxiety), with possible consequence of subdued mood/depression.
- Lowered self esteem – feeling of loss of role within partnership/family;
- Marital difficulties can arise as a consequence of all of above

Such difficulties can be experienced with different levels of intensity.

Therapeutic interventions are of two types: 1) Physical Treatments and 2) Advice, Counselling and Psycho –Sexual Therapy:

1. Physical Treatments for erectile dysfunction:
2. Tablets (PDE5 Inhibitors to assist erection, and SSRIs for treating changes to affect as a consequence of experiencing ED)
3. Injections and Pellets into the penis (Prostaglandins)
4. Mechanical (Vacuum pumps etc).

Counselling and Psycho-sexual Therapy

Assist men (and their partners/family) in coping with emotional reactions (anxiety, shock, depression) associated with loss of libido, ED and associated damage to self esteem and confidence, anxiety how partner will react etc. SSIs can help here.

It is suggested that skilful help in enabling men to talk about and share feelings and worries can be helpful, and improve overall sense of wellbeing.

More evidence is required to better understand which of these interventions, either individually or in combination, would best support men on long term androgen suppression to deal with any sexual dysfunctions, along with the psycho-sexual sequelae, that they are experiencing.

How the information will be searched

Sources to be searched	
Can we apply date limits to the search	This topic is an update of one in the original 2008 guideline so we will search for studies published since.
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	A randomised trials filter will be used
List useful search terms.	

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? List subgroups here and planned statistical analyses	We will use the evidence table for randomised trials (NICE guidelines manual appendix J). The RCT checklist will be used (NICE guidelines manual appendix C).

Methods

Selection of studies

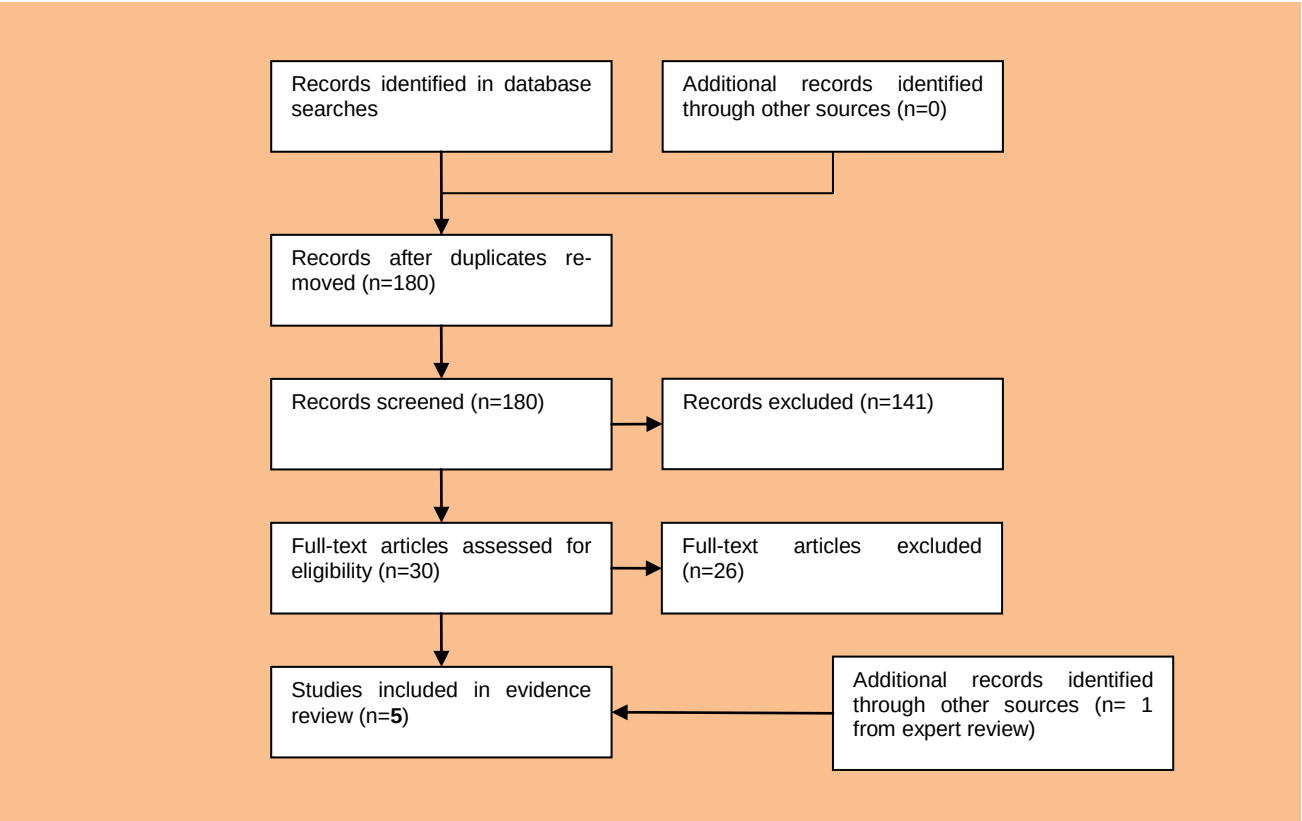
The information specialist (EH) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing the title and abstract to the inclusion criteria in the PICO question. The full articles were then obtained for possibly eligible studies and checked against the inclusion criteria.

Analysis

Where possible, data were pooled into a meta-analysis.

Results

Results of the literature searches



The literature searches identified 180 possibly relevant studies (16 from the updates) of which 30 were ordered as full text articles and 5 were included.

One RCT (Watkins-Bruner et al., 2011), 3 systematic reviews (Chisholm et al., 2012; Khera & Goldstein, 2011; Miles et al., 2007) and 1 case-series study (Teloken et al., 2007).

Evidence statements

Only one RCT addressing the PICO was identified (Watkins-Bruner et al., 2011). One case-series study was identified from an expert review comparing response rates to Sildenafil in men treated with and without androgen deprivation therapy (ADT) (Teloken et al., 2007). Therefore, evidence from 3 systematic reviews are reported, which included men with prostate cancer receiving any treatment (Chisholm et al., 2012; Khera & Goldstein, 2011; Miles et al., 2007). In the previous guideline the evidence reviewed also related to all men receiving any treatment for prostate cancer. Some studies did not state if men have been treated with ADT and some studies excluded those on ADT.

A majority of the studies evaluated sexual function using the self-administered International Index of Erectile Function (IIEF).

PDE5 inhibitors

One placebo-controlled crossover trial (Watkins-Bruner et al., 2011) evaluated Sildenafil in treating erectile dysfunction (ED) in patients treated with RT and neoadjuvant and concurrent ADT. Based on the improvement in erectile function (IIEF score of ≥4 out of a total possible score of 5), overall 40 patients (66%) did not respond to either placebo or Sildenafil; 10% responded to both placebo and Sildenafil; 21% responded to Sildenafil but not placebo; and 3% responded to placebo but not Sildenafil. The percentage of patients responding to Sildenafil but not placebo could only be as large as 31%. Patients who received a shorter duration of ADT (≤120 days) appeared to receive a greater benefit in erectile response to sildenafil than was noted in the overall study group. The

mean improvement from placebo to Sildenafil on the IIEF erectile function domain was 4.03 (p< 0.001) (range of possible scores = 0-30). There was no Sildenafil effect on the Sexual Adjustment Questionnaire (18% placebo only vs. 23% Sildenafil only). Mild adverse events were reported by 4% of all patients (2 mild changes in vision, 1 moderate flushing, 2 severe headaches).

In the previous guideline, 4 RCTs demonstrated the effectiveness of Sildenafil, Tadalafil and Vardenafil for the treatment of ED after external beam radiotherapy and prostatectomy (Incrocci et al., 2001; 2006; Brock et al., 2003; Montorsi et al., 2004). All studies excluded men on ADT, except for Brock et al. who excluded men with low serum testosterone levels.

A systematic review of the 4 RCTs reviewed in the previous guideline provided evidence that oral phosphodiesterase type 5 (PDE5) inhibitors are effective in the medium term (up to 4 months) when used to treat erectile dysfunction after EBRT or radical bilateral nerve-sparing or unilateral nerve-sparing retropubic prostatectomy (Miles et al., 2007).

The overall quality of trials was fair. Two studies reported the method of randomisation sequence generation. The method of concealment of allocation was not described adequately in any of the trials. Recruitment rates, where reported, were low. The risk of attrition bias was low.

The combined results of the two parallel group RCTs for improvements in erections resulted in a significant odds ratio (OR 10.09, 95% CI 6.20, 16.43) in favour of PDE5 inhibitors (Brock, 2003; Montorsi, 2004). Three trials found significant improvements in successful vaginal intercourse in favour of PDE5 inhibitors. Overall, the PDE5 inhibitors led to improved erectile function in about two-thirds of patients. However, in a subgroup of men with more severe dysfunction at baseline (Brock et al., 2003), many fewer reported achieving successful sexual intercourse.

All trials reported negative effects of PDE5 inhibitors. Adverse events were mild to moderate and included headache, dyspepsia, flushing, nausea and nasal congestion. All the side-effects were more frequent in the PDE5 inhibitor groups. In one trial of Vardenafil (Brock et al., 2003) more serious adverse events were reported in the intervention group, including tachycardia (6/223) and chest pain (6/223). It is unclear if events occurred in the same individuals.

One prospective case-series study (Teloken et al., 2007) explored the effects of ADT on response to Sildenafil in patients with erectile dysfunction (ED) following radiotherapy. Mean erectile function domain score and percent who experienced erectile function domain normalization at each time-point were lower in those with versus those without ADT. The percentage of men responding to Sildenafil at 24 months post-radiotherapy was 61% for those without ADT and 47% for those with ADT (p=0.032). This could be because tissue androgenisation is required for optimal response to PDE5 inhibitors. The duration of ADT treatment and testosterone recovery was not reported in this study.

No trials which directly compared different PDE5 inhibitors were indentified.

Prostaglandins

No studies assessing the efficacy of prostaglandins on sexual dysfunction in men treated with ADT were found.

From the previous guideline, a review of placebo-controlled trials in patients with ED of mixed aetiology concluded that intraurethral alprostadil (prostaglandin E1) was beneficial in increasing the proportion of men achieving at least one successful attempt at sexual intercourse [OR in favour of prostaglandin E1 7.22 (5.68 to 9.18)] (Urciuoli et al., 2004). Increased penile pain was reported more frequently in the intervention groups (30% alprostadil versus 3% placebo; OR 7.39, CI 5.40 to 10.12). It was not clear what proportion of patients had ED due to prostate cancer. All the trials included in the review pre-selected men who had a good response to alprostadil before randomisation. One further trial evaluated the use of prostaglandin E1 in men receiving sexual counselling (Titta et al., 2006, see below).

Psychosexual counselling

No trials were indentified which assessed the efficacy of psychosexual counselling specific to men with sexual dysfunction following ADT.

One systematic review was identified which evaluated the effectiveness of psychosocial interventions in improving sexual and/or relationship functioning for men with prostate cancer and their partners (Chisholm et al., 2012 – included all studies reported in the previous guideline). Five out of 11 studies which used a measure of sexual functioning reported significant improvement for at least one arm of their intervention (Canada et al., 2005; Giesler et al., 2005; Molton et al., 2008; Penedo et al., 2007; Titta et al., 2006). Four out of these 5 studies had sexual functioning as a major focus of the intervention and used a face-to-face format run by psychologists/training psychologists. Specific intervention strategies that were unique to those interventions that had a positive effect on sexual functioning were the explicit use of sex therapy techniques, including taking a sexual history, teaching sensate focus, and challenging negative thoughts related to sexuality and masculinity. Of the six studies that found no impact of the intervention on sexual functioning (Mishel et al., 2004; Campbell et al., 2007; Lepore et al., 2003; McCorkle et al., 2007; Northouse et al., 2007; Weber et al., 2004), five had sexual functioning as a minor focus and five used supportive/educative strategies. Only two interventions were delivered face-to-face and nurses were more likely to deliver these interventions, with psychologists delivering two programs. Most studies included in the systematic review were of low methodological quality.

Vacuum devices

No studies were indentified which evaluated the use of vacuum devices for men with ED following ADT.

In the systematic review by Miles et al. (2007) one trial was reported which evaluated the effectiveness of a vacuum constriction device (VCD) for inducing erection in 109 men with ED following retropubic prostatectomy (Raina, 2006). 81% (60/74) of the intervention group using the VCD successfully had sexual intercourse. At nine months there was a significant difference in overall sexual function in favour of the intervention group [WMD 4.30 (CI 2.53 to 6.07)]. There was no significant difference in EF between the two trial arms [OR 0.78 (CI 0.33 to 1.88)]. 23% in the intervention group discontinued treatment, mostly because of discomfort (55%) or penile bruising (20%).

Prostheses

No studies were indentified which evaluated the use of penile prosthesis for men with ED following ADT. The systematic review by Khera & Goldstein (2011) found no systematic reviews or RCTs about penile prostheses in men with erectile dysfunction of any cause. Khera & Goldstein (2011) state that prostheses are likely to be beneficial and are usually considered only after less invasive treatments have failed. Mechanical failure and infections are the most serious complications of prosthesis implantation (data cited from one prospective cohort study).

Table 118 Study Characteristics

PCa=prostate cancer; EBRT=external bean radiation therapy; ADT=androgen deprivation therapy; ED=erectile dysfunction; IIEF=International Index of Erectile Function; EF= erectile function; RRP=radical retropubic prostatectomy; SAQ=sexual adjustment questionnaire; GAQ=Global Assessment Question

Reference	Participants (n randomised)	Intervention	Comparison	Outcomes	Additional comments
Watkins-Bruner 2011	(115) T1b-T4 PCa, no known nodal or distant metastases, PSA≤100 ng/ml before ADT. Patients treated with EBRT + neoadjuvant and concurrent ADT without brachytherapy. 83% within 24 months of RT completion. ED at baseline as measured by IIEF.	N=30 12 weeks sildenafil. 50mg (1 pill) dose 1-hour prior to desired sexual activity and increasing to 100mg (2 pills) daily as needed. Patients requested to take at least 2 pills per month.	N=31 Identical placebo followed by crossover to sildenafil treatment after 1 week washout phase	IIEF SAQ	Large amount of missing data (55% completed all 3 IIEF assessments). Underpowered study.
Brock 2003	(440) ED secondary to unilateral or bilateral nerve-sparing RRP. All men had tumescence after RRP. Surgery at least 6 months ago	(i) N=114, 10mg vardenafil (ii) N=119, 20mg vardenafil 12 week treatment. One dose maximum a day. Treatment taken one hour before sexual intercourse	N=97 Identical placebo	IIEF GAQ	25% lost to follow-up
Incrocci 2001	(60) Men with ED treated with RT in stable relationship and prepared to perform sexual activity at least 1x/week. Mean time since RT=39 months	N=30 50mg sildenafil for 2 weeks; at week 2 dose was increased to 100mg. After 6 weeks patients crossed over to control arm. 12 week total treatment duration.	N=30 Identical placebo for 6 weeks followed by crossover to intervention for 6 weeks	IIEF GAQ	No details on randomisation provided. No 'washout' period reported before crossover
Incrocci 2006	(60) Men with ED after 3D-conformal EBRT. RT ≥12 months before trial entry.	N=30 20mg tadalafil taken at discretion at least 1x/week and no more than once daily. Crossover at 6 weeks	N=30 Identical placebo followed by crossover at 6 weeks	IIEF GAQ	
Montorsi 2004	(303) men with ED after bilateral non-nerve sparing RRP. Men were not excluded if they had no tumescence after RRP. Surgery 12-48 months before study	N= 201 10mg tadalafil for 12 weeks	N=106 Identical placebo	IIEF GAQ SEP	

Table 119 Psychosocial counselling

PCa=prostate cancer; CBT=cognitive behavioural therapy; CBSM= cognitive behavioural stress management; IIEF=International Index of Erectile Function

Reference	Participants (n randomised)	Intervention	Aspect of intervention related to sexual function	Comparison	Outcomes	Additional comments
Campbell 2007	(40) African-American men with localised PCa (beyond acute phase and treatment	6-weekly telephone-based CBT sessions.	Information on how PCa affects relationship and the need to include partner. Communication skills.	Usual care	EPIC: sexual function,	
Canada 2005	(84) men with localised PCa treated with RT or surgery in previous 3-6 months	4 sessions of sex therapy with or without partner	Major focus on relationship and sexual functioning. Education around PCa and sexual dysfunction. Communication skills. Sensate focus exercises. Also addressed partners sexual needs	No control group	IIEF ED medical treatment use DAS: relationship quality and satisfaction	Excluded men on ADT
Giesler 2005	(99) men with localised PCa scheduled to have or had surgery, radiation or brachytherapy.	Computer assisted symptom management program. 6 monthly session (2 face-to-face, 4 telephone)	All patients given video on PCa and sexual functioning. Program tailored to individual needs. Teaching dyadic communication skills and information about medical ED interventions	Usual care	PCQoL: sexual function, sexual bother	
Lepore 2003	(279) men with localised PCa treated in last month (range of treatments)	6-weekly group lectures (1) Education: (2) Education plus discussion	One education session on relationships and sexuality by psychologist. Education plus discussion arm had an additional 45 minutes of facilitated group discussion.	Usual care	UCLA-PCI: sexual function	
McCorkle 2007	(126) men with a variety of diagnoses (including metastatic PCa)	8 weekly post-hospital standardised nursing intervention with 16 contacts (50% home and 50% telephone)	Content focusing on reinforcing open communication, ways to convey love and support, sharing concerns about intimacy	Usual care	CARES: sexual function (sexual interest/dysfunction). Marital interaction	
Mishel 2002	(252) men with localised PCa with 2 weeks post-catheter removal after surgery and/or 3 weeks into current radiation therapy.	8 weekly telephone calls for uncertainty management	Information on potency enhancement methods, ways of expressing intimacy in other ways than intercourse, and general problem solving	Usual care and printed health information material unrelated to PCa	SDS: sexual function and sexual satisfaction	
Molton 2008	(121) men recovering from surgery for localised PCa within 18 months	10 weekly group CBSM focusing on promotion of sexual functioning	Promotion of sexual functioning by providing information on treatment options for ED, broadening definition of sexuality, developing skills to discuss ED with partners	Control (4-hour workshop on stress management skills)	UCLA-PCI: sexual function CASF: sexual function and masculine identity	
Northouse 2007	(263) men newly diagnosed with PCa (65%), biochemical recurrence (14%) or advanced PCa (21%)	10 weekly couple FOCUS sessions (3 home visits and 2 telephone calls)	Couple intervention focused on communication about illness and providing each other with support.	Usual care (standard clinic care and support)	EPIC: erectile function FACT-G: one item related to satisfaction with sex life	
Penedo 2007	(93) men with localised PCa treated by surgery or RT in past 21 months	10 weekly group CBSM sessions	Focus on relaxation skills with CB approaches to stress management. Skills were partially designed to assist with management of ED. Some information provided on the management and treatment of sexual dysfunction.	Control (half day education seminar on stress management skills)	EPIC: erectile function FACT-G: one item related to satisfaction with sex life	

Titta 2006	(57) 88% of sample were men treated for PCa with surgery	Intercavernosal injection therapy (ICT) plus psychodynamic counselling	Counselling aimed at increasing use of erectile medical aids. Used sexual therapy techniques to consider couples sexual behaviour and relationship. Investigate fears and difficulties with ICT.	ICT only	IIEF: erectile function, intercourse satisfaction Level of responsiveness to sildenafil.	
Weber 2004	(32) men with localised PCa recruited 6 weeks after surgery which resulted in urinary and sexual dysfunction	Dyadic peer support program. Met 8 times in 8 weeks	Recent patients were paired with long-term survivors (3+ years) who had surgery resulting in urinary and sexual dysfunction. Encouraged to talk about sensitive topics including sexual dysfunction	Usual care	UCLA-PCI: sexual function	

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Included studies

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Titta M, Tavolini IM, Dal Moro F, Cisternino A, Bassi P. Sexual counselling improved erectile rehabilitation after non-nerve-sparing radical retropubic prostatectomy or cystectomy - Results of a Randomised Prospective Study. *Journal of Sexual Medicine* 2006;3:267-73.

Weber BA, Roberts BL, Resnick M, Deimling G, Zauszniewski JA, Musil C, et al. The effect of dyadic intervention on self-efficacy, social support, and depression for men with prostate cancer. *Psycho-Oncology* 2004;13:47-60.

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*Reported in evidence review in previous guideline

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Reason: expert review

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Reason: more recent review available

Brotto, L. A., Yule, M., Breckon, E. (2010). Psychological interventions for the sexual sequelae of cancer: A review of the literature. *Journal of Cancer Survivorship-Research and Practice, 4(4),* 346-360.

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6.2.4 Osteoporosis

What is the most effective intervention for osteoporosis as a result of long-term androgen suppression for prostate cancer?

Rationale

Long term androgen deprivation therapy for prostate cancer is commonly used in locally advanced and metastatic disease. Osteoporosis is common in the ageing man and may be present in men about to commence androgen deprivation therapy and such therapy may result in the development and/or worsening of osteoporosis. There is uncertainty about the appropriate tests for osteoporosis in men about to commence long term androgen deprivation therapy particularly with the use of DEXA scans. In addition there is a lack of guidance on the monitoring of men who are on long term androgen deprivation therapy and what the criteria are for treatment with intervention.

PICO question

Population	Intervention	Comparator	Outcomes
Men treated with long term androgen suppression for non-metastatic prostate cancer	Interventions for osteoporosis: • Exercise • Bisphosphonates • Denosumab • Calcium & vitamin D	• Each other • No intervention	• Overall survival • Skeletal related events • Fracture rate (location) • Osteonecrosis of the jaw • Bone mineral density loss • Change in FRAX score • Health-related quality of life

How the information will be searched

Sources to be searched	
Can we apply date limits to the search	No date limit
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	A randomised trials filter will be used
List useful search terms.	

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? List subgroups here and planned statistical analyses	We will use the evidence table for randomised trials (NICE guidelines manual appendix J). The RCT checklist will be used (NICE guidelines manual appendix C).

Methods

Search strategy

The full strategy will be available in the full guideline. The search was restricted to randomised controlled trials (RCTs) but not by date.

Selection of studies

The information specialist (EH) did the first screen of the literature search results. Due to the wide availability of RCTs on the use of bisphosphonates for prostate cancer treatment-induced bone loss, conference abstracts were not ordered for this intervention. A number of good quality systematic reviews on this intervention were used to identify all relevant primary RCTs.

For exercise, denosumab and calcium/vitamin D interventions, one reviewer (KC) then selected possibly eligible studies by comparing their title and abstract to the inclusion criteria in the PICO question. A second reviewer (NB) checked the included studies. The full articles were then obtained for possibly eligible studies and checked against the inclusion criteria.

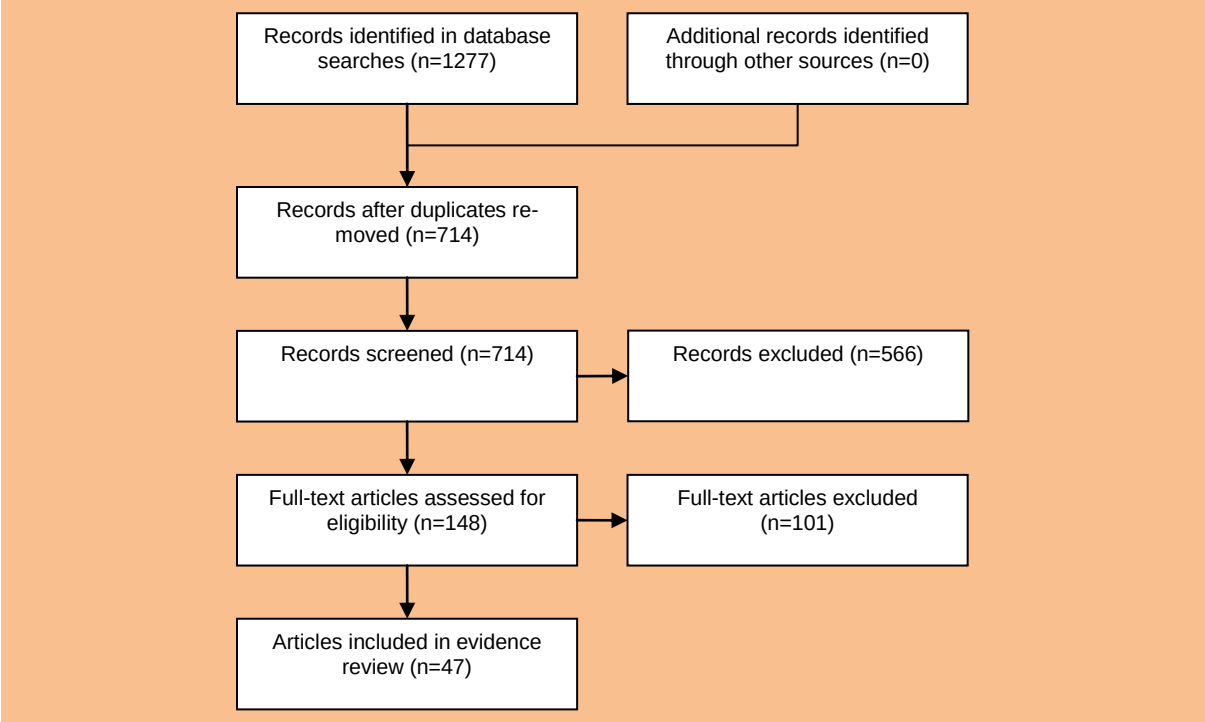
Following agreement with the GDG, only studies in men with non-metastatic prostate cancer were included.

Analysis

All outcomes were dichotomous, with the exception of bone mineral density (BMD) which was continuous. Where the number of events (e.g. cases or deaths) was reported, data were pooled into a meta-analysis and risk ratios calculated. For BMD, where the number of events, total number of patients analysed, and standard deviation were available or could be calculated, data were pooled into a meta-analysis and the mean difference in BMD percentage change between treatment groups calculated. Where available, data for different types of bisphosphonate therapy were summarised in sub-group analyses.

Results

Results of the literature searches



The literature searches identified 714 possibly relevant articles of which 148 were ordered in full text. Forty-seven articles referring to 22 different studies were included.

Characteristics of included studies

Three of the studies were only available as abstracts (Phooshkooru 2006; Papaioannou 2007; Denham 2011).

Population

Seventeen studies only included patients without metastatic disease, four (Papaioannou 2007; Ryan 2007; Denham 2011; Klotz 2011) did not specify disease stage, and one (Smith 2012) only included patients with non-metastatic disease but who were at high risk of metastases and who had had no prior hormone therapy.

ADT duration

Ten studies required included patients to be either already receiving ADT or to have undergone an orchidectomy (Phooshkooru 2006; Greenspan 2007; Michaelson 2007; Papaioannou 2007; Rodrigues 2007; Smith 2009; Galvao 2010; Choo 2011; Kapoor 2011; Smith 2012). Of these, one study specified that patients receiving medicated ADT (not surgical) had been receiving it for 2-3 years at the start of the study (Choo 2011), one study specified ≥ 6 months (Smith 2012), and one study specified > 2 months exposure to ADT (Galvao 2010). One study required that the ADT had been started within the previous 9 months at study entry (Phooshkooru 2006). While another of the studies instead required that patients receiving medicated ADT have a expected on-study treatment duration of ≥ 12 months (Smith 2009).

Four studies also accepted patients that were starting ADT at study entry (as well as those already on and responding to ADT) (Ryan 2006; Israeli 2007; Ryan 2007; Bhoopalam 2009). Three of which, required that patients already receiving medicated ADT should only have been receiving it for ≤ 1 year (Ryan 2006; Israeli 2007; Ryan 2007).

Two studies only included patients who were starting ADT at study entry (unless they had previously undergone orchidectomy) (Smith 2003; Taxel 2010).

Six studies provided ADT as part of the trial, in both the intervention and control groups (Smith 2001; Morabito 2004; Casey 2006; Rao 2008; Denham 2011; Klotz 2011). Of these, three placed no restriction on receipt of ADT prior to the start of the trial (Smith 2001; Morabito 2004; Denham 2011) while three only included patients who had not received any previous ADT (Casey 2006; Rao 2008; Klotz 2011). During the trials, ADT treatment duration was between 6 and 18 months (where reported).

Intervention

Only one RCT (Galvao 2010) was found which analysed an exercise intervention in patients undergoing ADT. Two RCTs were found which compared denosumab to placebo in this population (Smith 2009; Smith 2012). Nineteen studies were included which assessed the relevant outcomes for the use of bisphosphonates in patients undergoing ADT.

Eleven bisphosphonate studies (Smith 2003; Casey 2006; Phooshkooru 2006; Ryan 2006; Israeli 2007; Michaelson 2007; Ryan 2007; Rao 2008; Bhoopalam 2009; Denham 2011; Kapoor 2011) assessed zoledronic acid, two studies assessed alendronate (Greenspan 2007; Klotz 2011), two assessed risedronate (Taxel 2010; Choo 2011), one study assessed pamidronate (Smith 2001), one assessed neridronate (Morabito 2004), one assessed ibandronic acid (Papaioannou 2007), and one study assessed the use of either zoledronic acid or clodronate (Rodrigues 2007).

Control

The exercise intervention study used usual care as a control. Two studies compared denosumab together with calcium and vitamin D supplements to the supplements alone. Of the 19 bisphosphonate studies, three (Papaioannou 2007; Rodrigues 2007; Denham 2011) compared a bisphosphonate to no intervention while 15 studies compared a bisphosphonate together with calcium and vitamin D supplements to the supplements alone (Smith 2001; Smith 2003; Morabito 2004; Casey 2006; Phooshkooru 2006; Ryan 2006; Greenspan 2007; Isreali 2007; Michaelson 2007; Rao 2008; Bhoopalam 2009; Taxel 2010; Choo 2011; Klotz 2011; Kapoor 2011). One study compared a bisphosphonate with calcium carbonate to calcium carbonate alone (Ryan 2007).

Evidence statements

Overall survival

One study (Rao 2008) provided low quality evidence of no significant improvement in overall survival between patients receiving bisphosphonates compared to those receiving no intervention.

One study (Smith 2012) provided moderate quality evidence of no significant improvement in overall survival between patients receiving denosumab, compared to no intervention (though the number of patients surviving was not reported). The study also reported no significant difference in median survival time between the two groups.

Skeletal-related events

None of the studies included in this review reported the number of skeletal-related events.

Fracture rate (any location)

One study (Klotz 2013) provided low quality evidence of no significant difference in overall fracture rate between patients treated with alendronate and those receiving no intervention (p=0.43).

One study (Smith 2009) provided moderate quality evidence of no significant difference in overall fracture rate between patients treated with denosumab and those receiving no intervention. However, this study did find a significant reduction in the occurrence of more than one fracture at any site in the denosumab group (p=0.006).

Fragility fracture rate

One study (Greenspan 2007) provided low quality evidence of no significant difference in the rate of fragility fractures between patients receiving a bisphosphonate (alendronate) and those receiving no intervention.

Vertebral fracture rate

Smith et al. (2003) found moderate quality evidence of no significant difference in the number of newly diagnosed or worsening vertebral fractures between patients receiving zoledronic acid or no intervention.

One moderate quality study (Smith 2009) found a significant reduction in vertebral fractures in patients receiving denosumab compared to those receiving no intervention (RR 0.39 95% CI 0.20 – 0.78). The results suggest that for every 1,000 patients, 23 fewer vertebral fractures occur in those receiving denosumab alongside their ADT.

Osteonecrosis of the jaw

Seven studies (Casey 2006; Ryan 2006; Israeli 2007; Michaelson 2007; Bhoopalam 2009; Kapoor 2011; Choo 2011), ranging from 12 to 24 months in follow-up, provided low quality evidence of no occurrence of osteonecrosis of the jaw (ONJ) in those receiving bisphosphonates or no intervention.

One study (Smith 2012) provided very low quality evidence of an increased risk of ONJ in patients receiving denosumab compared to those receiving no intervention at 30 months (incidence of 2.3% compared to 0.0%). Another study (Smith 2009) found no occurrence of ONJ in either the denosumab or no intervention group at 36 months.

Bone mineral density loss: lumbar spine

Sixteen studies provided moderate quality evidence of a lower risk of bone mineral density (BMD) loss at the lumbar spine in patients receiving bisphosphonates than those receiving no intervention. There was a mean BMD increase of 4.1% in the bisphosphonates group and a mean decrease of 2.7% in the no intervention group. Seven of the studies (Smith 2003; Ryan 2006; Greenspan 2007; Israeli 2007; Michaelson 2007; Ryan 2007; Rao 2008) contributed data to the meta-analysis which suggests a mean difference of 7.2% change (95% CI 5.7% - 8.7%; p<0.0001) between those receiving bisphosphonates and those receiving no intervention. Six of the studies assessed the effect of zoledronic acid and found a significant mean difference of 7.7% (95% CI 6.1% - 9.2%) compared to a no intervention group. The seventh study (Green-

span 2007) assessed the effect of alendronate and found a significant mean difference of 5.1% (95% CI 3.5% - 6.7%) compared to the no intervention group.

One high quality study (Smith 2009) reported a significant difference in lumbar spine BMD change between patients receiving denosumab and those receiving no intervention. A BMD increase of 5.6% was reported in the denosumab group compared to a decrease of 1.0% in the no intervention group ($p<0.001$).

Bone mineral density loss: total hip

Twelve studies provided low quality evidence of a lower risk of bone mineral density (BMD) loss at the hip in patients receiving bisphosphonates than those receiving no intervention. There was a mean BMD increase of 1.0% in the bisphosphonates group and a mean decrease of 1.6% in the no intervention group. Five of the studies (Smith 2003; Ryan 2006; Greenspan 2007; Israeli 2007; Michaelson 2007) contributed data to the meta-analysis which suggests a mean difference of 3.0% change (95% CI 2.0% - 4.1%; $p<0.0001$) between those receiving bisphosphonates and those receiving no intervention. Four of these studies assessed the effect of zoledronic acid and found a significant mean difference of 3.6% (95% CI 2.9% - 4.3%) compared to a no intervention group. The fifth study (Greenspan 2007) assessed the effect of alendronate and found a significant mean difference of 1.4% (95% CI 0.4% - 2.4%) compared to the no intervention group.

One high quality study (Smith 2009) reported a significant difference in total hip BMD change between patients receiving denosumab and those receiving no intervention, but did not report the estimated percentage change.

Bone mineral density loss: femoral neck

Ten studies provided low quality evidence of a lower risk of bone mineral density (BMD) loss at the femoral neck in patients receiving bisphosphonates than those receiving no intervention. There was a mean BMD increase of 1.2% in the bisphosphonates group and a mean decrease of 2.1% in the no intervention group. Five of the studies (Smith 2003; Ryan 2006; Greenspan 2007; Michaelson 2007; Ryan 2007) contributed data to the meta-analysis which suggests a mean difference of 2.9% change (95% CI 2.1% - 3.8%; $p<0.0001$) between those receiving bisphosphonates and those receiving no intervention. Four of the studies assessed the effect of zoledronic acid and found a significant mean difference of 3.3% (95% CI 2.2% - 4.4%) compared to a no intervention group. The fifth study (Greenspan 2007) assessed the effect of alendronate and found a significant mean difference of 2.3% (95% CI 0.9% - 3.7%) compared to the no intervention group.

Bone mineral density loss: trochanter

Three studies provided low quality evidence of a lower risk of bone mineral density (BMD) loss at the trochanter in patients receiving bisphosphonates than those receiving no intervention. Two of these studies (Smith 2003; Michaelson 2007) contributed data to the meta-analysis which suggests a mean difference of 4.0% change (95% CI 2.2% - 5.8%; $p<0.0001$) between those receiving the bisphosphonate zoledronic acid and those receiving no intervention.

Change in FRAX score

None of the studies included in this review reported change in FRAX score.

Health-related quality of life

One study (Galvao 2010) provided moderate quality evidence of the impact of an exercise intervention on the health-related quality of life of prostate cancer patients undergoing ADT. The Short Form-36 (SF-36) was used to assess general quality of life status and found significantly better scores for general health, vitality and physical health in the exercise group. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ) C30 was also used to assess cancer specific quality of life and found the exercise group to have significantly better scores for role, cognitive, fatigue, nausea and dyspnea measures.

Figure 78 Forest plot of lumbar spine BMD percentage change in studies comparing bisphosphonates with no intervention in patients undergoing long-term ADT

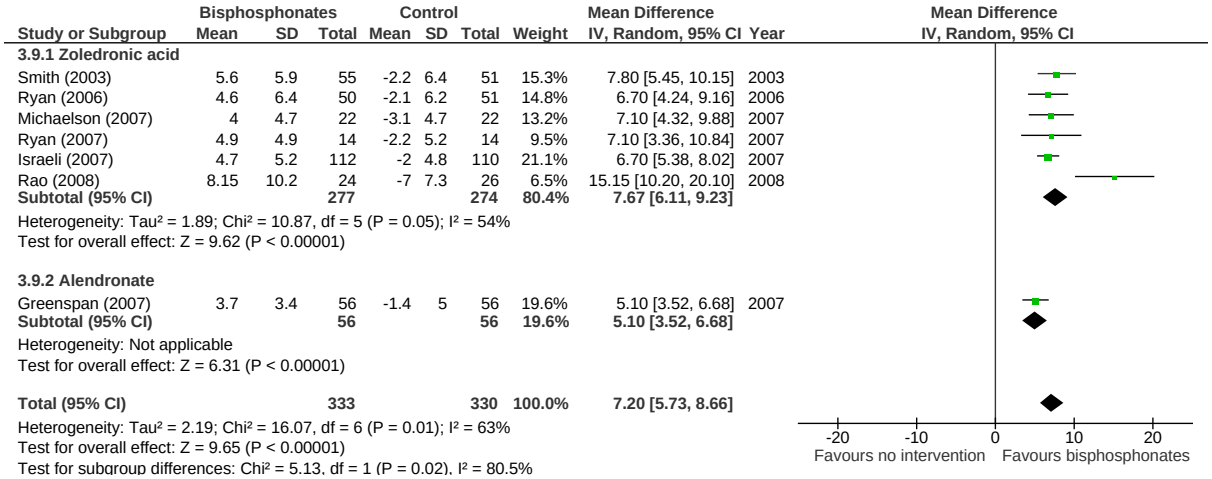


Figure 79 Forest plot of total hip BMD percentage change in studies comparing bisphosphonates with no intervention in patients undergoing long-term ADT

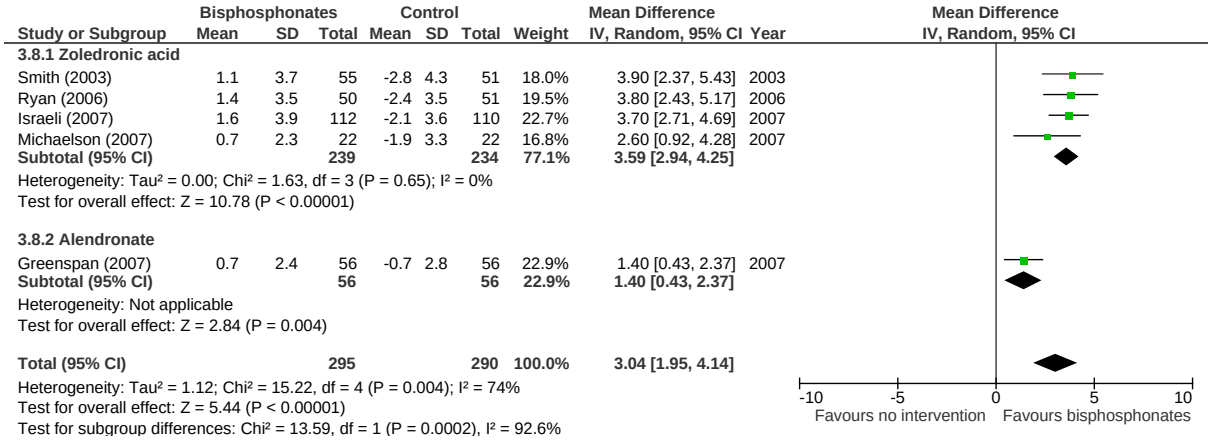


Figure 80 Forest plot of femoral neck BMD percentage change in studies comparing bisphosphonates with no intervention in patients undergoing long-term ADT

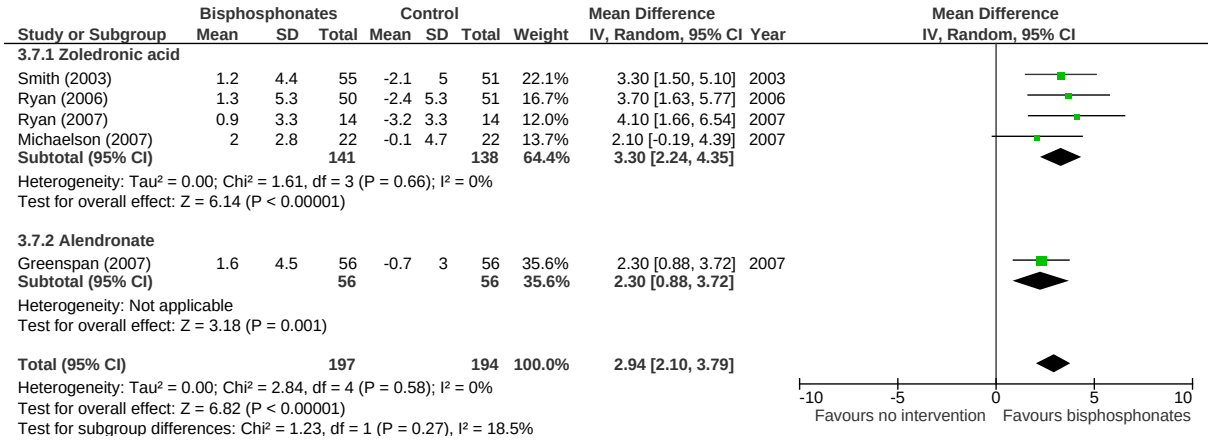


Figure 81 Forest plot of trochanter BMD percentage change in studies comparing bisphosphonates with no intervention in patients undergoing long-term ADT

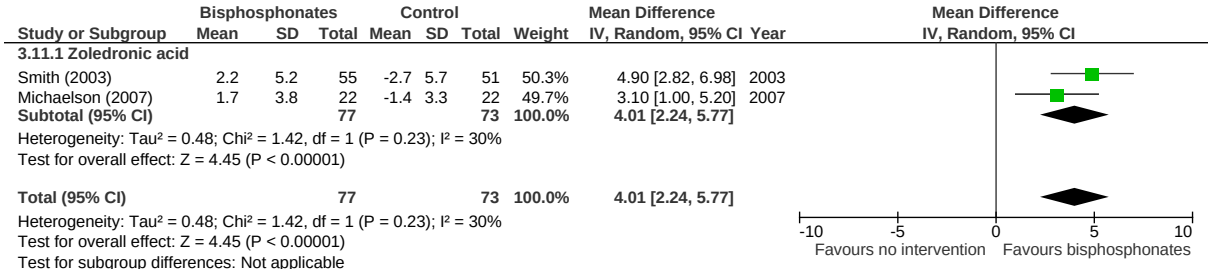


Table 120 Summary of randomised controlled trial characteristics

Abbreviations: ADT = androgen deprivation therapy; BMD = bone mineral density; PCa = prostate cancer; PSA = prostate specific antigen; RCT = randomised controlled trial; sc = subcutaneously; im = intramuscularly; iv = intravenously

Study	Country/ies	Recruitment period	No. of patients randomised	Length of study	Inclusion criteria	Exclusion criteria	Intervention group	Comparator group
Galvao et al. (2010)	Australia	2007 - 2008	57	12 weeks	PCa patients with prior ADT exposure > 2 months, without PSA evidence of disease activity or metastatic bone disease.	Musculoskeletal, cardiovascular or neurological disorders which could inhibit exercise; inability to walk 400m or undertake upper and lower limb exercise or resistance training in previous 3 months.	Combined progressive resistance and aerobic training twice a week for 12 weeks.	Usual care.
Smith et al. (2009)	US & Europe	2004 - 2008	1468	36 months	Men with non-metastatic PCa receiving ADT with an expected on-study treatment duration ≥ 12 months; with low baseline BMD or history of an osteoporotic fracture if aged < 70 years	Concurrent antineoplastic therapy or radiotherapy; PSA > 5 mg/ml after anti-androgen therapy for > 1 month; current or previous bisphosphonate use; current treatment for osteoporosis; BMD < -4 at lumbar spine, total hip, or femoral neck.	60 mg denosumab sc every 6 months + 1 mg calcium & ≥ 400 IU vitamin D daily for 3 years.	Matching placebo + 1 mg calcium & ≥ 400 IU vitamin D daily for 3 years.
Smith et al. (2012)	30 countries	2006 - 2008	1432	30 months	Non-metastatic PCa patients aged ≥ 18 years who had received a bilateral orchidectomy or continuous ADT with a GnRH agonist or antagonist for ≥ 6 months. Patients were to be castration-resistant within 3 consecutive increasing PSA tests with high risk for bone metastases.	Previous or current metastasis (except lymph nodes); history of osteomyelitis or osteonecrosis of jaw; previous secondary malignant disease within 5 years; previous denosumab or bisphosphonate treatment.	120 mg denosumab sc every 4 weeks. Daily supplemental calcium (≥ 500 mg) and vitamin D (≥ 400 IU) strongly recommended.	Placebo sc every 4 weeks. Daily supplemental calcium (≥ 500 mg) and vitamin D (≥ 400 IU) strongly recommended.
Smith et al. (2001)	US	-	47	48 weeks	Men with locally advanced, lymph node positive, or recurrent PCa and no bone metastases.	Paget's disease; hyperthyroidism; Cushing's disease; hyperprolactinemia; chronic liver disease; chronic renal insufficiency; anti-androgen deprivation, glucocorticoids, bisphosphonates, calcitonin or thyroxine within previous year.	60 mg pamidronate disodium iv every 12 weeks + 22.5 mg leuprolide im every 12 weeks for 48 weeks + 50 mg bicalutamide orally daily for 4 weeks + 500 mg calcium carbonate & 400 IU vitamin D daily.	22.5 mg leuprolide im every 12 weeks for 48 weeks + 50 mg bicalutamide orally daily for 4 weeks + 500 mg calcium carbonate & 400 IU vitamin D daily.
Smith et al. (2003)	US	2000 - 2000	106	12 months	Men with non-metastatic PCa beginning initial ADT with a GnRH agonist +/- anti-androgen or who had undergone orchidectomy within 2 weeks of first visit	Previous androgen deprivation therapy, anti-androgen, bisphosphonate, calcitonin, gallium nitrate or mithramycin treatment within 1 year; high creatinine; severe hepatic disease; other major organ dysfunction; high lumbar spine BMD.	4 mg zoledronic acid sc every 3 months for 1 year + 500 mg calcium & 400 IU vitamin D supplement daily.	Placebo + 500 mg calcium & 400 IU vitamin D supplement daily.
Morabito et al. (2004)	Italy	-	60	12 months	Osteoporotic patients with locally advanced PCa (T2-4 NX M0); none of which had undergone surgery, chemotherapy or radiotherapy.	Paget's disease; hyperthyroidism; Cushing's disease; hyperparathyroidism; hyperprolactinemia; chronic liver disease; chronic renal insufficiency; previous androgens, glucocorticoids, bisphospho-	25 mg neridronate sc every month + 500 mg calcium & 400 IU cholecalciferol daily + ADT (50 mg triptorelin depot & bicalutamide daily OR 150 mg bicalu-	500 mg calcium & 400 IU cholecalciferol daily + ADT (50 mg triptorelin depot & bicalutamide daily OR 150 mg bicalutamide daily).

						nates, calcitonin or thyroxine.	tamide daily).	
Casey et al. (2006)	Canada	2003 - 2004	187	24 months	ADT-naive men with locally advanced, lymph node positive, or recurrent PCa and no metastases aged ≥ 18 years.	Prior ADT, calcitriol or bisphosphonate therapy; thyroxine treatment within 12 months; concomitant or prior long-term systemic glucocorticoid therapy; Paget's disease; hyperthyroidism; Cushing's disease; hyperprolactinemia; chronic liver disease; chronic renal insufficiency.	Goserelin + 4 mg zoledronic acid every 3 months for 24 months + 500 mg calcium & 400 IU vitamin D supplements.	Goserelin alone + 500 mg calcium & 400 IU vitamin D supplements.
Phoosh-kooru et al. (2006)	-	-	22	15 months	Asymptomatic PCa patients undergoing ADT, started within the last 9 months.	None reported.	4 mg zoledronic acid iv every 3 months + 500 mg calcium & 200 vitamin supplements three times daily for 1 year.	500 mg calcium & 200 vitamin supplements three times daily.
Ryan et al. (2006)	US	2003 – 2004	120	12 months	PCa patients aged ≥ 18 years with non-metastatic PCa beginning ADT or had initiated ADT within previous 12 months; life expectancy ≥ 12 months.	High serum creatinine; previous bisphosphonate treatment; long-term systemic corticosteroids within previous 12 months; anabolic steroids or growth hormone within previous 6 months; parathyroid hormone for > 1 week or systemic sodium fluoride > 3 months in previous 2 years; drugs known to affect the skeleton within 2 weeks of randomisation.	4 mg zoledronic acid sc every 3 months for 4 treatments + 500 mg calcium & 400-500 IU vitamin D daily.	Placebo + 500 mg calcium & 400-500 IU vitamin D daily.
Green-span et al. (2007)	US	2002 – 2003	112	12 months	Men aged ≤ 85 years receiving ADT (gonadotrophin-releasing agonists and/or anti-androgens) for non-metastatic PCa.	Other malignancy within 5 years; elevated PSA; testosterone level out of castrate range; any illness or taking any medication that would affect bone and mineral metabolism; previous bisphosphonate therapy	70 mg alendronate orally once per week + 500 mg calcium carbonate & 200 UI vitamin D supplements.	Placebo once per week + 500 mg calcium carbonate & 200 UI vitamin D supplements.
Israeli et al. (2007)	US	2003 – 2005	222	52 weeks	Men with non-metastatic PCa within 1 year of starting ADT (LHRH agonist +/- anti-androgen for an intended duration of ≥ 12 months or orchidectomy), life expectancy ≥ 12 months.	Previous treatment for osteoporosis; previous bisphosphonate therapy or systemic corticosteroids within 12 months; anabolic steroids/growth hormones within 6 months; receiving diethylstilbestrol; concomitant or previous malignancies or other comorbid conditions; history of lumbosacral spine surgery, bilateral hip replacement or surgery; abnormal renal function.	4 mg zoledronic acid sc every 3 months for 48 weeks + 500 mg calcium & 400-500 IU/L vitamin D daily.	Placebo sc every 3 months for 48 weeks + 500 mg calcium & 400-500 IU/L vitamin D daily.
Michael-son et al. (2007)	US	2003 – 2005	44	12 months	PCa patients being treated with a GnRH agonist at study entry, without bone metastases or evidence of progressive disease.	Metabolic bone disease; history of treatment for osteoporosis; history of deep venous thrombosis or pulmonary embolus; low serum calcium; high serum creatinine; chronic use of glucocorticoids, anticonvulsants, thyroxine or bisphosphonate treatment within 1 year.	4 mg zoledronic acid sc on day 1 only + 500 mg calcium carbonate & 400 U vitamin D daily.	Placebo on day 1 only + 500 mg calcium carbonate & 400 U vitamin D daily.
Papaio-annou et al. (2007)	Greece	-	44	12 months	Non-metastatic PCa patients receiving a GnRH agonist.	None reported.	6 mg ibandronic acid iv once only.	Placebo.

Rodrigues et al. (2007)	Brazil	-	94	36 – 54 months*	Men with relapsed hormone-sensitive PCa (defined as rising PSA after radical prostatectomy with no evidence of metastatic disease) who are receiving LHRH agonists or have undergone orchidectomy.	Chronic renal failure; radiotherapy in previous 3 months.	1500 mg clodronate iv every 28 days. OR 4 mg zoledronic acid sc every month.	None.
Ryan et al. (2007)	US	2000 – 2002	42	12 months	PCa patients with life expectancy of ≥ 1 year, receiving ADT (LHRH agonist or orchidectomy) for ≤ 1 year or scheduled to begin ADT at start of study.	None reported.	4 mg zoledronic acid sc every 3 months for 4 treatments + 260 mg calcium carbonate in 4 tablets daily.	Placebo + 260 mg calcium carbonate in 4 tablets daily.
Rao et al. (2008)	India	2003 – 2004	50	12 months	Men with locally advanced PCa without distant metastases, who are unfit or unwilling for primary therapy, with no previous hormonal therapy.	Already received hormone therapy 4-6 weeks prior to enrolment; previous bisphosphonate therapy; severe cardiovascular, hepatic or other major organ dysfunction; baseline creatine >1.8 mg/dl; severe arthritis; previous lumbar vertebral fractures.	4 mg zoledronic acid iv + bilateral orchidectomy or GnRH agonist or total androgen blockade + 500 mg calcium twice daily & 400 IU vitamin D daily	Placebo + bilateral orchidectomy or GnRH agonist or total androgen blockade + 500 mg calcium twice daily & 400 IU vitamin D daily
Bhoopalam et al. (2009)	US	2003 – 2006	93	12 months	PCa patients with no distant metastatic disease, who are on or initiating ADT with LHRH (with or without anti-androgen) or bilateral orchidectomy.	Pre-existing osteopenia or osteoporosis; metabolic bone disease; corticosteroid use within 12 months; use of anabolic steroids, growth hormone, estrogen or estrogen-like medcations; renal insufficiency; high serum creatinine; low serum calcium; uncontrolled infection or diabetes; major organ dysfunction; concomitant malignancy.	4 mg zoledronic acid iv every 3 months for 12 months + 1,000 mg calcium & 400 U vitamin D daily supplements.	Placebo every 3 months for 12 months + 1,000 mg calcium & 400 U vitamin D daily supplements.
Taxel et al. (2010)	US	-	47	6 months	Non-metastatic PCa patients aged > 55 years within a month of receiving an initial ADT injection.	Chronic kidney, gastrointestinal or liver disease; previous cancer diagnosis; metabolic bone disorders; medications that interfere with bone metabolism.	35 mg risedronate weekly + 600 mg calcium & 400 IU vitamin D supplements daily.	Placebo + 600 mg calcium & 400 IU vitamin D supplements daily.
Choo et al. (2011)	Canada	2004 – 2007	104	24 months	Non-metastatic PCa patients undergoing radiotherapy and 2-3 years of ADT with a LHRH analogue.	None reported.	35 mg risedronate orally once weekly for 2 years + calcium & vitamin D supplements.	Placebo + calcium & vitamin D supplements.
Denham et al. (2011)	Australia & New Zealand	2003 – 2007	1071	24 months	Men with locally advanced PCa.	None reported.	18 months 4 mg zoledronic acid iv + 6 months neoadjuvant leuprolide + radiation with or without 12 months adjuvant leuprolide.	6 months neoadjuvant leuprolide + radiation with or without 12 months adjuvant leuprolide.
Kapoor et al. (2011)	US	2003 - 2008	41	12 months	Men aged ≤ 85 years with non-metastatic PCa receiving GnRH analogs (leuprolide or goserelin acetate) with evidence of osteopenia or osteoporosis.	Previous bisphosphonate, calcitonin, chronic steroid use, or estrogens; medical history of metabolic bone disorders; other malignancy; raised serum creatinine.	4 mg zoledronic acid iv every 3 months + 1,000 mg calcium & 500 IU vitamin D supplements daily for 12 months.	Placebo + 1,000 mg calcium & 500 IU vitamin D supplements daily for 12 months.
Klotz et al. (2011)	Canada	2005 - 2008	186	12 months	Hormone-naive PCa patients.	None reported.	70 mg alendronate orally once weekly + 30 mg leuprolide ace-	Placebo + 30 mg leuprolide acetate im every 4 months

							tate im every 4 months + 500 mg calcium & 400 IU vitamin D supplements for 1 year.	+ 500 mg calcium & 400 IU vitamin D supplements for 1 year.

*Mean given where median not available; range reported for all treatment groups where overall follow-up not given.

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Health Economic Evidence

Information sources and eligibility criteria

The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, COCHRANE, NHS EED. Studies conducted in OECD countries other than the UK were considered (Guidelines Manual 2009).

Studies were selected for inclusion in the evidence review if the following criteria were met:

Both cost and health consequences of interventions reported (i.e. true cost-effectiveness analyses)

Conducted in an OECD country

Incremental results are reported or enough information is presented to allow incremental results to be derived

Studies that matched the population, interventions, comparators and outcomes specified in PICO

Studies that meet the applicability and quality criteria set out by NICE, including relevance to the NICE reference case and UK NHS

Note that studies that measured effectiveness using quality of life based outcomes (e.g. QALYs) were desirable but, where this evidence was unavailable, studies using alternative effectiveness measures (e.g. life years) were considered.

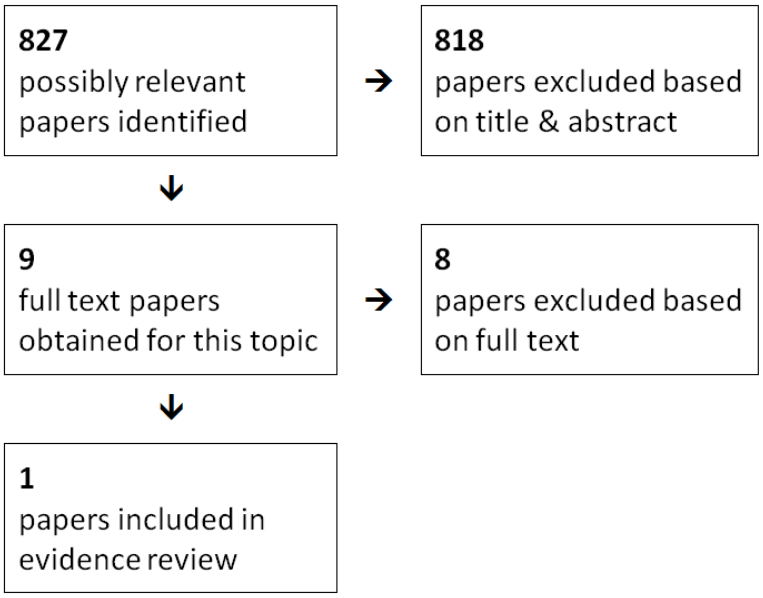
Selection of studies

The health economist screened the literature search results obtained by the information specialist by checking the article's title and abstract for relevance to the review question. The full articles of non-excluded studies were then attained for appraisal and compared against the inclusion criteria specified above.

Results

The diagram below shows the results of the search and sifting process. It can be seen that 827 possibly relevant papers were identified. Of these, nine full papers relating to this topic were requested for appraisal. Eight of these papers were excluded based on the full text as they were not applicable to the PICO or did not include an incremental analysis of both costs and health effects. Therefore one paper (Ito et al. 2010) was included in the current review of published economic evidence for this topic. The paper was a cost-effectiveness analysis, which quantified health effects in terms of quality adjusted life years (QALYs) and thus can be considered a cost-utility analysis.

Figure 82: Summary of evidence search and sifting process for this topic



Quality and applicability of the included study

The study was deemed only partially applicable to the guideline. This was mostly a result of the study considering a country other than the UK (analysis considered a U.S. setting). Minor limitations were identified with the study, with some minor concerns around the use of author assumptions and estimates. However, these were only used where no evidence could be sourced. Furthermore, there were no conflicts of interest identified so there is no reason to suspect that these assumptions were not made objectively.

The table below summarises the quality and applicability of the included study.

Table 121: Table showing methodological quality and applicability of the included study

Methodological quality	***Applicability***	
	Directly applicable	**Partially applicable**
Minor limitations		Ito et al. 2010
Potentially serious limitations		
Very serious limitations		

Modified GRADE table

The primary results of the analysis by Ito et al. 2010 are summarised in the modified GRADE table below.

Table 122 Modified GRADE table showing the included evidence (Ito et al. 2010) comparing methods of managing and treating osteoporosis

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
Ito et al. 2010	Men with prostate cancer	No BMD test or alendronate therapy	$75,474	6.5930	Reference case			One- and two-way sensitivity analysis was conducted in which patient age, history of fractures, cost of alendronate and mean BMD were varied. The results showed that a BMD test with selective alendronate therapy remained the most cost-effective option in most scenarios. However, the strategy of universal alendronate therapy is cost-effective in patients with a high risk of hip fractures. Probabilistic sensitivity analysis (PSA) was not conducted.	Partially applicable Minor limitations
		BMD test and selective alendronate therapy	$75,652	6.5957	$178	0.0027	$66,800		
		No BMD test, universal alendronate therapy	$77,153	6.6041	$1,501	0.0084	$178,700		
	Comments:								

Evidence statements

The base case results from Ito et al. 2010 suggest that that the use of alendronate therapy in prostate cancer patients with osteoprosis improves effectiveness in QALY terms but that this comes at an increased cost. A strategy of selective alendronate therapy using BMD tests is shown to reduce the additional costs by reducing the number of patients that are treated unnecessarily (i.e. reducing 'over-treatment'). In comparison to no alendronate therapy, selective alendronate therapy provided an additional QALY at a cost of $66,800.

Since the study is US based, it is difficult to draw firm conclusions from the analysis when applying it to the UK setting. However, it does show that selective alendronate therapy is more likely to be cost-effective than universal alendronate therapy.

In addition, the QALYs estimated in the study are potentially underestimates since they are based only on hip fractures. Including other fractures would potentially further increase incremental QALYs and thus improve the cost-effectiveness of selective alendronate therapy in comparison to no alendronate therapy.

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Full evidence table

The full details of the study included in the evidence review are presented in the evidence table below.

Table 123 Full evidence table showing the included evidence (Ito et al. 2010) that compared the methods of radical prostatectomy

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Study 1						
Author: Ito et al. **Year:** 2010 **Country:** United States	**Type of analysis:** Cost-effectiveness analysis **Model structure:** Markov state transition model **Cycle length:** Not stated **Time horizon:** Lifetime **Perspective:** Societal **Source of base-line data:** Cohort characteristics were based on an analysis of Radiation Therapy Oncology Group (RTOG) protocol 92-02, a natural history study of patients with rising PSA after ADT. Author assumptions were also used to inform baseline characteristics. Base case estimates of disease progression were derived from RTOG protocol 92-02 and a previous cost-effectiveness model for localised prostate cancer. (Hummel et al. 2003). It was assumed that the prevalence of osteoporosis was 1.91 times higher in patients with a previous fracture. Background mortality rates were based on US life tables (2004). **Source of effectiveness data:** No direct data shows that alendronate reduces fracture rates in prostate cancer patients receiving ADT. Thus, BMD was used as a surrogate The incidence of hip fractures was estimated as a function of age and BMD (both of which were simulated over time). The function was sourced from a published cross-sectional	**Inclusion criteria:** The hypothetical cohort consisted of men with locally advanced or high-risk localised prostate cancer (T2c to T4N0) **Exclusion criteria:** The hypothetical cohort did not include men receiving ADT as monotherapy for low or intermediate risk localised prostate cancer. Patients with a history of fragility fractures (this assumption was tested in the sensitivity analysis). **Base case (population):** Hypothetical cohort of men with locally advanced or high-risk localised prostate cancer (T2c to T4N0) starting a 2 year course of ADT after radiation therapy. **Sample size:** Not stated (hypothetical cohort is modelled). **Age:** 70 years old	A. No BMD test or alendronate therapy B. BMD test followed by selective alendronate therapy for patients with osteoporosis C. Universal alendronate therapy without BMD test	**Effectiveness (QALYs per strategy)** A. No BMD test or alendronate therapy B. BMD test followed by selective alendronate therapy for patients with osteoporosis C. Universal alendronate therapy without BMD test **Expected cost per patient:** A. No BMD test or alendronate therapy B. BMD test followed by selective alendronate therapy for patients with osteoporosis C. Universal alendronate therapy without BMD test **ICER (cost per QALY):** A. No BMD test or alendronate therapy B. BMD test followed by selective alendronate therapy for patients with osteoporosis C. Universal alendronate therapy without BMD test **Uncertainty:** One- and two-way sensitivity analysis was conducted in which patient age, history of fractures, cost of alendronate and mean BMD were varied. Probabilistic sensitivity analysis (PSA) was not conducted.	6.5930 6.5957 6.6041 $75,474 $75,652 $77,153 Reference $66,800 $178,700	**Funding:** No funding for study No potential conflicts of interest reported.

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	analysis of BMD and the risk of hip fracture in men and women. N.B. Hip fractures were the only fractures considered in the analysis. The rate of BMD loss in the absence of ADT was assumed to follow the rate reported in the Framingham Osteoporosis Study. The rate of BMD loss during ADT was estimated by fitting a linear regression to cross-sectional data of total hip BMD over a range of therapy durations up to 10 years. The effect of treatment of fracture risk was modelled under the assumption that patients had no BMD loss throughout the course of alendronate therapy. 100% adherence was assumed in the base case. The effect of zoledronic acid on the risk of hip fracture in patients with castrate metastasis was based on a published systematic review of bisphonates' effect on skeletal morbidity in metastatic cancer. It was assumed that 0.8% of patients had serious upper gastrointestinal side-effects in the first year of alendronate therapy. **Source of utility data:** Health state utilities were obtained from studies that used standardised methods (time trade off or standard gamble) to elicit preferences. No utility values were found for prostate cancer patients in the rising PSA state. Thus, the authors assumed that patients in this state had a slightly lower utility value than patients in the localised disease state. A utility multiplier associated with hip fractures was obtained from a Swedish prospective study of fracture patients. A utility value associated with a complicated peptic ulcer that required hospitalisation was used for serious upper gastrointestinal side effects.	**Gender:** Male **Subgroup analysis:** None stated				

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Source of cost data: The costs of dual-energy x ray absorptiometry, physician visit and hospitalisation for serious upper gastrointestinal side effects were based on average Medicare reimbursement rates. Retail prices reported by the New York State Board of Pharmacy were used for alendronate and a proton-pump inhibitor. Patients that did not adhere to alendronate therapy accrued the medication cost for only 6 months. Fracture costs were taken from a population-based cost analysis in Olmsted County, Minnesota. The cost of treating prostate cancer was assumed to be independent of BMD and fracture status. **Currency unit:** United States dollars ($) **Cost year:** 2008 (inflated using the CPI for Medical Care for All Urban Consumers. **Discounting:** 3% per year for health and cost outcomes					

6.2.5 Fatigue

What is the most effective intervention for fatigue as a result of long-term androgen suppression for prostate cancer?

Rationale

Long term androgen deprivation therapy for prostate cancer is commonly used in locally advanced Whilst long term androgen suppression is the treatment of choice for men with advanced prostate cancer, the suppression of testosterone can cause side effects including fatigue and loss of muscle mass which can negatively affect quality of life.

In a bid to alleviate the side effect of fatigue, it has been suggested that moderate intensity exercise (e.g. resistance, aerobic) of regular frequency may be of benefit. Some studies have suggested that resistance exercise may reduce fatigue, improve quality of life and reduce loss of muscle mass in men on long term androgen suppression

Others advocate counselling, in particular cognitive behavioural therapy as successful in reducing fatigue in men on long term androgren suppression and still others advocate a combination of the two interventions.

If intervention by either exercise, counselling or a combination could be seen to have a positive effect, it may be that pre-emptive steps could be taken at diagnosis.

PICO question

Population	Intervention	Comparison	Outcomes
Men treated with long term androgen suppression for prostate cancer	• Exercise • Counselling	• Each other • No intervention	• Fatigue • Health-related quality of life

How the information will be searched

Sources to be searched	
Can we apply date limits to the search	No date limit
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	A randomised trials filter will be used
List useful search terms.	

The review strategy

What data will we extract (what columns will we included in our evidence table) and how will we analyse the results? Which quality checklist will we use for appraisal? List subgroups here and planned statistical analyses	We will use the evidence table for randomised trials (NICE guidelines manual appendix J). The RCT checklist will be used (NICE guidelines manual appendix C).

Methods

Selection of studies

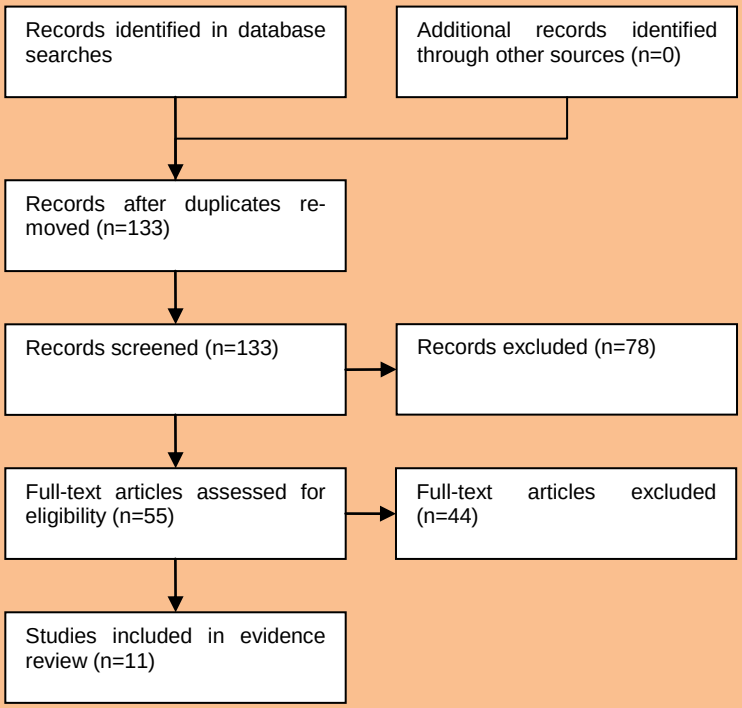
The information specialist (EH) did the first screen of the literature search results. One reviewer (JH) then selected possibly eligible studies by comparing the title and abstract to the inclusion criteria in the PICO question. The full articles were then obtained for possibly eligible studies and checked against the inclusion criteria.

Analysis

Where possible, data were pooled into a meta-analysis.

Results

Results of the literature searches



The literature searches identified 127 possibly relevant studies of which 53 were ordered as full text articles and 11 were included.

1 systematic review of exercise interventions was identified (Velthius et al., 2010), and the meta-analysis was updated with 3 extra RCTs; 8 RCTs were indentified comparing exercise interventions with control groups; 1 RCT comparing interpersonal counselling with health education (Badger, 2011); and 1 RCT comparing physical training and information with either physical training or information on their own (Berglund, 2007).

Evidence statements

Counselling

One moderate quality RCT compared interpersonal counselling with health education for men with prostate cancer (42% treated with hormone therapy) (Badger et al., 2011). Improvements in fatigue were significantly higher for patients in the health education group than for those in the counselling group, although wide confidence intervals suggest there could be little difference between the two interventions (MD in favour of the health education group 5.12, CI -3.08 to 13.32). Health-related quality of life scores were higher in the health education group, but this outcome also lacked precision due to wide confidence intervals (MD in favour of health education group -2.78, CI -6.60 to 12.16).

Berglund et al (2007) provided moderate quality evidence where men with prostate cancer were randomised to one of four groups (Physical training; information; physical training + information; or control). There was no significant effect of treatment on fatigue or quality of life. Fatigue and quality of life scores for each group were not reported.

Exercise

Nine RCTs provided high quality evidence. Monga et al (2007) was the only study not to include men on ADT, with all participants undergoing radiation therapy for prostate cancer. Oneill et al. (2012) did not provide details of the exercise intervention to allow this study to be included in sub-group analysis. Overall there was a significant mean difference in both fatigue and health-related quality of life between exercise interventions and the no intervention group of 0.38 (95%CI 0.11-0.66) and 0.20 (95% CI 0.04-0.36) ($p \leq 0.01$) respectively.

Home-based exercise

In one high-quality study (Windsor, 2004), patients in the intervention group were offered a home-based exercise programme during radiotherapy, consisting of walking 3 times a week for 30 minutes with an intensity of 60-70% HRmax, for the duration of radiotherapy. In another home-based exercise study (Culos-Reed, 2010), men undergoing ADT were given an individualised physical activity program consisting of walking, stretching and light resistance exercises.

Supervised exercise programmes

Six studies investigated the effectiveness of supervised exercise during radiotherapy and androgen deprivation therapy. In two studies (Monga 2007; Segal 2009), patients allocated to the intervention group participated in a supervised aerobic exercise program 3-times a week, consisting of aerobic exercises with an intensity of 65% HRmax, adjusted for age, and 50-70% of the VO_2 peak (15-45mins). In two supervised resistance exercise programmes the intervention consisted of resistance exercises two or three times a week with an intensity of two sets of 8-12 repetitions at 60-70% of one repetition maximum (Segal 2003; Segal 2009). Two studies randomised men receiving ADT to an intervention of combined aerobic and resistance exercise or a control group for 12-weeks (Bourke et al., 2011; Galvao et al., 2010). The intervention group in the study by Bourke et al (2011) also received dietary advice.

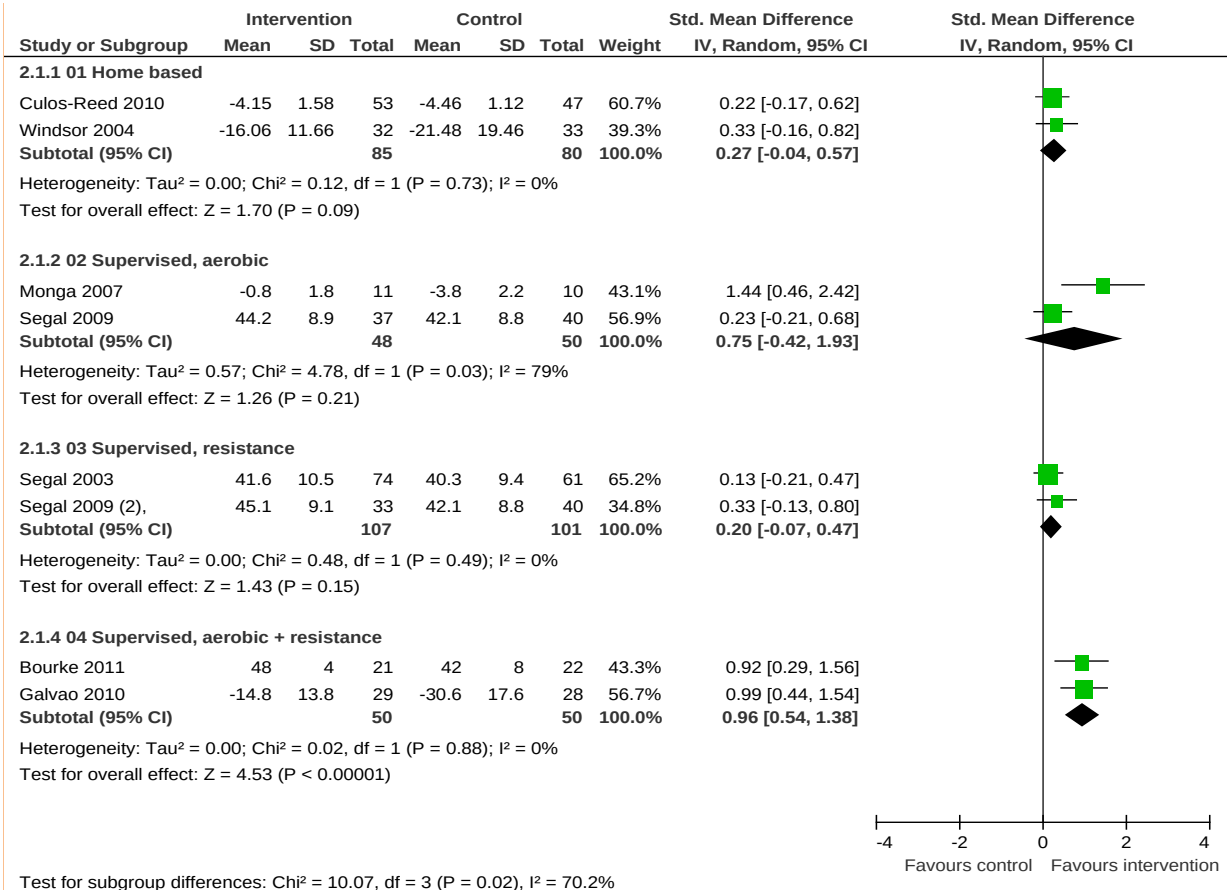
The results of the studies were pooled for aerobic and resistance exercise separately (see Figure 83). The pooled results for the home-based exercise studies showed a medium-sized, non-significant reduction in fatigue in favour of the exercise group (SMD 0.27, CI -0.04 to 0.57).

The results from two studies after supervised aerobic exercise showed a large though non-significant reduction in fatigue in favour of the exercise group (SMD 0.75, CI -0.42 to 1.93). Because statistical heterogeneity was present (p=0.03) a sensitivity analysis was performed in which the outlying study (Monga 2007) was excluded. This reduced the effect size to a small-sized and non-significant reduction in fatigue (SMD 0.23, CI -0.21 to 0.68).

The pooled results for two studies of resistance exercise showed a small-sized non-significant reduction in fatigue in favour of the exercise group (SMD 0.20, CI -0.07 to 0.47).

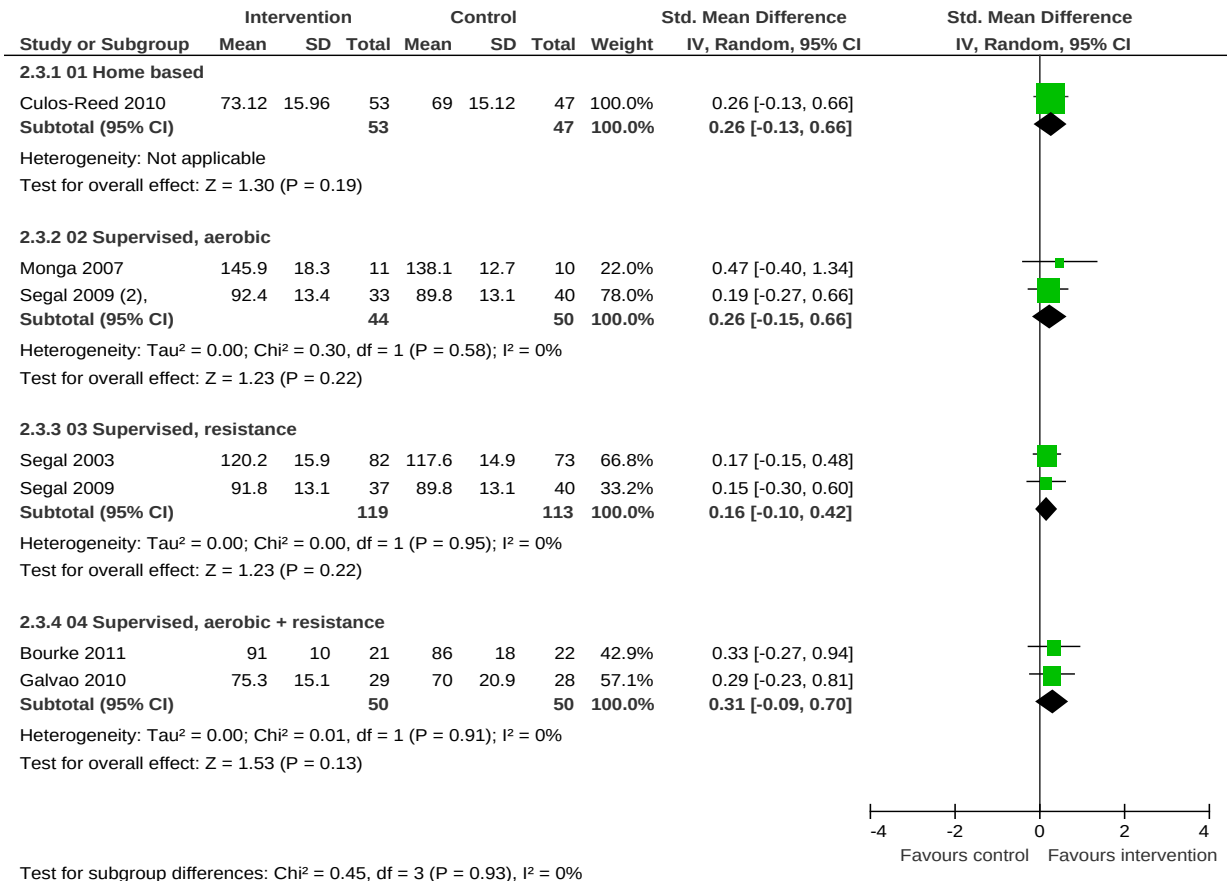
The pooled results of two studies of combined aerobic and resistance exercise showed a large-sized significant reduction in fatigue in favour of the exercise group (SMD 0.96, CI 0.54 to 1.38).

Figure 83 Forest plot of comparison: Exercise interventions versus control, by exercise type, Outcome: Fatigue



Six RCTs assessed the impact of exercise interventions on health-related quality of life (see Figure 84).

Figure 84 Forest plot of comparison: Exercise interventions versus control, by exercise type, Outcome: Health-related quality of life



Study Characteristics

Table 124 Interpersonal counselling versus health education

Reference	Participants	Cancer treatment	Intervention	Intervention duration	Adherence to intervention	Outcome measures	Adverse events
Badger 2011	Total: 71 (IPC: 36, HE: 35) Stage: I-IV Mean age: 67	39% surgery, 56% RT, 42% ADT, 10% watchful waiting	Telephone interpersonal counselling addressed mood and affect management, emotional expression, interpersonal communication and relationships. Telephone health education group received written material about cancer diagnosis, treatment, coping with side-effects etc	8 weeks	86% adherence in counselling group 89% adherence in education group	MFI UCLA-PCI	Not reported

Table 125 Physical training and information intervention

Reference	Participants	Cancer treatment	Intervention	Intervention duration	Adherence to intervention	Outcome measures	Adverse events
Berglund 2007	Total: 211 (53 phys, 55 info, 52 phys+info, 51 control) Stage: I-IV Mean age: 69	30% watchful waiting, 26% surgery, 26% ADT, 9% RT	PHYS = physiotherapist led 7 weekly 60 min sessions including movement and fitness training, relaxation, breathing exercises. Booster session held 2 months after. INFO= 60 min nurse led sessions giving information about PCa treatment, side effects PHYS+INFO = physical training + information given in seven 135-minute sessions	7 weeks	Not reported 20% attrition rate	EORTC QLQ – global QOL & fatigue	Not reported

PCa: Prostate cancer; RT: radiation therapy; ADT: androgen deprivation therapy; MFI: Multidimensional Fatigue Inventory; UCLA-PCI: Prostate Cancer Index; EORTC QLQ: Quality of Life Questionnaire

Table 126 Exercise interventions

Reference	Participants	Cancer treatment	Intervention	Intervention duration	Completion exercise	Outcome measures	Adverse events
Windsor 2004	Total:65 (I: 32, C: 33) Stage: localised Mean age = 69	EBRT (4 weeks treatment). 29% adjuvant ADT.	Home- based aerobic exercise – walking at least 3x/week 30 mins at 60-70% HRmax constant speed during RT treatment. (Men recruited whilst on RT waiting list)	Duration of RT (4 weeks)	100% completed intervention (≥1.5 hr exercise per week)	BFI Physical functioning	Not reported
Monga 2007	Total:21 (I:11 , C: 10) Stage: localised Mean age = 69	Radiotherapy (7-8 weeks treatment)	Supervised clinical aerobic exercise 3x/week 30 endurance training on treadmill before receiving daily RT	Duration of RT (8 weeks)	82% completed intervention	r-PFS FACT-P	Not reported
Segal 2009	Total: 110 (I: 37 aerobic, 33 resistance; C:40) Stage: I-IV; Mean age = 66	Radiotherapy with or without ADT (61% on ADT)	Supervised aerobic (3x/week 15-45 mins, 50-75% $V0_2$max) or resistance exercise (2x/week, 2 x 8-12 repetitions, 60-70% 1-RM) (appears to be before/during RT/ADT)	24 weeks	Not reported	FACT-F FACT-P FACT-G	1 chest pain; 1 myocardial infarction
Segal 2003	Total: 135 (I:74, C:61) Stage: I-IV Mean age = 68	ADT (mean duration = 388 days)	Supervised resistance exercise. 3x/week, 9 resistance exercises, 2x12 repetitions, 60-70% 1-RM. All men scheduled to receive ADT for at least 3 months after recruitment into intervention.	12 weeks	79% attendance (28/36 sessions)	FACT-F FACT-P	1 knee injury
Culos-Reed 2010	Total:100 (I: 53, C: 47) Stage: I-IV Mean age = 67	≥ 6 months ADT	3-5x/week home-based exercise walking program with moderate intensity (walking, light resistance training) plus 1x/week 90 min group session (during ADT treatment)	16 weeks	78% attendance (12/16 sessions). 34% dropped out before post-testing	FSS EORTC QLQ	Not reported
Galvao 2010	Total: 57 (I:29, C:28) Stage: I-IV Mean age = 70	>2 months ADT	Supervised resistance and aerobic training 2x/week. 8 full body resistance exercises 2-4 sets of 12-6 repetition maximum. 15-20 mins aerobic exercise, 65-80% HRmax (intervention received during ADT treatment)	12 weeks	1 patient withdrew from exercise group. 94% attendance (23/24 sessions)	EORTC QLQ – global QOL & fatigue	None
Bourke 2011	Total:50 (I:25, C:25) Stage: non-localised Mean age = 72	≥ 6 months ADT	Supervised aerobic and resistance exercise. 30 min aerobic, 55-85% HRmax. 2-4 sets resistance exercise 1-2x/week. Self-directed exercise 30 mins 1-2x/week. Intervention given during ADT treatment.	12 weeks	95% attendance (360/378 sessions). 87% completed independent exercise (329/378 sessions). 14% attrition	FACT-F FACT-P FACT-G	2 knee pain
Oneill 2012	Total: 94 (I: 47, C: 47) Stage: NR; Mean age = NR	ADT	Diet and physical activity intervention.	6-months	NR	Fatigue FACT-P	NR

EBRT: External beam radiation therapy; BFI: Brief Fatigue Inventory; r-PFS: revised Piper Fatigue Scale; FACT-P/ FACT-F/FACT-G: Functional Assessment of Cancer Therapy-Prostate/Fatigue/General; 1-RM: one repetition maximum; FSS: Fatigue Severity Scale; EORTC QLQ: Quality of Life Questionnaire

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Reason: outcomes not available/relevant

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7 Metastatic Prostate Cancer

7.1 Hormonal therapy

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

Short summary

Orchidectomy versus medical castration

Evidence came from a systematic review of thirteen randomised trials of hormonal monotherapy in prostate cancer (Seidenfeld *et al.* 2000; Seidenfeld *et al.* 2001). Meta-analysis suggested comparable overall survival benefit between orchidectomy and LHRH agonists. The evidence about adverse effects was less reliable due to reporting inconsistencies between trials, although adverse event rates appeared similar in orchidectomy and LHRH agonist treatment groups.

Castration versus combined androgen blockade

Evidence from 27 randomised trials, summarised in two systematic reviews (Prostate Cancer Trialists 2000; Seidenfeld *et al.* 2001), shows a small survival advantage with combined androgen blockade using non steroidal antiandrogens. The estimate of five year overall survival from meta-analysis was 28% for men treated with combined androgen blockade compared with 25% for those treated with castration alone (Prostate Cancer Trialists 2000). Using the rate of treatment withdrawal as a index of treatment toxicity, Seidenfeld and co-workers (Samson *et al.* 2002; Seidenfeld *et al.* 2001) reported that men treated with an LHRH agonist alone withdrew from therapy at a rate of 4% or less compared with a rate of 8% or more in men receiving CAB.

Antiandrogen monotherapy

Meta-analysis of thirteen randomised trials of hormonal monotherapy (Seidenfeld et al. 2000; Seidenfeld et al. 2001) showed a trend towards poorer overall survival with anti-androgen monotherapy than with castration. The two therapies had different toxicity profiles. Gynaecomastia was more likely with nonsteroidal antiandrogens, whereas hot flushes and reduced sexual function were more likely with castration. The proportion withdrawing from anti-androgen monotherapy and LHRH antagonist treatment was similar, however, suggesting comparable tolerability (Seidenfeld et al. 2000; Seidenfeld et al. 2001).

Evidence Summary

Medical castration versus orchiectomy

Evidence came from a systematic review of randomised trials of hormonal monotherapy in prostate cancer (Seidenfeld *et al.* 2000; Seidenfeld *et al.* 2001). Thirteen trials were included comparing LHRH agonists or diethylstilbestrol with orchiectomy, or LHRH agonists with diethylstilbestrol. Ten publications included only patients with metastatic disease, two publications included men with either locally advanced or metastatic disease, and two publications included only men with locally advanced disease.

Overall Survival

There was no evidence that medical castration was better than orchiectomy in terms of overall survival. Two trials compared diethylstilbestrol (DES) with orchiectomy and did not find a significant difference in median, two year or five year overall survival. In meta-analysis, the hazard ratio for 2 year mortality with DES compared to orchiectomy was 0.9927 [95%C.I. 0.762–1.294].

Nine trials compared LHRH agonists with diethylstilbestrol or orchiectomy, none reported any significant differences in overall survival. In meta-analysis the hazard ratio for 2 year mortality with LHRH agonists compared to orchiectomy was 1.1262 [95%C.I. 0.915–1.386].

Disease specific survival

Seidenfeld and co-workers (Seidenfeld *et al.* 2000; Seidenfeld *et al.* 2001) did not analyse this outcome in detail, since only the VACURG trial of oestrogen and orchiectomy reported disease specific survival. The investigators in this trial reported that oestrogen was associated with fewer prostate cancer deaths but this was offset by increased cardiovascular mortality.

Symptom control

This outcome was not reported in the review.

Side effects

The review summarized adverse events in three categories: cardiovascular events, endocrine events and gastrointestinal events. Adverse cardiovascular events appeared more likely with DES than with LHRH agonists or orchiectomy. Hot flushes were less likely with DES than the other treatments, while orchiectomy appeared associated with less gastrointestinal toxicity. The authors did not have confidence in this analysis, due to inconsistency in the categorisation of adverse events. Adverse events leading to withdrawal from therapy were considered a more reliable estimate of treatment toxicity (see Table 127 below), and showed an excess of treatment withdrawals with DES therapy. Orchiectomy, being irreversible, is not included in the table.

Table 127. Estimates of the proportions of men discontinuing their medical castration therapy due to treatment toxicity.

Treatment	Proportion Discontinuing Therapy
DES 1 mg/day	14.3%
DES 3 mg/day	18.7%
Leuprolide 1 mg/day	0.0%
Goserelin 3.6 mg/month	2.0%
Goserelin 10.8 mg every 3 months	1.3%
Buserelin 0.4 mg/day	4.2%

Quality of life

There was no evidence from randomised trials comparing the quality of life in men treated with orchiectomy or LHRH agonists. In two bicalutamide trials, patients in the comparison group were

offered the choice of orchiectomy or an LHRH agonist. Thirty percent of the patients opted for orchiectomy.

Castration versus maximum androgen blockade (MAB)

Overall Survival

Meta-analysis by the prostate cancer trialists' collaborative group (Prostate Cancer Trialists 2000) combined individual data from 8275 men in 27 randomised controlled trials of MAB versus castration (usually orchiectomy). The relative rate of mortality in the MAB vs. castration groups was 0.958 [95% C.I. 0.907–1.009]. The absolute difference between groups in overall survival was 2% [95% C.I. 0.04–3.96] in favour of MAB.

When the meta-analysis was restricted to trials of MAB using non-steroidal antiandrogens (NSAA), MAB was associated with a 3% increase in 5 overall year survival (27.6% MAB vs. 24.7% castration only; difference 2.9% [95% C.I. 0.352–5.448]; log rank p=0.005). If the meta-analysis was restricted to trials of MAB using cyproterone acetate, MAB was associated with a 3% decrease in 5 year survival (15.4% MAB vs. 18.1% castration only; difference -2.8% [95% C.I. -7.504–1.904]; log rank p=0.04).

The meta-analysis of Samson and co-workers (Samson et al. 2002; Seidenfeld et al. 2001) used published data from twenty randomised trials. Their meta-analysis estimated the hazard ratio of two year mortality for men treated using MAB compared to orchiectomy alone. Results of sub-group analyses for four classes of MAB are shown in Table 128 below.

Table 128. Estimates of relative mortality for MAB vs. orchiectomy, from meta-analysis.

MAB type	HR of 2 year mortality, relative to orchiectomy [95% C.I.]
Orchiectomy + NSAA	0.977 [0.781–1.222]
LHRH agonist + NSAA	0.945 [0.779–1.147]
Orchiectomy+ cyproterone acetate	1.073 [0.595–1.935]
LHRH agonist+ cyproterone acetate	1.335 [0.988–1.803]

None of the differences was statistically significant, although results suggested worse two year survival in men treated with the combination of LHRH agonist and cyproterone acetate.

The meta-analysis of five year overall survival in the Samson and co-workers review (Samson et al. 2002; Seidenfeld et al. 2001), however, showed an overall survival advantage for MAB (HR 0.871; 95% C.I. 0.805–0.942). Only ten studies reported five year overall survival, compared with twenty reporting two year survival.

Another meta-analysis considered the effect of disease flare at the initiation of LHRH agonist therapy (Collette et al. 2001) in MAB trials. Colette and co-workers (Collette et al. 2001) included only trials in which men in the LHRH agonist only arm also had short term anti-androgen therapy at the start of treatment. Trials of MAB versus orchiectomy were also included. Meta-analysis of the fifteen included trials gave a hazard ratio of mortality (MAB vs. castration) of 0.95 [95% C.I. 0.89–1.02]. These results showed no statistically significant benefit of MAB over castration, when the effect of disease flare is excluded.

A systematic review conducted in 2003 for a Cancer Care Ontario guideline reviewed additional evidence published since the meta-analyses. Results from one new trial, and an update from a trial included in the original analyses were consistent with the findings of the original meta-analysis: with no significant difference in overall survival between MAB and castration groups.

The survival meta-analyses (Prostate Cancer Trialists 2000; Samson et al. 2002; Collette et al. 2001) did not include any trials of MAB using bicalutamide. Intermediate results from a Japanese trial of bicalutamide 80 mg/day versus placebo in addition to LHRH agonist have since been published (Akaza et al. 2004; Usami M et al. 2007), but with insufficient follow-up to analyse overall survival.

Another meta-analysis (Klotz et al. 2004) used indirect comparison to estimate the effect of MAB using bicalutamide versus castration, by combing trials with a common arm. This review estimated the hazard ratio of overall mortality of MAB using bicalutamide versus castration as 0.80 [95% C.I. 0.66–0.98], a significant overall survival benefit of MAB.

Disease specific survival

The systematic review of Sampson and co-workers (Samson et al. 2002; Seidenfeld et al. 2001) identified six trials reporting prostate cancer specific survival: five trials using NSAA in the MAB arm and one using cyproterone acetate. Three of the trials reported improved disease specific survival in the MAB arm, all three of these trials used orchiectomy in the castration only arm and a NSAA in the MAB arm. The remaining trials found no significant difference in disease specific survival between treatment arms.

Symptom control

This outcome was not reported in the review.

Side effects

Samson and co-workers (Samson et al. 2002; Seidenfeld et al. 2001) used the rate of withdrawal from treatment as an index of treatment toxicity. Men treated with an LHRH agonist alone withdrew from therapy at a rate of 4% or less compared with a rate of 8% or more in men receiving MAB.

Akaza and co-workers (Akaza et al. 2004; Usami M et al. 2007) reported the rates of withdrawal due to adverse events as 8.8% for MAB (using bicalutamide) compared with 10.9% for LHRH agonist only. The estimated difference between groups was 2.1% fewer withdrawals with MAB [95% C.I. -10.7%–6.4%].

Quality of life

There was a lack of relevant evidence on quality of life. The review of Samson et al (Samson et al. 2002; Seidenfeld et al. 2001) found a single published quality of life analysis from a subset of patients in a randomised trial. Patients who were treated with MAB (orchiectomy plus flutamide) reported significantly more diarrhoea at 3 months ($p<0.001$), and worse emotional functioning at 3 and 6 months ($p<0.003$), than did those given orchiectomy plus placebo.

Rosendahl and co-workers (Rosendahl et al. 1999) calculated quality adjusted survival by applying published utility values to the survival data from a randomised trial of MAB versus orchiectomy. Their analysis suggested a small benefit of 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.

Antiandrogen monotherapy versus castration

The systematic review of Seidenfeld and co-workers (Seidenfeld et al. 2000; Seidenfeld et al. 2001) found eight studies (2717 patients) comparing NSAA monotherapy with castration (orchiectomy, DES or a choice of orchiectomy or LHRH agonist). Five of these studies used bicalutamide and three flutamide. A further five trials (1123 patients) compared cyproterone acetate with castration (orchiectomy, DES or LHRH agonists).

Table 129. Details of the antiandrogens and patient groups of trials included in (Seidenfeld et al. 2001; Seidenfeld et al. 2000). Comparison was medical or surgical castration in all cases.

Antiandrogen	No. of trials	Patient groups
flutamide 250 mg three times daily	3	M1 (2 trials), M1 or locally advanced (1 trial)
bicalutamide 150 mg/day	2	M1 (1 trials), locally advanced (1 trial)
bicalutamide 50 mg/day	3	M1 (3 trials)
cyproterone acetate 100 mg/day	1	M1 (1 trial)
cyproterone acetate 250 mg/day	1	M1 or locally advanced (1 trial)
cyproterone acetate 300 mg/day	3	M1 (1 trials), locally advanced (2 trials)

Abbreviations: M1, metastatic disease;

Overall Survival

Three trials reported significantly better overall survival in the control (castration) arms. One of these trials was of flutamide, the others were of bicalutamide. None of the other NSAA or cyproterone trials reported a significant overall survival difference.

Meta-analysis of two year mortality for different treatment subgroups did not show statistically significant differences (see Table 130 below) between overall survival with antiandrogen monotherapy and with orchiectomy. There was a clear trend, however, towards poorer two year overall survival with antiandrogen monotherapy.

Table 130. Estimates of two year relative mortality for antiandrogen monotherapy versus orchiectomy, from (Seidenfeld et al. 2001; Seidenfeld et al. 2000) meta-analysis.

Antiandrogen monotherapy type	HR of 2 year mortality, relative to orchiectomy [95% C.I.]
Bicalutamide	1.203 [0.973 1.487]
Flutamide	1.958 [0.369–10.394]
Any NSAA	1.216 [0.988–1.496]
Cyproterone acetate	1.201 [0.592–2.433]
Any antiandrogen	1.219 [0.995–1.494]

Disease specific survival, symptom control

Seidenfeld and co-workers (Seidenfeld et al. 2001; Seidenfeld et al. 2000) did not identify antiandrogen monotherapy trials reporting these outcomes.

Adverse effects

The review summarized adverse events due to monotherapy using three categories: cardiovascular events, endocrine events and gastrointestinal events. Adverse cardiovascular events appeared more likely with DES and cyproterone acetate than with other monotherapies. NSAAs tended to be associated with more gastrointestinal symptoms than castration.

NSAA monotherapy had a different profile of endocrine adverse events to castration. Gynaecomastia was much more likely with nonsteroidal antiandrogens (38%); compared with orchiectomy (5%) and LHRH agonists (4%).The estimated rate of hot flushes was highest with orchiectomy at 51%, followed by LHRH agonists at 49% and nonsteroidal antiandrogens at 11%. The rate of impotence was highest with LHRH agonists at 21%, followed by orchiectomy at 13% and NSAAs at 5%. These impotence rates are much lower than those reported in trials of MAB or in case series, possibly due to measurement error or reporting inconsistencies. For these reasons, the review authors considered events leading to withdrawal from therapy a more reliable estimate of treatment toxicity (see Table 131 below).

A more recent report of one of the trials of bicalutamide 150 mg/day versus castration (Iversen et al. 2000) reported a withdrawal rate of 4.1% due to treatment toxicity in the bicalutamide arm. For men in the bicalutamide arm rates of gynaecomastia and breast pain were 49.4% and 40.1% respectively, compared with 4.4% and 1.9% in the castration group. 50% of the men in the castration group experienced hot flushes, compared with 13% of those in the bicalutamide group.

Table 131. Estimates of the proportions of men discontinuing antiandrogen monotherapy due to treatment toxicity (Seidenfeld et al. 2001; Seidenfeld et al. 2000).

Treatment	Proportion Discontinuing Therapy
Flutamide 750 mg/day	9.8%
Bicalutamide 50 mg/day	4.0%
Cyproterone acetate 250 mg/day	1.2%
Cyproterone acetate 300 mg/day	4.2%

There was a lack of evidence in the Seidenfeld review (Seidenfeld et al. 2001; Seidenfeld et al. 2000) about endocrine adverse effects associated with steroidal antiandrogens.

Quality of life

The review of Seidenfeld and co-workers (Seidenfeld et al. 2001; Seidenfeld et al. 2000)) identified two randomised trials of bicalutamide versus a choice of surgical or medical castration that reported quality of life on validated scales. Men treated with bicalutamide reported significantly higher sexual interest and physical capacity than those treated with castration.

Evidence Tables

Seidenfeld, Samson, Aronson, Albertson, Bayoumi, Bennett, Brown, Garber, Gere, Hasselblad, Wilt & Ziegler . Relative effectiveness and cost-effectiveness of methods of androgen suppression in the treatment of advanced prostate cancer. [Review] [330 refs]. Evidence Report: Technology Assessment (Summary) [4]. 2001.
Design: Systematic review of RCTs (therapy), evidence level: 1++ **Inclusion criteria** Reports of efficacy outcomes were limited to RCTs. Phase II studies reporting withdrawals from therapy and any studies reporting on quality of life. The literature search covered the period 1966 to March 1998. **Exclusion criteria** - **Population** - **Interventions** The review was conducted as a health technology appraisal of the relative methods of androgen suppression in the treatment of prostate cancer. The review covered 3 main comparisons 1) a comparison of hormonal monotherapies 2) combined androgen blockade versus castration 3) Immediate versus deferred therapy. **Outcomes** Overall survival, cancer-specific survival, progression-free survival, time to hormone refractory status, time to treatment failure, adverse effects of treatment, quality of life, patient preferences or satisfaction. **Results** See evidence summary document for results.

Prostate . Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Prostate Cancer Trialists' Collaborative Group. Lancet 355[9214]. 2000.
Design: Systematic review of RCTs (therapy), evidence level: 1+ **Inclusion criteria** Randomised trials of MAB versus castration alone for men with , that began before 1991. Antiandrogen therapy of at least one year or until disease progression. Individual patient data were obtained from the original investigators. **Exclusion criteria** - **Population** number of patients = 8275. **Interventions** MAB versus castration alone. 31 eligible trials were identified. MAB was orchiectomy or LHRH agonist (leuprolide, goserelin or buserelin) plus an antiandrogen (flu-

tamide, nilutamide or cyproterone acetate). Castration was orchiectomy or LHRH agonist.

The duration of therapy was generally 24 months (range 18 to 36 months).

Outcomes Overall mortality

Results The combined overall mortality rate was over 70%.

27 trials were included in the analysis

COMPARISON IN MEN WITH ADVANCED PROSTATE CANCER	MAXIMUM ANDROGEN BLOCKADE	CASTRATION	OVERALL RESULT
Overall mortality rate	2902/4122 (70.4%)	2962/4093 (72.4%)	Slightly favours MAB, relative mortality 0.958 [95% C.I. 0.907-1.009]
COMPARISON IN MEN WITH ADVANCED PROSTATE CANCER (NSAA TRIALS ONLY)	MAXIMUM ANDROGEN BLOCKADE	CASTRATION	OVERALL RESULT
5 year overall survival	27.6%	24.7%	Favours MAB, difference 2.9% [95% C.I. 0.352-5.448]; log rank p=0.005
COMPARISON IN MEN WITH ADVANCED PROSTATE CANCER (CYPROTERONE TRIALS ONLY)	MAXIMUM ANDROGEN BLOCKADE	CASTRATION	OVERALL RESULT
5 year overall survival	15.4%	18.1%	Favours castration, difference -2.8% [95% C.I. -7.504-1.904]; log rank p=0.04

7.2 Oestrogens and steroids

What is the most effective corticosteroid for the treatment of men with castration refractory prostate cancer?

Short summary

Evidence, from observational studies, suggests a PSA response rate of 50% or more with low dose dexamethasone therapy in men with castration refractory prostate cancer, compared with 21–34% for prednisolone and 21.5% for hydrocortisone.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Men with castration refractory prostate cancer.	Corticosteroids	Corticosteroids (different doses or types)	• Biochemical control

Evidence summary

Venkitaraman and co-workers (Venkitaraman *et al.* 2007) summarised the findings of case series and randomised trials involving corticosteroids in this population, see Table 132 below. Evidence, from seven case series, suggests a PSA response rate of 50% with low dose dexamethasone in men with castration refractory prostate cancer. Prospective studies reported response rate of between 21–26% with prednisolone and a PSA response rate of 21.5% was reported in the hydrocortisone only arm of a randomised trial.

Bhattacharya and co-workers (Bhattacharyya *et al.* 2003) reported a retrospective comparison of dexamethasone with hydrocortisone in addition to stilboestrol in men with hormone refractory prostate cancer. PSA response rates were similar in both groups: 73% for those treated with hydrocortisone and 78% for men treated with dexamethasone.

Table 132 Study characteristics and PSA response rate

Study	Corticosteroid	Daily dose	N	PSA response rate (decline of at least 50%)	Median TTPSA progression (months)
(Akakura *et al.* 2003)	dexamethasone	1.5 mg	25	44%	
(Nishimura *et al.* 2000)	dexamethasone	0.5 to 2 mg	37	62%	9 (in responders)
(Nishiyama & Terunuma 1998)	dexamethasone	1.5 mg	7	57%	
(Storlie *et al.* 1995)	dexamethasone	1.5 to 2.25 mg	38	61%	8 (in responders)
(Morioka *et al.* 2002)	dexamethasone	1.5 mg	27	59%	5.4
(Saika *et al.* 2001)	dexamethasone	1.5 mg	19	28%	7.3 (in respond-ers)
(Kobayashi *et al.* 2000)	dexamethasone	-	15	-	-
(Patel *et al.* 1990)	dexamethasone	1.5 mg	23	-	-
(Venkitaraman *et al.* 2007)	dexamethasone	0.5 mg	102	50%	7.4
(Fossa *et al.* 2007; Sternberg *et al.* 2005; Tannock *et al.* 1996; Tannock *et al.* 2004; Petrylak *et al.* 2004; Berry *et al.* 2002; Amato *et al.* 1996; Sar-tor *et al.* 1998; Fuse *et al.* 2006)	prednisolone			range 21–34%	
(Kantoff *et al.* 1999b)	hydrocortisone	40 mg		21.5%	

Evidence Tables

Randomized controlled trials

(Abratt *et al.* 2004)
Design: Randomized controlled trial (therapy), evidence level: 3 Country: International, setting: Tertiary care **Inclusion criteria** Men with progressive histological confirmed prostate cancer, who had failed prior androgen deprivation therapy and with castrate levels of testosterone. PSA 10 ng/ml or more. Age between 18 and 85 years. KPS of at least 60%. **Exclusion criteria** Prior chemotherapy, symptoms of brain metastases, uncontrolled infection, concurrent bisphosphonate treatment. **Population** number of patients = 414, age range 48 to 83 years, median age = 68 years. **Interventions** Men were randomised to receive vinorelbine plus hydrocortisone 40 mg/day or hydrocortisone 40 mg/day only. Treatment was given for at least 9 weeks, unless there was early disease progression or excessive toxicity. treatment was continued beyond 9 weeks if patients had PSA response or stable disease, until disease progression or excessive toxicity. **Outcomes** PSA response (50% or more decline in PSA sustained for at least 6 weeks). **Follow up** PSA response was evaluated after 9 weeks of treatment. **Results** 208 men received hydrocortisone only. PSA response for the hydrocortisone only group was 19.2% (95% CI 14% to 25%) **General comments** Level 3 evidence (only the control arm results are considered)

(Berry *et al.* 2002)
Design: Randomized controlled trial (diagnosis, screening), evidence level: 3 Country: United States, setting: Tertiary care **Inclusion criteria** Symptomatic hormone refractory prostate cancer that had progressed on at least one hormonal therapy regimen. Men had to have adequate liver, heart and kidney function and ECOG performance status of 0 or 2. **Exclusion criteria** Other malignancy within the previous 5 years, brain metastases, prior chemo therapy, concurrent use of corticosteroids.

Population number of patients = 63, age range 51 to 90 years, median age = 74 years.

Interventions Men were randomised to receive either mitoxantrone and prednisone or prednisone only (in addition to their hormonal therapy). Men in the prednisone only arm received 5mg orally bid.

Outcomes PSA response (50% reduction lasting at least 2 months without decrease in performance status). Median time to disease progression from the start of treatment.

Follow up Outcomes were assessed after 6 weeks of treatment

Results 63 men received prednisone only. The PSA response rate was 15/63 (24%) in this group. The median time to disease progression was 8.1 months (range 1 to 50 months).

(Datta *et al.* 1997)

Design: Randomized controlled trial (therapy), evidence level: 3

Country: United Kingdom, setting: Tertiary care

Inclusion criteria Men with metastatic hormone refractory prostate cancer. Life expectancy of at least 6 weeks, and adequate performance status to allow outpatient treatment and monitoring.

Exclusion criteria -

Population number of patients = 20.

Interventions Men were randomised to either flutamide or prednisolone (5 mg twice daily). Treatment was continued until progression, when men switched to the other treatment arm.

Outcomes PSA response rate (any decrease in PSA sustained for at least 3 months).

Follow up Men were assessed at 6 weeks after randomisation and then 3 monthly thereafter.

Results PSA response rate was 11/20 (55%) in men taking prednisolone

General comments Criterion for PSA response differs from most other studies in this area.

(Fossa *et al.* 2001)

Design: Randomized controlled trial (therapy), evidence level: 3

Country: International, setting: Tertiary care

Inclusion criteria Men with symptomatic metastatic prostate cancer that had progressed after treatment with LHRH analogues or orchiectomy. Testosterone levels within the castration range. WHO performance status of 0 to 3.

Exclusion criteria Previous use of flutamide, prednisone or any oral antiandrogen for more than 4 weeks. Previous systemic cancer treatment (apart from LHRHa). Serious cardiovascular problems or other malignancy.

Population number of patients = 101, mean age = 72 years.

Interventions Men were randomised to receive either flutamide (250 mg orally 3 times a day) or prednisone 5mg orally four times a day.

Outcomes PSA response to treatment (decrease of PSA from baseline value of at least 50% at a minimum of 6 weeks after start of treatment). Time to disease progression

Follow up Response was evaluated at 6 week intervals from the start of treatment. Median follow up was 330 days.

Results 101 men received prednisone alone. The PSA response rate was 21/101 (21%). Median time to progression was 3.4 months.

General comments Level 3 - only control arm results used

(Fossa *et al.* 2007)

Design: Randomized controlled trial (therapy), evidence level: 3

Country: Norway, setting: Tertiary care

Inclusion criteria Men androgen independent prostate cancer. Distant metastases with PSA at least 10 ng/ml and increasing. Serum testosterone within the castration range. ECOG performance status of 2 or less. Age less than 85 years.

Exclusion criteria New systemic therapy after the diagnosis of hormone refractory disease. Other malignancy (excluding BCC), major haematological disturbances, abnormal liver or kidney function tests.

Population , age range 54 to 84 years, median age = 72 years.

Interventions Men were randomised to receive either docetaxel and prednisolone or prednisolone alone (5 mg orally bid). After 36 weeks of treatment non progressing patients carried on with oral prednisolone (5mg orally bid).

Outcomes PSA response rates at 6 weeks and 12 weeks of treatment. PSA response was defined as a decrease of at least 50% in serum PSA after 6 weeks of treatment.

Follow up Men had clinical examination every 6 weeks for 8 months and then every 12 weeks thereafter.

Results 52 men received prednisolone only. The PSA response rates in this group were 26% and 36% at 6 and 12 weeks respectively.

General comments Level 3 evidence, because only the control arm results are used.

(Kantoff *et al.* 1999a

Design: Randomized controlled trial (therapy), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men with hormone refractory metastatic prostate cancer. Adequate liver, kidney and bone marrow function.

Exclusion criteria -

Population number of patients = 123, median age = 72 years.

Interventions Men were randomised to receive mitoxantrone plus hydrocortisone or hydrocortisone only. Hydrocortisone was taken orally at a dose of 30 mg in the morning and 10 mg in the evening. Men not surgically castrated continued taking LHRHa.

Outcomes PSA response.

Follow up PSA response was determined between 28 and 56 days after the start of treatment.

Results 123 Men received hydrocortisone only. The PSA response rate in this group was 13/95 (14.3%).

(Small *et al.* 2000)

Design: Randomized controlled trial (therapy), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men with painful bone metastases from prostate cancer, who were being treated with opioid analgesics. Serum testosterone less than 50 ng/ml, PSA more than 10 ng/ml, KPS of at least 60% and expected survival of at least 3 months. Increasing PSA despite hormonal therapy. Normal liver and kidney function and normal blood values.

Exclusion criteria Systemic corticosteroids, prior non-hormonal systemic therapy, or recent radiotherapy.

Population number of patients = 222, age range 39 to 87 years, median age = 68 years.

Interventions Men were randomised to receive suramin plus hydrocortisone or placebo plus hydrocortisone (40 mg per day) . Men with testicles continued on LHRH agonist

Outcomes PSA response (at least 50% decline from baseline, for at least a month).

Results 222 men received hydrocortisone only. The PSA response rate was 16%.

General comments -

(Sternberg *et al.* 2005)

Design: Randomized controlled trial (therapy), evidence level: 3

Country: Italy, setting: Tertiary care

Inclusion criteria Men with documented evidence of progressing prostate cancer despite hormone treatment. WHO performance status of 0 to 2, analgesic pain score of 0 to 3. Adequate liver and kidney function. Life expectancy of at least 6 months.

Exclusion criteria -

Population number of patients = 23, age range 42 to 80 years, median age = 70 years.

Interventions Men were randomised to receive satraplatin plus prednisone or prednisone only (10 mg bid).

Outcomes PSA response rate (Bubley criteria)

Follow up Clinical examination and biochemical tests were carried out every 5 weeks until the end of treatment, and then every 3 months.

Results 23 men received prednisone only. The PSA response rate was 2/23 (8.7%).

General comments Evidence level 3 (prospective study) - only the control arm results are considered.

(Tannock *et al.* 1996)

Design: Randomized controlled trial (therapy), evidence level: 3

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

Inclusion criteria Men with metastatic hormone refractory prostate cancer, enrolled in a randomised trial of chemotherapy. Men had ECOG performance status of at least 3, life expectancy of at least 3 months

Exclusion criteria Prior malignancy, prior chemotherapy, recent radiotherapy, uncontrolled cardiac failure or active infection.

Population number of patients = 81, median age = 67 years.

Interventions Men were randomised to receive mitoxantrone plus prednisone (80 patients) or prednisone alone (81 patients).

Outcomes PSA response (at least 50% reduction from the baseline).

Follow up PSA was assessed at baseline and at least one other visit in 54/81 men in the prednisone only group.

Results PSA response rate was 12/54 (22%).

Prospective case series

(Amato *et al.* 1996)

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

Country: United States, setting: Tertiary care

Inclusion criteria Men with progressive hormone refractory prostate cancer.

Exclusion criteria -

Population number of patients = 16.

Interventions Prednisone 40 mg per day (10 mg taken orally 4 times per day) continued until disease progression or unacceptable side effects.

Outcomes PSA response (at least 50% reduction from baseline, maintained for at least 2 months).

Follow up Clinical assessment every 2 weeks. PSA tests every 2 months

Results PSA response rate was 0/16 (0%) .

General comments PSA response criterion stricter than other studies, - response of 2 months duration was required.

(Nishimura *et al.* 2000)

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

Country: Japan

Inclusion criteria Men with hormone refractory prostate cancer, KPS of 40% or more and life expectancy of at least 3 months.

Exclusion criteria -

Population number of patients = 37.

Interventions Dexamethasone only (doses ranged from 0.5 to 2 mg per day) continued until disease progression or unacceptable side effects.

Outcomes PSA response, time to PSA disease progression.

Follow up Median duration of treatment was 7 months (range 1 to 22 months)

Results PSA response rate 23/37 (62%). In PSA responders the median time to PSA disease progression was 9 months (range 3 to 21 months)

(Saika *et al.* 2001)

Design: Prospective case series (therapy), evidence level: 3

Country: Japan, setting: Secondary care

Inclusion criteria Men with metastatic prostate cancer with disease progression after hormonal therapy. Performance status 0 to 3, and expected survival at least 3 months. Castrate levels of testosterone.

Exclusion criteria -

Population number of patients = 18.

Interventions Castration + dexamethasone (1.5 mg per day). Treatment was continued for at least 12 weeks unless progression or severe complications occurred.

Outcomes PSA response

Follow up Median duration of treatment was 6.2 months (range 0.9 to 21 months)

Results PSA response was 9/18 (50%)

Retrospective case series

(Sartor *et al.* 1998

Design: Retrospective case series (), evidence level:

Country: United States, setting: Tertiary care

Inclusion criteria Men with hormone refractory prostate cancer.

Exclusion criteria -

Population number of patients = 29.

Interventions Castration plus prednisone orally 20 mg per day (10 mg taken twice daily).

Outcomes PSA response rate

Follow up Men were assessed at approximately monthly intervals

Results PSA response rate was 10/29 (34%)

(Akakura *et al.* 2003)

Design: Retrospective case series (therapy), evidence level: 3

Country: Japan

Inclusion criteria Men with prostate cancer with biochemical failure after medical or surgical castration

Exclusion criteria -

Population number of patients = 25.

Interventions Castration + dexamethasone (1.5 mg per day tapered to 0.5 mg per day)

Outcomes PSA response

Results PSA response rate was 11/25 (44%)

(Bhattacharyya *et al.* 2003)

Design: Retrospective case series (therapy), evidence level: 3

Country: United Kingdom, setting: Tertiary care

Inclusion criteria Men with rising PSA while on primary hormonal therapy for prostate cancer.

Exclusion criteria -

Population number of patients = 114.

Interventions Stilboestrol + hydrocortisone (20mg bid) (S+HC)

Stilboestrol + dexamethasone (2mg daily) (S+D)

Outcomes PSA response

Results PSA response rate was 73% in the S+HC group and 78% S+D group.

(Fuse *et al.* 2006)

Design: Retrospective case series (therapy), evidence level: 3

Country: Japan, setting: Tertiary care

Inclusion criteria Men with hormone refractory prostate cancer, who had previously undergone hormone therapy.

Exclusion criteria -

Population number of patients = 15, age range 60 to 80 years, mean age = 72 years.

Interventions Low dose prednisolone

Outcomes PSA response (any decline and decline of more than 50%). Improvement of bone metastases. Pain relief. One year overall survival. Side effects of prednisolone.

Results PSA values decreased in 11/15 cases. 4/15 men (27%) had PSA decreases of more than 50%. 2/8 men with bone metastases showed improvement of the lesion. The one year overall survival rate was 58%. The authors reported that treatment related side effects were mild and manageable in the outpatient setting.

(Heng & Chi 2006)

Design: Retrospective case series (therapy), evidence level: 3

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

Inclusion criteria Men with asymptomatic hormone refractory prostate cancer, (no pain and ECOG score of 2 or less).

Exclusion criteria Concurrent chemotherapy

Population number of patients = 49.

Interventions prednisone 10 mg daily.

Outcomes PSA response (decline of 50% or more from the baseline value).

Follow up Median follow-up was 15.5 months (range 3.8 to 45 months).

Results PSA response rate was 11/49 (22%). Median time to progression was 4.3 months (0.89 to 30 months)

(Morioka *et al.* 2002)

Design: Retrospective case series (therapy), evidence level: 3

Country: Japan, setting: Tertiary care

Inclusion criteria Men with prostate cancer with biochemical failure after medical castration or combined androgen blockade.

Exclusion criteria -

Population number of patients = 27.

Interventions LHRH + dexamethasone (1.5 mg per day tapered to 1 mg per day)

Outcomes PSA response (decline of at least 50% over a period of 3 months).

Follow up Clinical assessment every 4 to 8 weeks

Results PSA response rate was 16/27 (59.3%).

(Storlie *et al.* 1995)

Design: Retrospective case series (therapy), evidence level: 3

Country: United States, setting: Tertiary care

Inclusion criteria Men with progressive hormone refractory prostate cancer after orchidectomy.

Exclusion criteria -

Population number of patients = 38.

Interventions Dexamethasone (usually 0.75 mg twice daily).

Outcomes PSA response (50% or more reduction from baseline).

Results PSA response rate was 23/38 (61%).

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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7.3 Imaging

In patients with known bone metastases and no symptoms or signs of spinal cord compression, does routine MRI scan of spine at the time of diagnosis of bone metastases improve outcome?

Evidence Summary

A prospective case series (Bayley *et al.* 2001) reported screening for sub-clinical spinal cord compression using MRI in a group of men with vertebral bone metastases from prostate cancer but without symptoms of spinal cord compression. 32% of the group had sub-clinical spinal cord compression on MRI. Another series (Venkitaraman *et al.* 2007) reported the results of spinal MRI in men with prostate cancer considered at high risk of developing spinal cord compression, but without functional neurological deficit. Radiological spinal canal compromise was seen in 27% of these men. Neither of the studies reported outcomes following MRI screening for spinal cord compression.

Risk factors for radiological spinal cord compression in men with metastatic prostate cancer were extensive bone metastasis (Venkitaraman *et al.* 2007; Bayley *et al.* 2001), duration of hormonal therapy (Bayley *et al.* 2001) and back pain (Venkitaraman *et al.* 2007)

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Patients with known bone metastases and no symptoms or signs of spinal cord compression	Routine MRI scan of spine at the time of diagnosis of bone metastases	No routine MRI scan of spine (unless symptoms or signs develop).	• Incidence of sub-clinical spinal cord compression • Freedom from symptomatic spinal cord compression • Freedom from paraplegia • Accuracy of diagnosis of spinal cord compression.

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

Evidence Tables

(Venkitaraman *et al.* 2007)
Design: Retrospective case series (diagnosis, screening), evidence level: 3 Country: United Kingdom, setting: Tertiary care **Inclusion criteria** Men with skeletal metastases and prostate cancer who had MRI for the detection of clinically occult spinal cord compression (SCC). **Exclusion criteria** Functional neurological deficit. Any previous spinal cord compression. **Population** number of patients = 150. **Interventions** MRI of the spine, carried out with 1.5T whole body scanner. Images were acquired with a spinal coil. **Outcomes** MRI findings were classified as overt SCC, occult SCC or no SCC. Overt and occult SCC were combined for analysis as 'radiological spinal canal compromise' (rSCC). Risk factors for rSCC were also analysed. **Results** 41/150 (27%) of men had radiological spinal canal compromise 24/150 (16%) men had overt SCC and 17/150 (11.3%) men had occult SCC. On multivariate analysis, back pain (OR = 5.1; 95% CI 1.44 to 18.25; p=0.012) and extensive bone metastasis (OR = 2.9; 95% CI 1.01 to 8.35; p=0.047) significantly predicted for radiological spinal canal compromise

(Loblaw *et al.* 2003)
Design: Retrospective cohort study (prognosis), evidence level: 2+ County: Canada (federal state, Commonwealth Realm), setting: Community **Inclusion criteria** Patients newly diagnosed with prostate cancer between 1990 and 1995 in Ontario. **Exclusion criteria** - **Population** number of patients = 32497. **Outcomes** Data about diagnosis of, and death from, prostate cancer were obtained from the cancer registry. Data about episodes of SCC were obtained from hospital records. The authors calculated the cumulative probability of experiencing SCC in the 5 years preceding death. **Results** There were 32497 incident cases of prostate cancer in the 6 year study period, 709

cases of SCC and 8059 deaths. The probability of SCC in the 5 years preceding death from prostate cancer was 7.24%, 95% CI [6.63% to 7.85%].

Numeric results

Risk of spinal cord compression	
Outcome: Cumulative incidence of SCC in the 5 years preceding death	7.24%; 95% CI [6.63% to 7.85%]
Outcome: Proportion of men with clinical SCC	709/32497

Prospective case series

(Bayley *et al.* 2001)

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

County: Canada (federal state, Commonwealth Realm), setting: Tertiary care

Inclusion criteria Patients with vertebral bone metastases from prostate cancer and normal neurologic examination (no symptoms indicative of spinal cord compression), were accrued from outpatient radiation oncology clinics.

Exclusion criteria Previous spinal cord compression or a contraindication to MRI.

Population number of patients = 68, age range 50 to 84 years, median age = 71 years.

Interventions A bone scan was obtained in all patients within 1 week of study entry. MRI of the entire spine (sagittal T1-weighted, spin-echo sequence followed by a sagittal T2-weighted, fast spin-echo sequence).

Outcomes Sub clinical spinal cord compression: visible sub-arachnoid space (SAS) or spinal cord (SC) compression, without neurologic abnormalities. The risk of developing clinical spinal cord compression in the 2 years following a negative screening MRI was estimated using the Meier method.

Results Bone scans were negative for metastatic disease in 3/68 patients (4%).

39/68 patients (57%) had received hormonal therapy as their initial therapy. 64/68 patients (94%) were receiving continuous hormone treatment at the time of entry into the study, and 61 of these patients had hormone refractory tumours.

Vertebral metastases were identified by MRI in 65/68 patients (96%). Clinically occult SAS/SC

compression was identified in 22/68 patients (32%). In all cases compression was due to direct extension of metastatic tumour from the vertebral body.

4 of the 46 patients (9%) with no evidence of SAS/SC compression on the screening MRI went on to develop clinically evident spinal cord compression.

Potential prognostic factors for spinal cord compression were examined using multivariate logistic regression. The extent of disease on bone scan and the duration of continuous hormonal therapy were independent predictors of SAS/SC compression.

Numeric results

Risk of spinal cord compression	
Outcome: Risk of sub clinical spinal cord compression	22/68
Outcome: Risk of developing clinical spinal cord compression within 1 year of a negative screening MRI	3.2 %
Outcome: Risk of developing clinical spinal cord compression within 2 years of a negative screening MRI	13.7%

General comments Important outcomes (survival, quality of life etc.) are not reported. It is unclear how the initial vertebral bone metastases were discovered (before entry to the study).

It is assumed that MRI is the gold standard for the diagnosis of sub clinical spinal cord compression, but it is not reported how many of those with sub clinical compression went on to develop symptoms. The management of these patients with clinically occult SAS/SC compression diagnosed by MRI was at the discretion of individual doctors, but patients usually received radiotherapy.

Retrospective case series

(Colletti *et al.* 1996)

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

County: United States, setting: Tertiary care

Inclusion criteria 100 sequential patients with known primary tumours and suspected spinal metastases were evaluated retrospectively and 30 prospectively. The most common tumour types were breast cancer (n=27), prostate cancer (n=17) and lung cancer (n=11).

Exclusion criteria -

Population number of patients = 130, age range 19 to 85 years, mean age = 54 years.

Interventions MRI of the spine using a spin echo short TR, TE technique with sagittal and axial acquisitions

Outcomes Change of therapy: discontinuation, initiation or change in radiotherapy ports or dose, chemotherapy, steroid usage or surgical intervention.

Results 108 patients had symptoms of spinal metastases, 22 were asymptomatic. 52/108 (48%) symptomatic patients had a change in management based on the results of the MRI, compared with 7/22 (32%) asymptomatic patients.

12/17 (71%) of patients with prostate cancer had a change in therapy based on the MRI findings, but it is not reported how many were asymptomatic.

Numeric results

Change in therapy based on MRI findings	
Outcome: Proportion with change in therapy	12/17

General comments -

(Kuban *et al.* 1986)

Design: Retrospective case series (prognosis), evidence level: 3

County: United States, setting: Tertiary care

Inclusion criteria Men with histologically confirmed prostate cancer seen at a single institution between 1973 and 1983.

Exclusion criteria 2 patients with simultaneous lung and bladder cancer were excluded.

Population number of patients = 611.

Interventions -

Outcomes Development of spinal cord compression

Results 41/611 (6.7%) patients developed spinal cord compression at a median of 24 months after primary diagnosis.

Numeric results

Risk of spinal cord compression	
Outcome: Proportion of men with clinical SCC	41/611

General comments Pre PSA and MRI-era study?

Systematic review of diagnostic studies

(Loblaw *et al.* 2005)

Design: Systematic review of diagnostic studies (diagnosis, screening), evidence level: 2-

County: International, setting: Other

Inclusion criteria RCTs comparing imaging modalities; phase II studies or retrospective reviews describing imaging modalities; all raters had to be blinded from clinical information and the test.

Exclusion criteria -

Population -

Interventions MRI, myelography for investigating suspected malignant spinal cord compression.

Outcomes Sensitivity and specificity of tests for malignant spinal cord compression.

Results 4 relevant papers were identified (not restricted to prostate cancer). The authors conclude that the evidence supports the use of whole spine MRI for patients with known malignancy and suspected spinal cord compression. Estimates of the sensitivity of MRI for detection of SCC ranged from 44% to 93%, with specificity 90% to 98%. The corresponding figures for myelography were 71% to 97% and 88% to 100%.

Numeric results

-

General comments Evidence comes from studies of cancer patients with suspected spinal cord compression (not screening studies in patients with newly diagnosed spinal metastases). The review was conducted to inform a Cancer Care Ontario guideline on malignant spinal cord compression.

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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7.4 Bone targeted therapies

7.4.1 Bisphosphonates

In men with hormone refractory prostate cancer and confirmed bone metastases, can bisphosphonates delay or improve the complications of bone metastases?

Short Summary

Evidence came from a systematic review of ten randomised trials (Yuen *et al.* 2006). Meta-analysis showed a trend favouring bisphosphonates over placebo for the relief of pain from bone metastases in men with prostate cancer. There was no significant difference, however, between the analgesic consumption of bisphosphonate and placebo groups.

Meta-analysis showed a modest reduction in skeletal events with bisphosphonate treatment (using trial authors' definitions of skeletal events). The estimated rates for skeletal events were 37.8% and 43.0% for the bisphosphonate and placebo groups respectively: an absolute risk difference of 5.2%.

There was inconsistent evidence about the effect of bisphosphonates on the rate of pathological fractures. The rates of spinal cord compression, bone surgery and bone radiotherapy did not differ significantly between bisphosphonate and placebo groups. There were no significant group differences in overall survival or in quality of life.

PICO question

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

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Men with confirmed bone metastases from prostate cancer	Bisphosphonate treatment	▪ placebo, ▪ no bisphosphonate treatment (open control) or ▪ another bisphosphonate treatment (active control) ▪ Studies with an active control could compare different types of bisphosphonates, or different doses, different durations or different routes of administration of the same bisphosphonate. ▪ Comparisons involving active control were analysed separately. ▪ Concurrent or sequential use of other types of treatment, such as hormones, chemotherapy or radiotherapy were allowed, provided that all arms in the study used the same protocol.	▪ Control of pain ▪ pathologic fractures ▪ Pain response ▪ Time till palliative RT ▪ Overall survival ▪ Quality of life ▪ Toxicity ▪ Spinal cord compression

Evidence Summary

Pain secondary to bone metastases

The reports provided by the above evidence indicate that pain can be effectively managed using bisphosphonates, that is, pain relief was reported in a meta analysis of studies (which evaluated oral clodronate or sodium etidronate or Zoledronic acid) of evaluable patients.

Skeletal Related Events

The reports (which evaluated oral clodronate, pamidronate disodium or zoledronic acid) provided indicate that bisphosphonates may have a role in decreasing skeletal complications in patients with metastatic prostate cancer. The Cochrane Review described the rates for skeletal events were 37.8% and 43.0% for the treatment group and the control group respectively, with an absolute risk difference of 5.2%. A multiple event analysis conducted as part of an important RCT reported that Zoledronic acid reduced the risk of skeletal complications by 36% at 24 months.

Two trials, included in the systematic review, reported the rate of pathological fracture, but results were inconsistent. In Saad et al (2002) the rates of pathological fracture in zoledronic acid and placebo groups were 61/435 and 46/208 respectively (significantly fewer fractures with bisphosphonates than placebo, OR=0.57, 95% CI 0.38–0.88). In the trial reported by Small et al (2003) 25/182 men treated with pamidronate experienced pathological fractures compared with 22/196 in the control group (no significant difference between groups, OR=1.26, 95%CI 0.68–2.32). The rate of fractures in the control group of Small and control workers was much lower than that observed by Saad and co-workers: 11% versus 22% respectively.

Quality of Life

Some contention exists about the clinically meaningful and beneficial effects of bisphosphonates (namely Zoledronic acid) on the quality of life of men with prostate cancer. The Cochrane Review reported no evidence of effect of bisphosphonates (clodronate or Zoledronic acid) on the quality of life.

Overall survival

No evidence about the effect of bisphosphonates on overall survival was found.

Adverse Effects

The most common adverse effects included nausea, vomiting, anaemia, bone pain and renal toxicity.

A significant increase in nausea was observed in patients who received bisphosphonates compared to placebo. No increase in other adverse events was observed.

Comparisons Between Different Routes Of Administration, Doses And Types Of Bisphosphonates

The Cochrane Review reported that there was insufficient data to guide the choice of bisphosphonates or the dose and the route of administration. However, an RCT included in the Cochrane Review found that serum creatinine levels were elevated for patients given 8mg Zoledronic acid and the trial protocol was changed in view of renal toxicity. FDA recommendations also indicated a lower dose of 4mg Zoledronic acid 15 minute infusion every 3 to 4 weeks.

Another RCT included in the Cochrane Review evaluated intramuscular VS oral clodronate and reported a significant fall in analgesic consumption but not pain measured by visual analogue scale.

Evidence tables

Systematic Reviews

(Yuen *et al.* 2006)

Design Systematic Review of randomised trials. Evidence level 1++

Inclusion criteria Eligible participants include those with confirmed bone metastases from prostate cancer. All participants in the eligible studies were included. There was no restriction on age, performance status, life expectancy or previous treatment of the participants. Studies including non-metastatic prostate cancer or other primary sites of cancer were excluded. Animal studies were excluded.

Population Twenty-three studies were identified as potential trials for inclusion in this review. Thirteen studies were excluded from the analysis. These included eight uncontrolled studies, two non-randomized studies and three studies evaluating histomorphometric or biochemical outcomes. The details were described in the 'characteristics of excluded studies' section. A total of 1663 patients from ten trials were included.

Interventions - The studies must include a bisphosphonate as one of the studied interventions. Any type of bisphosphonate was considered eligible. However, radioactive bisphosphonates were excluded. There was no restriction on the dose, route or duration of bisphosphonate treatment.

The control arm could be placebo, no bisphosphonate treatment (open control) or another bisphosphonate treatment (active control). Studies with an active control could compare different types of bisphosphonates, or different doses, different durations or different routes of administration of the same bisphosphonate. Comparisons involving active control were analysed separately.

Concurrent or sequential use of other types of treatment, such as hormones, chemotherapy or radiotherapy were allowed, provided that all arms in the study used the same protocol.

Outcomes

control of pain (pain response, change in pain, use of analgesia)

skeletal events

adverse effects

patient survival

disease progression

PSA response

radiological response

quality of life

performance status

Results

Numeric results

PAIN RESPONSE

The rates for pain response were 27.9% and 21.1% for the treatment group and the control group respectively, with an absolute risk difference of 6.8%.

4 studies reported a pain response (and were included in a meta-analysis). One study that reported pain response was not included in this analysis due to missing data; however, it showed that there was no statistically significant difference between active (different doses and duration of oral clodronate) and control (placebo) groups. Meta-analysis suggested a trend favouring bisphosphonates over placebo in terms pain relief (overall OR = 1.54, CI=0.97-2.44, p=0.07, intention to treat analysis). A sensitivity analysis (for evaluable patients) showed statistical significance that favoured bisphosphonates treatment for pain relief (OR=1.64, CI=1.02-2.61, p=0.04).

MEAN PAIN CHANGE

Mean Pain change was reported by 4 studies but pooling results was not possible. Individual study results for mean pain change were not provided.

PROPORTION OF PATIENTS WITH REDUCED ANALGESIC CONSUMPTION

4 studies reported a proportion of patients with reduced analgesic consumption (and were included in a meta-analysis). One study that reported a proportion of patients with reduced analgesic consumption and was not included in this analysis due to missing data, however it showed that there was no statistically significant difference between active (different doses and duration of oral clodronate) and control (placebo) groups.

Meta-analysis showed no difference between bisphosphonates and placebo in terms of reducing analgesic consumption (OR=1.27, 95% CI=0.82-1.98, p=0.28).

MEAN DIFFERENCE IN ANALGESIC CONSUMPTION

Pooling results was shown not to provide meaningful conclusions. One study reported a statistically significant decrease in analgesic consumption after the administration of clodronate and another reported a non statistical significant difference between treatment and control groups in analgesic consumption.

SKELETAL EVENTS

(Hypercalcemia, pathological fractures, requiring RT for bone pain or to treat or prevent fractures or SCC, surgery to bone or symptomatic and asymptomatic bone progression)

Meta-analysis was conducted using data from 1332 patients.
Results for any skeletal events:
The rates for skeletal events were 37.8% and 43.0% for the treatment group and the control group respectively, with an absolute risk difference of 5.2%.

Overall OR=0.79, CI=0.62-1.00, p=0.05. Marginal significant difference favouring bisphosphonates. Sensitivity analysis with evaluable patients indicated the same result and statistical pooling data was valid. Sensitivity analysis comparing different doses of Zoledronic Acid-ZA (4mg or 8 followed by 4mg (8/4mg)) showed a statistical significant reduction in skeletal events for patients given 4mg ZA and no difference for patients given 8mg followed by 4mg ZA.

When active arms of the study that compared different doses of Zoledronic Acid-ZA (4mg or 8 followed by 4mg (8/4mg)) were analysed separately the meta-analysis indicated a statistically significant difference, however, when the active arms were combined in a meta-analysis, the difference was not observed.
Results for pathological fractures statistical pooling data not valid - no appropriate conclusions could be made from results
Results for patients having vertebral fractures (statistical pooling data not valid - no appropriate conclusions could be made from results)
Results for patients having non-vertebral fractures: Overall OR=0.74, 95%CI=0.49-1.12, p=0.15, indicating no significant difference between bisphosphonates (pamidronate iv infusion and 4mg or 8/4mg ZA) and control (placebo).
Results for patients having SCC: Overall OR=0.82, 95%CI=0.44-1.55, p=0.54, indicating no significant difference between bisphosphonates (pamidronate iv infusion and 4mg or 8/4mg ZA) and control (placebo).
Results for patients receiving RT to bone: OR=0.83, 95%CI=0.62-1.11, p=0.21, indicating no significant difference between bisphosphonates (pamidronate iv infusion and 4mg or 8/4mg ZA or clodronate till disease progression) and control (placebo).
Results for patients receiving surgery to bone: OR=0.80, 95%CI=0.38-1.70, p=0.57, indicating no significant difference between bisphosphonates (pamidronate iv infusion and 4mg or 8/4mg ZA) and control (placebo).

QUALITY OF LIFE
2 studies reported QoL outcomes. Results not pooled.
Study 1. Pain score recorded using Present Pain Intensity and QoL used Prostate Cancer Specific Quality of Life Instrument (PROSQOLI). No statistical significant difference between clodronate and placebo group in terms of QoL response. No significant difference in the median changes from baseline in the PROSQOLI scores in 8 out of 9 domains. The pain domain had a significant difference (p=0.022) in favour of the clodronate group.
Study 2. QoL parameters included pain score (Brief Pain Inventory), analgesic scores, ECOG performance status and 2 QoL questionnaires (Functional Assessment of Cancer Therapy General and EURO Quality of life EQ-5D). No statistical difference among 3 study groups in the scores from the QoL questionnaires was found. This study evaluated Zoledronic acid.

PATIENT SURVIVAL
4 studies reported patient death and were included in a meta-analysis. This analysis showed no statistical significant difference between the bisphosphonate group and control group. The overall OR=0.82, 95%CI 0.61-1.11, p=0.21.
1 study was not included in the meta-analysis, reported median time of survival of 464 days for placebo compared to 546 days for 4mg ZA, p=0.091 versus placebo, and 407 days 8/4mg ZA, p=0.386.
Bone and non-bone disease progression was evaluated by 2 studies which were included in a meta-analysis. No statistical significant difference between bisphosphonate group and control group was shown, overall OR=0.76, 95%CI 0.53-1.8, p=0.12.

ADVERSE EVENTS
8 studies reported adverse events, the most common included nausea, vomiting, anaemia, bone pain and renal toxicity.
For Nausea: Treatments evaluated were pamidronate iv infusion and 4mg or 8/4mg ZA. Overall OR = 1.35, 95%CI 1.02-1.77, p=0.03 indicating that a statically significant result of more patients in the bisphosphonate group experienced nausea than the control group. Proportions having nausea: 39.2% (treatment group) and 29.7% (control group), absolute risk difference = 9.5%.
For vomiting: Treatments evaluated were pamidronate iv infusion and 4mg or 8/4mg ZA. Overall OR = 1.22, 95% CI 0.89 - 1.69, p=0.22. No significant difference between bisphosphonate group and control group. Proportion of patients having vomiting were 22.8% (treat-

ment group) and 18.3% (control group), absolute risk difference = 4.5%
For anaemia: Treatments evaluated were pamidronate iv infusion and 4mg or 8/4mg ZA and iv clodronate. Overall OR = 1.04, 95%CI 0.76-1.41, p=0.83. No significant difference between bisphosphonate group and control group. Proportion of patients having anaemia were 20.2% (treatment group) and 19.8% (control group), absolute risk difference = 0.4%.
For bone pain: Treatments evaluated were pamidronate iv infusion and 4mg or 8/4mg ZA. Overall OR = 0.93, 95% CI 0.72-1.21, p=0.58. No statistically significant difference between bisphosphonate group and control group. Proportion of patients having bone pain 51.5% (treatment group) and 50 %(control group), absolute risk difference =1.5%
For renal toxicity: Treatments evaluated were pamidronate iv infusion and 4mg or 8/4mg ZA and iv/oral clodronate.
No renal failure due to iv/oral clodronate was reported. Rates of urinary symptoms were reported, 2% for the oral clodronate group and 6% for the placebo group. Deteriorated renal function was reported in 15.2%, 20.7% and 11.5%f of patients for ZA 4mg group, ZA 8/4mg group, and placebo group respectively. Kaplan-Meier estimates of time to first renal function deterioration was not stat significant for either 4mg or 8/4mg when compared to placebo group. Patients treated with 8mg ZA had a higher incidence of elevated serum creatinine levels than did patients treated with 4mg ZA. Trial protocol was amended and patients were then only given 4mg = 8/4mg zoledronic acid
No change from mean baseline serum creatinine for both pamidronate group and placebo group was reported.

COMPARISONS B/N DIFFERENT ROUTES OF ADMINISTRATION, DOSES AND TYPES OF BISPHOSPHONATES
Intramuscular VS oral clodronate: a significant fall in analgesic consumption was reported but not pain measured by visual analogue scale.
ZA, 4mg VS 8mg (initially 8mg then reduced to 4mg - 8/4mg) VS placebo: At 15 months stat. significant change in mean pain score in favour of 8/4mg over placebo (p=0.026). No significant difference in analgesic scores. No direct comparison between ZA 4mg VS 8/4mg in pain and analgesic scores.

General comments –

Author's comments:
A lack of standardisation in pain measurement hindered meta-analysis. Different definitions of pain response and the differing manner in the way pain results were reported was also problematic.
The method of analysis posed queries. Analyses using number of evaluable patients favoured bisphosphonate treatment (for pain relief) compared to intention to treat analysis which showed no difference. Patient withdrawal was approx 10% and had a significant impact on the result.
Statically analysis was limited by small sample sizes and heterogeneity in study design.
Reviewer Comment:
The results from this review indicate that bisphosphonates do have an effect in decreasing pain and skeletal complications in men with metastatic prostate cancer.

(Saad *et al.* 2004)

Design RCT

(This trial is an extension of a trial included in the Cochrane Review with 24 month follow-up compared to 15 month follow up)

Inclusion criteria

Men with hormone refractory PCa and a history of bone metastasis.

Exclusion criteria

Population number of patients entered trial = 186, number of patients who completed trial = 122.

Interventions

Active arm 1: zoledronic acid 4mg, 214 patients
Active arm 2: zoledronic acid 8mg, 221 patients
Control arm: placebo q3w in 20 cycles (15 months), 208 patients.Ca supplement and vitamin D.

Outcomes

primary endpoints of trial were the proportion of participants having at least one SRE which was prospectively defined as a pathological fracture, SCC, RT or surgery to bone or change in the antineoplastic therapy to treat bone pain. Secondary endpoints time to first SRE, annual incidence of SREs, multiple event analysis using Anderson-Gill model and mean change from baseline brief pain inventory score (BPI)

Follow up

24 months

Results

Numeric results

SREs: Zoledronic acid (4 mg via a 15-minute infusion every 3 weeks for 15 months) reduced the incidence of skeletal-related events (SREs) in men with hormone-refractory metastatic prostate cancer. Among 122 patients who completed a total of 24 months on study, fewer patients in the 4-mg zoledronic acid group than in the placebo group had at least one SRE (38% versus 49%, difference –11.0%, 95% confidence interval [CI] –20.2% to –1.3%; P = 0.028), and the annual incidence of SREs was 0.77 for the 4-mg zoledronic acid group versus 1.47 for the placebo group (P = 0.005). The median time to the first SRE was 488 days for the 4-mg zoledronic acid group versus 321 days for the placebo group (P= .009). Compared with placebo, 4 mg of zoledronic acid reduced the ongoing risk of SREs by 36% (risk ratio 0.64, 95% CI 0.485 to 0.845; P= 0.002). Patients in the 4-mg zoledronic acid group had a lower incidence of SREs than did patients in the placebo group, regardless of whether they had an SRE prior to entry in the study.
Extended follow up results demonstrated continued benefit among patients who remained in the trial (an extra 9 months of follow up). During the extended trial follow up time (15 to 24

month period) fewer patients in the 4mg ZA group than in placebo group had at least one SRE (19% VS 38%, difference of -19%, 95%CI -34.3 to -3.7%, p=.017).

Bone Pain: Periodic measures of BPI scores (at 3-month intervals) demonstrated statistically significant and durable palliation of bone pain for patients treated with zoledronic acid (both 4- and 8/4-mg groups) compared with results of the placebo group. Changes from baseline pain scores showed a dose response. BPI score of 0.58 (4mg ZA) compared to BPI score of 1.05 (placebo group), 95% CI -0.88 to -0.06, p=0.024. A BPI score point difference of 0.47.

Adverse Events: The incidence of events (e.g., mild-to-moderate fatigue, myalgia, and fever) occurred more frequently in patients treated with zoledronic acid than with placebo during the initial trial (included in the Cochrane Review); the incidence of these adverse events was similar between the zoledronic acid and placebo groups during the extension phase (data not shown). Moreover, the rate of study discontinuation due to adverse events did not differ substantially among the three treatment groups.

General comments

Author's comment: Long-term treatment with 4 mg of zoledronic acid is safe and provides sustained clinical benefits for men with metastatic hormone-refractory prostate cancer. Reviewer's comment: Although the statistics show zoledronic acid is effective in reducing skeletal events and pain scores, the clinical relevance is remains unclear.

(Weinfurt *et al.* 2005)

Design

Secondary Analysis of the Saad et al RCT 04 (see above)

Population

Data were from a clinical trial of zoledronic acid versus placebo in the treatment of SREs associated with advanced prostate cancer metastatic to bone (see Saad 2002/2004 trial). Patients (n=248) were included if they experienced an SRE during the study.

Interventions

Active arm 1: zoledronic acid 4mg, 214 patients
Active arm 2: zoledronic acid 8mg, 221 patients
Control arm: placebo q3w in 20 cycles (15 months), 208 patients.Ca supplement and vitamin D.

Outcomes Outcome measures were assessed at fixed intervals. We used mixed-effects models to estimate changes in outcomes after each patient's first SRE.

Results

The relationship between SREs and patient reported outcomes was assessed. There were clinically meaningful and statistically significant declines in physical well-being after: radiation and pathologic fractures; functional well-being after radiation; and emotional well-being after radiation and pathologic fractures. There were meaningful and significant declines in prefer-

ence and utility scores after radiation and fracture. Pain intensity declined after radiation, but not after other SREs; no other pain measure changed substantively.

There were declines in physical well being after 3 categories of SREs (radiation to the bone, pathological fractures and other SREs- SCC, surgery to bone or change in antineoplastic therapy to treat bone pain) as well as significant declines in function ability after radiation to the bone and other SREs. These changes were not attributable to disease progression.

There were differences to which aspect of a patient's experience were affected: Radiation to the bone affected 4 out 5 FACT-G scores. (reflecting the side effects if RT) Pathological fractures were associated with changes to 2 out of 5 FACT-G scores and the 2 measures of the Euro score.
For other SREs no significant scores were reported, however numbers were very small and some deficits were seen across multiple domains of FACT-G.
BPI reported small changes in scores. This may have been due to the SRE definition and trial protocol not collecting SRE events more frequently. That is, outcome assessments were conducted every 90 days. If an event occurred early in this period by the time of the next assessment, the intensity of pain was possibly diminished also the assessment instrument (FACT-G) only records for the last 7 days.

General comments –

Author's CONCLUSIONS: SREs have important and significant effects on measures of health-related quality of life in men with prostate cancer. Treatments that prevent SREs may not demonstrate corresponding effects on outcomes if the effects of SREs occur between scheduled outcome assessments. Implications for trial design are discussed.

Reviewers comments:

This study presented a complex analysis of quality of life outcomes based on existing trial results. Interpretation of the outcomes is complicated and requires careful consideration.

Health Economic Summary

The literature review identified 153 potentially relevant papers, but none were obtained for appraisal as they did not include any economic evaluations. The GDG considered there to be insufficient clinical information available to enable robust economic modelling.

Reference List

Saad, F., Gleason, D. M., Murray, R., Tchekmedyian, S., Venner, P., Lacombe, L., Chin, J. L., Vinholes, J. J., Goas, J. A. & Zheng, M. (2004) Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *Journal of the National Cancer Institute,* 96: 879-882.

Weinfurt, K. P., Li, Y., Castel, L. D., Saad, F., Timbie, J. W., Glendenning, G. A. & Schulman, K. A. (2005) The significance of skeletal-related events for the health-related quality of life of patients with metastatic prostate cancer.[see comment]. *Ann Oncol,* 16: 579-584.

Yuen, K. K., Shelley, M., Sze, W. M., Wilt, T. & Mason, M. D. (2006) Bisphosphonates for advanced prostate cancer. [Review] [51 refs]. *Cochrane Database of Systematic Reviews,* CD006250.

In men with prostate cancer can bisphosphonates reduce the risk of bone complications from androgen deprivation?

Short summary

There was consistent evidence from randomised trials (Diamond *et al.* 2001; Greenspan *et al.* 2007; Michaelson *et al.* 2007; Ryan 2006; Magno *et al.* 2005; Smith *et al.* 2001; Smith *et al.* 2003; Israeli *et al.* 2007), that treatment with bisphosphonates increases the bone mineral density of the lumbar spine in men receiving hormonal therapy for prostate cancer. However, there was no evidence about the effect of bisphosphonates on the rate of symptomatic fractures: the single trial reporting this outcome had insufficient follow-up (Smith *et al.* 2003). There was no significant difference in the rate of severe adverse effects in bisphosphonate and placebo arms in five trials (Israeli *et al.* 2007; Ryan 2006; Greenspan *et al.* 2007; Smith *et al.* 2003; Smith *et al.* 2001).

PICO

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Men having Androgen Deprivation treatment	Bisphosphonate treatment	placebo, no bisphosphonate treatment (open control) or different types, doses or routes of administration of bisphosphonates	• Prevention of cancer treatment-induced bone loss (osteoporosis) • Bone mineral density (at multiple sites) • Skeletal related events (including fractures and spinal cord compression rates) • Cost effectiveness analysis • Adverse events

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

Evidence summary

Bone mineral density (BMD) of the lumbar spine

Six randomised trials reported the effect of bisphosphonates on BMD of the lumbar spine in men receiving ADT for prostate cancer (Diamond *et al.* 2001; Greenspan *et al.* 2007; Michaelson *et al.* 2007; Ryan 2006; Smith *et al.* 2001; Smith *et al.* 2003; Israeli *et al.* 2007). Diamond and co-workers (Diamond *et al.* 2001; Smith *et al.* 2001) included only men with bone metastases and Magno and co-workers (Magno *et al.* 2005) included only men with osteoporosis. The trials used different bisphosphonates and there were variations between trials in androgen deprivation therapy (combinations of GnRH and anti-androgens). The trials all had relatively short follow up, one year or less, during which very few symptomatic fractures would be expected (Shahinian *et al.* 2005).

In the placebo or standard care arms of these trials, patients experienced a significant decrease in BMD of between 1 and 5% over the first year of ADT. In contrast, patients in the bisphosphonate arms of the trials had mean increase of BMD of between 0.4 and 4.9% over the same period.

The difference between the change in BMD over the trial period, in bisphosphonate and placebo arms, was approximately 5% in favour of bisphosphonates (see Figure 85 below).

Symptomatic fractures

The single trial that reported this outcome did not observe any symptomatic fractures in the year following the initiation of ADT (Smith *et al.* 2003).

Asymptomatic (radiologically diagnosed) fractures

The single trial that reported this outcome did not observe any difference between the rate of radiologically diagnosed fractures in bisphosphonate and placebo arms in the year following the start of ADT (Smith *et al.* 2003).

Adverse effects

There was no significant difference in the rate of severe adverse effects in bisphosphonate and placebo arms in five trials that reported this outcome (Ryan 2006; Greenspan *et al.* 2007; Smith *et al.* 2001; Smith *et al.* 2003; Israeli *et al.* 2007) (see Figure 86 below). Michelson *et al* (2007) did not observe any treatment related severe adverse effects in either bisphosphonate or placebo groups in their study.

Figure 85 Change in bone mineral density of the lumbar spine for bisphosphonate and placebo groups.

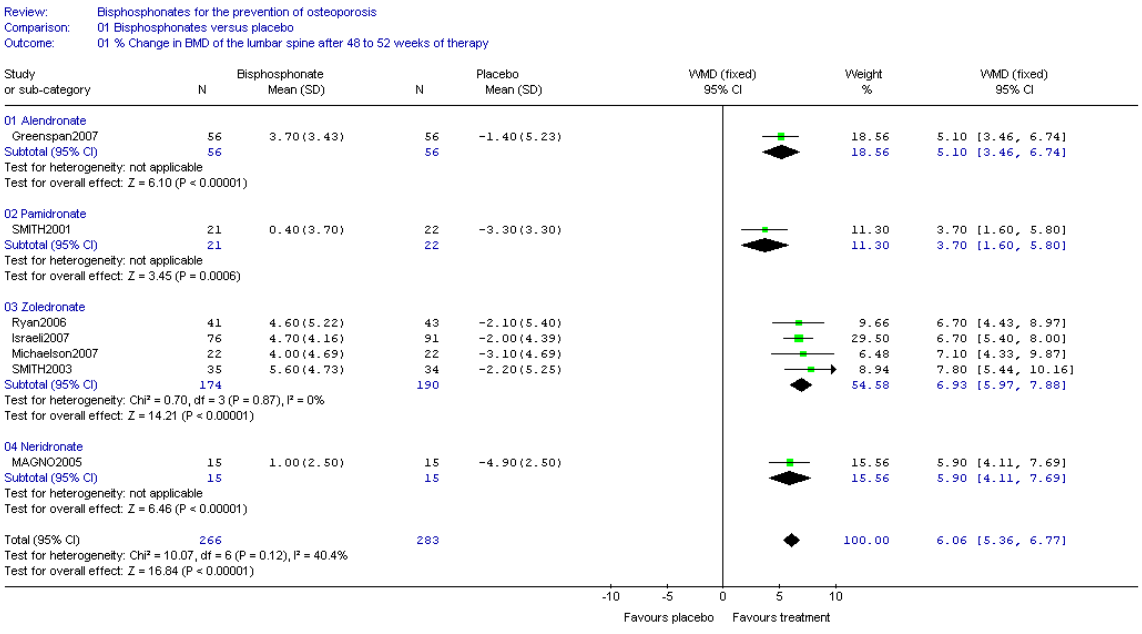
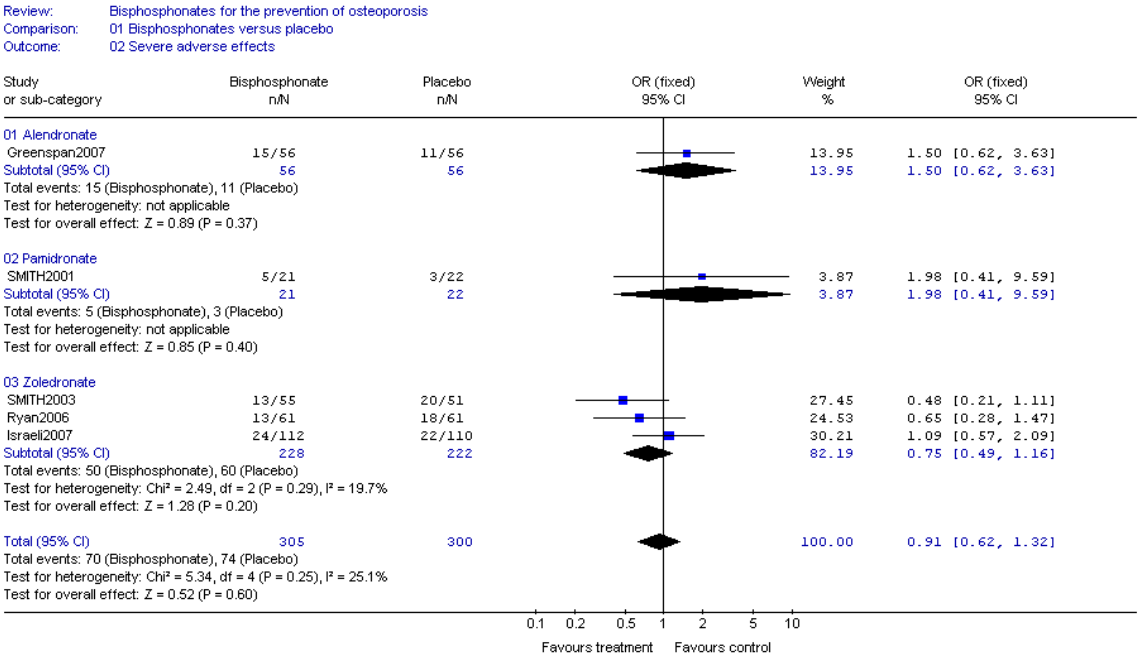


Figure 86. Rate of severe adverse events in bisphosphonate and placebo groups.



Evidence Tables

Randomized controlled trials

(Diamond *et al.* 2001)

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

Country: Australia

Inclusion criteria 21 men with metastatic prostate cancer, treated with ADT. Patients had evidence of bone metastases on radioisotope bone scans. An additional 10 men with prostate cancer (with no evidence of visceral metastases) treated with localised radiotherapy (but not ADT) were included for comparison.

Exclusion criteria 5 men were excluded because of radiological evidence of extensive spinal disease. Other exclusion criteria included refusal of IV infusion, biochemical evidence of renal disease; previous treatment with glucocorticoids, bisphosphonates or calcitrol therapy.

Population number of patients = 21.

Interventions ADT consisted of goserelin and an androgen antagonist (bicalutamide or flutamide) for at least 6 months before randomisation. Patients were randomly assigned to receive a single intravenous infusion of 500 mL of normal saline solution diluted with either pamidronate (90 mg) or placebo at baseline and with a crossover at 6 months.

Outcomes Lumbar-spine bone-mineral densities (BMDs) were measured by spinal quantitative computed tomography (QCT), femoral neck BMDs were measured by dual-energy X-ray absorptiometry (DEXA).

Follow up 18/21 completed both arms of the study. Patients were evaluated at baseline, 6 months and 12 months.

Results -

COMPARISON IN MEN WITH METASTATIC PROSTATE CANCER, RECEIVING ADT	PAMIDRONATE	PLACEBO	OVERALL RESULT
Bone mineral density: spine	Increased from baseline after therapy by 7.8% (SE 1.5%)	Decreased from baseline after therapy by 5.7% (SE 1.6%)	Favours pamidronate (p<0.001)
COMPARISON IN MEN WITH NON-METASTATIC PROSTATE CANCER TREATED WITH EBRT	PAMIDRONATE		OVERALL RESULT
Bone mineral density: spine	Increased from baseline after therapy by 0.9% (SE 1.5%)		Significantly better than the placebo arm (p<0.01)

General comments Small study, no data about adverse effects.

(Greenspan *et al.* 2007)

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

Country: United States, setting: Tertiary care

Inclusion criteria Men receiving androgen deprivation therapy for prostate cancer. Aged 85 years or less, with levels of testosterone in the castrate range. Men were recruited between 2002 and 2003.

Exclusion criteria Men with evidence of metastatic disease or other non-prostate cancer. Elevated PSA (not defined). Illness or medication that could affect bone and mineral metabolism

Population number of patients = 112.

Interventions Men were randomised to receive either alendronate 70mg or placebo. Treatment was once each week for one year. After one year patients in the placebo arm were given alendronate for a further year. After 1 year patients originally in the alendronate arm were randomised to continue alendronate or to receive a placebo for a further year. Daily supplements of calcium (500 mg) and vitamin D (200 IU) were provided.

Outcomes Change in bone mineral density of the spine, total hip, femoral neck and distal radius. BMD was measured using DEXA. Markers of bone turnover were monitored. Adverse events were recorded.

Follow up Outcomes were assessed at baseline, 6 months and 12 months. One man was lost to follow-up and 8 discontinued treatment, usually for medical reasons.

Results Groups did not differ significantly on the overall rate of adverse events, or on the rate of serious adverse events.

COMPARISON IN MEN RECEIVING LHRHA FOR PROSTATE CANCER	ALENDRONATE	PLACEBO	OVERALL RESULT
Bone mineral density: posterior-anterior spine	Mean change from baseline to 12 months: 3.7% (95% CI2.8% to 4.6%)	Mean change from baseline to 12 months: -1.4% (95% CI -2.7% to -0.03%)	Favours alendronate, mean difference 5.1% (95% CI 3.3 to 6.7%)
Bone mineral density: total hip	Mean change from baseline to 12 months: 0.7% (95% CI 0.1% to 1.4%)	Mean change from baseline to 12 months: -0.7% (95% CI -1.5% to -0.01%)	Favours alendronate, mean difference 1.4% (95% CI 0.5 to 2.4%)
Bone mineral density: femoral neck	Mean change from baseline to 12 months: 1.6% (95% CI 0.4% to	Mean change from baseline to 12 months: -0.7% (95% CI -1.5%	Favours alendronate, mean difference 2.3%

	2.8%)	to 0.1%)	(95% CI 1.0 to 3.7%)
Adverse effects	46/56 (82%)	43/56 (77%)	5% (95% CI -10 to 20%)
Serious adverse effects	15/56 (27%)	11/56 (20%)	Difference 7% (95% CI -8 to 23%)

General comments Study not designed to detect differences in fracture rate.

(Israeli *et al.* 2007)

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

Country: United States, setting: Tertiary care

Inclusion criteria Men with histologically confirmed non-metastatic prostate cancer within 1 year of starting androgen deprivation therapy (LHRHa with or without antiandrogen, or orchiectomy All men had T score of -2 or more in the lumbar spine and total hip. ECOG performance status of 2 or less. Life expectancy at least 12 months.

Exclusion criteria Previous treatment for osteoporosis, bisphosphonate therapy or system corticosteroids within previous 12 months. Anabolic steroids or growth hormone within the last 6 months. Diethylstilboestrol therapy. Current or previous non-prostate malignancy. Conditions that could affect study completion. History of bone surgery.

Population number of patients = 222, age range 44 to 89 years.

Interventions Men were randomised to receive either zoledronic acid 4 mg or placebo, administered intravenously over 15 minutes every 3 months for 48 weeks. All men were instructed to take a daily 500 mg calcium supplement and a multivitamin containing vitamin D (400-500 IU/L)

Outcomes Change in the bone mineral density (BMD) of the lumbar spine from baseline value. BMD was measured using DEXA devices. Secondary outcomes were BMD of the total hip and serum N-Telopeptide levels.

Adverse events were graded using the National Cancer Institute Common Toxicity Criteria. The rate of fractures (classed as trauma-related or not) was also reported.

Follow up 31% in the zoledronic acid group and 16% in the placebo group did not complete the study. 1 year outcome data were available for 72% in the zoledronic acid group and 83% in the placebo group.

Results -

COMPARISON IN MEN RECEIVING ANDROGEN DEPRIVATION FOR PROSTATE CANCER	ZOLEDRONIC ACID	PLACEBO	OVERALL RESULT

Bone mineral density: spine	Mean change at 1 year from baseline 4.7% (95%CI 3.74 to 5.66%)	Mean change at 1 year from baseline -2.0% (95%CI -2.9 to 1.1%)	Favours zoledronic acid, difference at 1 year 6.7% (95% CI 5.4 to 8%; p<0.0001)
Serious adverse events	24/112 (21%)	22/110 (20%)	No sig. difference.
Traumatic fractures	2/112 (2%)	3/110 (3%)	Event rate too low to compare groups
Non-traumatic fractures	0/112	0/110	Event rate too low to compare groups

General comments Large number of men did not complete the study

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(Ryan 2006)

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

Country: United States, setting: Tertiary care

Inclusion criteria Men aged 18 or older, who had started androgen deprivation therapy for prostate cancer in the last 12 months.

Exclusion criteria Bone metastases, life expectancy of at least 12 months, previous bisphosphonate therapy or other drug therapy known to affect bone, elevated serum creatinine. T score of -2.5 SD or less at the femoral neck or lumbar spine.

Population number of patients = 120.

Interventions Men were randomised to receive either zoledronic acid 4mg or placebo. Treatment was administered intravenously at 3 monthly intervals for a year. All men were advised to take a daily 500 mg calcium supplement and multivitamin containing 400 IU vitamin D.

Outcomes Change in the bone mineral density of the femoral neck, total hip or lumbar spine between baseline and 6 and 12 months of treatment. BMD was measured using DEXA. Serum markers of bone turnover were also measured. Adverse events, graded as mildly severe, moderately severe or severe.

Follow up Outcomes were measured made at baseline, then at 3,6, 9, and 12 months of treatment. 19 patients were excluded from the final analysis: 4 were lost to follow-up, the remainder were measured using differently calibrated DEXA machines. 101/120 were included in the efficacy analysis.

Results Nausea was more common in the zoledronic acid group than the placebo group, 9.8% vs. 0% respectively (although there was no severe nausea). There were no severe treatment-related side effects reported.

The fracture rate in the zoledronic acid group was 2/61 (3%), but the corresponding rate in the placebo group was not reported.

COMPARISON IN MEN RECEIVING LHRHa FOR PROSTATE CANCER	ZOLEDRONIC ACID	PLACEBO	OVERALL RESULT
Bone mineral density: femoral neck	Mean change from baseline to 1 year: 1.3% (95% CI -0.1 to 2.6%)	Mean change from baseline to 1 year: -2.4% (95% CI -3.7 to 1.0%)	favours zoledronic acid, difference 3.6%(95% CI 1.7 to 5.5%)
Bone mineral density: hip	Mean change from baseline to 1 year: 1.4% (95% CI 0.5 to 2.3%)	Mean change from baseline to 1yr: -2.4% (95% CI -3.3 to -1.5%)	favours zoledronic acid, difference 3.8% (95% CI 2.5 to 5.0%)
Bone mineral density: spine	Mean change from baseline to 1 year: 4.6% (95% CI 2.9 to 6.2%)	Mean change from baseline to 1 year: -2.1% (95% CI -3.7 to -0.5%)	favours zoledronic acid, difference 6.7% (95% CI 4.4 to 9.0%)
Severe adverse events	13/61	18/61	

General comments Some patients in the placebo arm were withdrawn due to BMD decrease of more than 8%. This would tend to reduce the estimate of the effectiveness of zoledronic acid therapy.

(Smith *et al.* 2001)

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

Country: United States

Inclusion criteria Patients with locally advanced, lymph-node positive or recurrent prostate cancer, with no bone metastases according to radionuclide bone scan.

Exclusion criteria Men with Paget's disease, hyperthyroidism, Cushing's disease, hyperprolactinemia, chronic liver disease or chronic renal insufficiency. Men were excluded if they had received androgen deprivation therapy (although some appear to have been included), glucocorticoids, bisphosphonates, calcitonin or suppressive doses of thyroxine within the previous year.

Population number of patients = 47.

Interventions Patients were randomised to receive either leuprolide alone or leuprolide and pamidronate (60 mg intravenously every 12 weeks for 48 weeks). All men also received bicalutamide for the first four weeks of treatment (to prevent tumour flare), and daily calcium carbonate (500 mg) and vitamin D (400 IU).

Outcomes Bone mineral density (BMD): the primary outcome was the change in the posteroanterior measurement of BMD in the lumbar spine at 48 weeks of treatment. Measure-

ments were made using DEXA.

Follow up Patients were evaluated at 2, 4, 8, 12, 24 and 48 weeks of treatment. 47 men were randomised, 43 completed the baseline evaluation and 41 completed 48 weeks of treatment. 3 of these 41 men discontinued ADT due to vasomotor flushing.

Results -

COMPARISON IN MEN WITH NON METASTATIC PROSTATE CANCER, RECEIVING ADT	PAMIDRONATE	STANDARD CARE	OVERALL RESULT
Bone mineral density: spine	Increase of 0.4% (SD 3.7%) (from graph). Not statistically significant.	decreased by 3.3% (SD 3.3%) at 48 weeks (p<0.001)	Absolute difference between groups at 48 weeks was 3.8% in favour of pamidronate (p=0.02)
Severe adverse effects	5/21 (24%)	3/22 (14%)	no sig. difference
Acute phase reaction	3/21 (14%)	0/22	no sig. difference
Anaemia	19/21 (90%)	20/22 (91%)	no sig. difference
Weight gain	2/21 (10%)	3/22 (14%)	no sig. difference
Vasomotor flushing	12/21 (57%)	17/22 (77%)	no sig. difference

General comments Small study, osteoporosis outcomes only.

(Smith *et al.* 2003)

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

Country: United States

Inclusion criteria Men with prostate cancer, and no evidence of distant metastases, who were beginning initial ADT.

Exclusion criteria Previous ADT, antiandrogens, bisphosphonates, calcitonin, gallium nitrate or mithramycin. Severe hepatic disease, creatinine more than 2 mg/dl, other major organ dysfunction or lumbar spine BMD more than 3 standard deviations below young adult normal values.

Population number of patients = 106.

Interventions All patients received ADT: a gonadotropin-releasing hormone agonist with or without an antiandrogen. In addition, patients were randomized to receive either 4 mg. zoledronic acid or placebo intravenously every 3 months for 1 year. All patients were instructed to take 500 mg calcium supplementation and vitamin D (400 IU) daily.

Outcomes Primary outcome was the percent change in BMD of the lumbar spine (L2-L4), from baseline to the end of the study. BMD was determined using DEXA. The incidence of new or worsening vertebral fractures was assessed using radiologic surveys at baseline and the end of the study. Adverse events.

Follow up 106 were randomised. 47/55 completed treatment in the zoledronic acid arm, and 43/55 completed treatment in the bisphosphonate arm. 27 men were excluded from the efficacy analysis because of protocol violation or missing data.

Results -

COMPARISON IN MEN WITH NON METASTATIC PROSTATE CANCER, RECEIVING ADT	ZOLEDRONIC ACID	PLACEBO	OVERALL RESULT
Bone mineral density: spine	Increased by 5.6% from baseline to end of treatment (p<0.001)	Decreased by 2.2% from baseline to end of treatment (p = 0.012)	Favours zoledronic acid (p<0.001)
Symptomatic fracture	0/55	0/51	no sig. difference
Radiologically diagnosed fracture	5/55 (10%) radiologically diagnosed new or worsening fractures	3/51 (6%) radiologically diagnosed new or worsening fractures	no sig. difference
Severe adverse effects (grade 3 or 4)	13/55 (24%)	20/51 (39%)	no sig. difference

General comments No intention-to-treat analysis. Study is underpowered to detect differences in fracture rate (especially with only 1 year of follow-up).

(Magno *et al.* 2005)

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

Country: Italy

Inclusion criteria Patients with locally advanced prostate cancer and osteoporosis (not defined). None had been treated with surgery, chemotherapy or radiotherapy.

Exclusion criteria Paget's disease, Cushing's disease, hyperparathyroidism, hyperthyroidism, hyperprolactinemia, chronic liver disease or chronic renal insufficiency. Previous treatment with drugs interfering with bone metabolism.

Population number of patients = 60, age range 68 to 80 years, mean age = 73 years.

Interventions The trial included four treatment arms: group A (30 patients) treated with maximum androgen blockade (MAB), and group B (30 patients) treated with bicalutamide 150 mg. Patients within each of the ADT arms were randomised to receive neridronate 25 mg, intramuscularly each month, or no bisphosphonate treatment. All patients received calcium and

cholecalciferol supplements (500 mg of elemental calcium and 400 IU cholecalciferol) daily.

Outcomes Bone mineral density (BMD) at the lumbar spine (L2 to L4) in anteroposterior projection. BMD of the total hip and femoral neck. BMD was measured using a DEXA densitometer.

Follow up BMD was measured at baseline and at 12 months. No losses to follow up are reported.

Results -

COMPARISON IN MEN WITH LOCALLY ADVANCED PROSTATE CANCER, RECEIVING MAXIMUM ANDROGEN BLOCKADE	NERIDRONATE	STANDARD CARE	OVERALL RESULT
Bone mineral density: spine	Increased by 1% (S.D. not reported). Not a significant change.	Decreased by 4.9% (S.D. 2.5%) from baseline to 12 months (p=0.002)	Favours neridronate (p<0.05)
Adverse events	3/30 patients in the combined neridronate group experienced a transient flu-like syndrome	None reported	
COMPARISON IN MEN WITH LOCALLY ADVANCED PROSTATE CANCER, RECEIVING ANTIANDROGEN THERAPY	NERIDRONATE	STANDARD CARE	OVERALL RESULT
Bone mineral density: spine	Increased by 2.5% (S.D. 1.5%) from baseline to 12 months (p<0.05)	Decreased by 1.5% (S.D. not reported). Change not significant	Favours neridronate (p<0.05)
Adverse effects	3/30 patients in the combined neridronate group experienced a transient flu-like syndrome	None reported	

General comments No blinding.

(Michaelson *et al.* 2007)

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

Country: United States, setting: Tertiary care

Inclusion criteria Men with prostate cancer receiving hormonal therapy (GnRH agonist)

Exclusion criteria Bone metastases or evidence of progressive disease. Men with metabolic bone disease, history of treatment for osteoporosis, deep vein thrombosis, low serum calcium or elevated serum creatinine. Chronic use of glucocorticoids, anticonvulsants or thyroxine.

Population number of patients = 44.

Interventions Men were randomised to receive a single intravenous injection of either zoledronic acid 4mg or placebo. Treatment was given on day 1 only.

Men continued with GnRH treatment and all received calcium carbonate (500mg daily) and a daily multivitamin tablet containing vitamin D (400 U).

Outcomes Bone mineral density (percent change in the bone mineral density of the posteroanterior lumbar spine from baseline to month 12 after treatment). BMD was measured using DEXA at 4 locations: the posteroanterior lumbar spine, total hip, femoral neck and trochanter. Adverse events. Biochemical markers of bone turnover were also recorded.

Follow up Men were evaluated at baseline and at 3,6,9 and 12 months

Results No treatment related adverse events were reported.

COMPARISON IN MEN RECEIVING LHRHA FOR PROSTATE CANCER	ZOLEDRONIC ACID	PLACEBO	OVERALL RESULT
Bone mineral density: spine	Mean 4.0% (S.E 1.0%) change from baseline	Mean -3.1% (S.E 1.0%) change from baseline	favours zoledronic acid: difference 7.1% [95% CI 4.2 to 10]
Bone mineral density: hip	Mean 0.7% (S.E 0.5%) change from baseline	Mean -1.9% (S.E 0.7%) change from baseline	favours zoledronic acid: difference 2.6% [95% CI 0.9 to 4.3]
Bone mineral density: femur (neck)	Mean 2.0% (S.E 0.6%) change from baseline	Mean -0.1% (S.E 1.0%) change from baseline	favours zoledronic acid: difference 2.1% [95% CI -0.1 to 4.4]
Bone mineral density: trochanter	Mean 1.7% (S.E 0.8%) change from baseline	Mean -1.4% (S.E 0.7%) change from baseline	favours zoledronic acid: difference 3.1% [95% CI 0.9 to 5.3]

Prospective case series

(Polascik *et al.* 2005)

Design: Prospective case series (therapy), evidence level: 3

Country: United States

Inclusion criteria Men with prostate cancer and bone metastases, who were receiving ADT. ECOG performance status of 2 or less.

Exclusion criteria Hormone refractory disease, bisphosphonate therapy within the last 6 months, abnormal renal function, or clinically significant brain metastases. Other therapies affecting osteoclast activity.

Population number of patients = 221.

Interventions All patients received zoledronic acid 4 mg as a 15 minute infusion every 3 weeks for a year. Patients were instructed to take a calcium supplement (500 mg) and vitamin D (400 to 500 IU) daily.

ADT was a GnRH agonist plus antiandrogen in 39% of patients, GnRH agonist only in 37%, antiandrogen only in 8% and unspecified in 16% of patients.

Outcomes Change in the bone mineral density of the lumbar spine (L2 to L4) over 1 year of treatment. BMD was measured using DEXA at baseline and 12 months. The rate of skeletal-related events, defined as bone surgery, radiotherapy of the bone, pathologic bone fractures and spinal cord compression.

Follow up Patients were assessed at each infusion (3 weekly intervals for a year). 120/221 (54%) patients completed the study. 25/221 (11%) discontinued because of adverse effects. 137/221 patients had follow-up DEXA scans.

Results -

COMPARISON IN MEN WITH METASTATIC PROSTATE CANCER, RECEIVING ADT	ZOLEDRONIC ACID	OVERALL RESULT
Bone mineral density: spine	Mean increase from baseline to 1 year was 7.7% (SD 9.4%) ($p<0.001$)	
Skeletal-related events	24/221 (11%) patients experienced one or more SREs.	

General comments No comparison group.

Health Economic Summary

The literature review identified 153 potentially relevant papers, but none were obtained for appraisal as they did not include any economic evaluations. No economic modelling was under-

taken as the GDG concluded evidence from one available RCT showed that bisphosphonates did not delay or reduce the rate of development of bone metastases.

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7.4.2 Bone-seeking radio-isotopes

In patients with hormone-refractory prostate cancer with bone metastases, does the addition of bone targeted radioisotopes to standard care improve outcomes?

Short Summary

Systematic reviews of placebo controlled randomised trials (Bauman *et al.* 2005; Brundage *et al.* 1998; Figuls *et al.* 2003; Finlay *et al.* 2005; Loblaw *et al.* 2003; McQuay *et al.* 1999) suggest that strontium-89 (^{89}Sr-chloride) and samarium-153 (^{153}Sm-EDTMP) are effective for the control of pain from bony metastases in men with prostate cancer. There was no evidence of an overall survival benefit for men treated with radioisotopes. Adverse events associated with radioisotope therapy were usually limited to mild myelosuppression. A systematic review of four studies comparing strontium-89 with samarium-153 or rhenium-188 found no significant differences in pain response rate or treatment toxicity (Finlay *et al.* 2005).

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Patients with hormone-refractory prostate cancer with bone metastases	Radioisotope in addition to standard care	Standard care	• PSA response • Pain control • time to further therapy • survival • quality of life • freedom from skeletal related events • side effects

Evidence Summary

The relevant evidence from the systematic reviews (Bauman *et al.* 2005; Brundage *et al.* 1998; Figuls *et al.* 2003; Finlay *et al.* 2005; Loblaw *et al.* 2003; McQuay *et al.* 1999) and a phase II randomised trial (Nilsson *et al.* 2007) is summarised below

<u>Strontium-89 versus placebo or no strontium</u>

Pain relief

Two RCTs compared strontium-89 to placebo (Lewington *et al.* 1991; Buchali *et al.* 1988). The low dose study (Buchali *et al.* 1988) did not find a significant difference in reported pain relief at 1 -3 years after treatment. The higher dose study (Lewington *et al.* 1991) noted significant pain reduction, five weeks after treatment.

The RCT of Porter et al (Porter *et al.* 1993) compared strontium-89 to placebo in addition to local field radiotherapy. When all pain sites were considered, the group receiving strontium-89 were more likely to experience reduction pain and analgesic use than the radiotherapy-only group. There was no difference between the two groups in the degree of pain reduction at the index site.

A second RCT of similar design (Smeland *et al.* 2003), using a lower dose of strontium-89 in addition to external beam radiotherapy, did not find a significant difference between treatment groups in physician-accessed pain response.

The systematic reviews concluded that strontium-89 is effective for the control of pain from bony metastases.

Overall survival

The patients treated with strontium-89 had better 2 year overall survival in the trial of Buchali (Buchali *et al.* 1988). Inconsistencies in the reporting of survival and the small size of this trial, however, limit the conclusions that can be drawn.

In the study of Porter et al (Porter *et al.* 1993), comparing strontium-89 to placebo in addition to local field radiotherapy, there was no overall survival difference between groups.

In the RCT of Tu et al (Tu *et al.* 2001) patients were given induction chemotherapy. Patients whose disease did not progress were then randomly assigned to receive doxorubicin with or without strontium-89. This study did not report pain outcomes but noted a progression-free and overall survival advantage for the strontium-89 group.

The systematic reviews concluded there was no evidence of an overall survival benefit for patients treated with strontium-89.

Quality of life

The single trial reporting this outcome (Smeland *et al.* 2003) did not find a significant difference between the strontium-89 and placebo groups.

Adverse effects

Strontium-89 was associated with haematological toxicity (thrombocytopenia, neutropenia) in approximately 30 to 50% of patients (usually mild, grade 2 or less).

<u>Strontium-89 versus external beam radiotherapy (EBRT)</u>

Two RCTs compared strontium-89 with EBRT (Oosterhof *et al.* 2003; Quilty *et al.* 1994). The trial by Oosterhof and co-workers (Oosterhof *et al.* 2003) compared strontium-89 and local EBRT. The other trial (Quilty *et al.* 1994) randomised patients who were suitable for either local or hemi-body EBRT to receive that EBRT or strontium-89.

Pain relief

The proportion of patients reporting pain relief was similar in each arm of the Oosterhof and co-workers trial (Oosterhof *et al.* 2003). Reported pain relief was similar in all treatment groups of the Quilty study (Quilty *et al.* 1994), but patients receiving strontium-89 reported significantly fewer new pain sites than those receiving either local or hemibody EBRT.

Overall survival

Overall survival was significantly better in the EBRT arm of the (Oosterhof *et al.* 2003) trial. Progression-free survival was comparable in both arms of this trial. Overall survival was similar in all treatment groups of the Quilty and co-workers trial (Quilty *et al.* 1994).

Adverse effects

The adverse effect rates (haematologic toxicity and nausea or vomiting) were similar in strontium-89 and EBRT treatment groups (Oosterhof *et al.* 2003; Quilty *et al.* 1994)

Strontium-89 versus other radioisotopes

Finlay *et al* (2005) considered evidence from two randomised trials and two non-randomised studies comparing strontium with other radioisotopes. These studies reported no difference in the pain response rate or treatment toxicity. Finlay *et al* (2005) concluded that the choice of radioisotope can be made on the basis of availability, cost and clinical preference or experience.

Samarium-153 versus placebo

Two phase III RCTs compared 37 MBq/kg samarium-153 with placebo (Sartor 1997; Serafini 1998). The Sartor *et al* trial included only men with metastatic prostate cancer, whereas 68% of the patients in the Serafini *et al* trial had metastatic prostate cancer (the remainder having other metastatic cancers).

Pain relief

Analgesic use was significantly lower in the samarium treatment group of Sartor *et al* (1997). In Serafini *et al* (1998) more patients treated with samarium-153 experienced complete pain response (34%) than those in the placebo group (14%).

Overall survival

There was no statistically significant difference in overall survival of the two treatment groups in Sartor *et al* (1997).

Adverse effects

Both Serafini *et al* (1998) and Sartor *et al* (1997) noted mild and transient myelosuppression as the only treatment related toxicity associated with samarium-153.

Rhenium-186 versus placebo

One randomised controlled trial compared rhenium-186 to placebo in men with metastatic prostate cancer (Han *et al.* 2002). A large number of patients were not included in the analysis, however, due to study withdrawal, missing data or loss to follow-up.

Pain relief

A greater pain response was reported in the rhenium-186 group than in the placebo group (65% and 36% respectively, p=0.01).

Overall survival

There was no difference in the overall survival of the two treatment groups

Adverse effects

Systematic reviews of rhenium-186 for the palliation of bone metastases, suggest a similar toxicity profile to that of strontium-89 or samarium-153 (Bauman *et al.* 2005; Finlay *et al.* 2005) with typically mild haematological side effects.

Radium-223 versus placebo

One phase II randomised trial (Nilsson, 2007) compared radium 223 with placebo in 64 men with prostate cancer receiving external beam radiotherapy for painful bone metastases.

Time to skeletal related events (SREs)

SRE was a composite endpoint including increased bone pain, increased analgesic use, pathological fractures and palliative treatment for bone metastases. The median time to the first SRE was 14 weeks in the radium-223 group compared with 11 weeks in the placebo group (p=0.257, log rank test).

Overall survival

Overall survival was significantly better in the group treated with radium-223. In a multivariate survival analysis, adjusting for baseline covariates, the hazard ratio for death in the placebo group was 2.12 (95% CI 1.13 to 3.98, p=0.02) when compared with the radium-223 group. Median overall survival was 65.4 weeks and 46.4 weeks in radium-223 and placebo groups respectively.

Adverse effects

12 serious adverse events were reported in eight men receiving radium-223 compared with 19 in 14 men in the placebo group. There were no statistically significant group differences in the rates of individual adverse events, apart from constipation which was more likely with radium-223 therapy. There were no substantial differences between groups in haematological toxicity.

Evidence tables

(Brundage *et al.* 1998)
Design: Systematic review of RCTs (therapy), evidence level: 1+ County: International, setting: Tertiary care **Inclusion criteria** Randomised trials 2 populations considered: Adult men with hormone refractory prostate cancer and multiple painful bony metastases Adult men with hormone refractory prostate cancer and isolated painful bony metastases (candidates for local XRT) **Exclusion criteria** - **Population** - **Interventions** Strontium 89 vs. conventional radiotherapy (1 trial) Strontium 89 vs. placebo (2 trials) Strontium 89 adjunctive to local radiotherapy (1 trial) **Outcomes** Pain relief (measure at different periods after therapy), survival and adverse effects **Results** The review concluded that, for men with multiple painful uncontrolled hormone refractory metastases from prostate cancer strontium-89 is recommended if multiple single field radiotherapy is not possible. Strontium-89 has proven efficacy in the palliation of pain in these patients but has not been proven to increase survival. For men with isolated painful hormone refractory metastasis from prostate cancer, strontium-89 is not recommended for routine use as an adjunct to local radiotherapy. Strontium 89 has been shown to reduce analgesic use in these patients, but the clinical significance of this is uncertain. Strontium has not been proven to increase survival. **General comments** Review was conducted for the Cancer Care Ontario Guideline program. Review updated in 2001. Many of the scales used by the individual trials were not validated.

(Figuls *et al.* 2003)
Design: Systematic review of RCTs (therapy), evidence level: 1+ County: International, setting: Tertiary care **Inclusion criteria** Randomised controlled trials of patients with metastatic bone pain that com-

pared treatment with radioisotopes and placebo, where the major outcome was either pain or complications of bone metastases

Exclusion criteria -

Population -

Interventions Radioisotopes: strontium-89 (3 trials), samarium-153 (1 trial)

Outcomes Pain from bony metastases, leucocytopenia, thrombocytopenia

Results The combined results suggested a small beneficial effect of radioisotopes on pain control in the short to medium term (1 to 6 months). There was no evidence about longer term effects (at 12 months).

Numeric results

Comparison: Strontium 89 plus standard care versus standard care			
	Strontium 89	Placebo	
Outcome: Complete pain relief	total N = 38	total N = 38	relative risk (random) 1.87; 95% CI [1.06 to 3.31]
Outcome: Partial pain relief	total N = 38	total N = 38	relative risk (random) 1.56; 95% CI [1.04 to 2.34]
	Strontium 89	Placebo	
Outcome: Any pain relief	1.16; N 34	; SD 0.49; N 39	
	Strontium 89	Placebo	
Outcome: Leucocytopenia	total N = 90	total N = 75	relative risk (random) 4.1; 95% CI [0.92 to 18.23]
	Strontium 89	Placebo	
Outcome: Thrombocytopenia	total N = 37	total N = 34	relative risk (random) 2.04; 95% CI [0.95 to 4.34]

General comments Authors comment that the trials had small sample sizes and evaluated only short-term outcomes. The appropriateness of meta-analysis is questionable (heterogeneity of doses and outcomes).

(McQuay *et al.* 1999)

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

County: International, setting: Tertiary care

Inclusion criteria Full journal publication, patients with pain due to bone metastases and random allocation to a radiotherapeutic intervention (external radiotherapy or radioisotope).

Exclusion criteria Trials not reporting pain outcomes

Population -

Interventions Radiotherapy (20 trials), radioisotopes (6/8 trials were of 89-Sr)

Outcomes Pain, quality of life, incidence of new pain sites, adverse effects

Results For more generalised disease radioisotopes produced similar analgesic results to external irradiation.

The strontium 89 trials were too heterogeneous to perform statistical meta-analysis.

(Bauman *et al.* 2005)

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

Country: International, setting: Tertiary care

Inclusion criteria RCTs that compared radioisotopes to: placebo, another radioisotope or another active treatment in patients with pain due to metastatic bone disease. Phase I or II trials and guidelines were also considered.

Study outcomes had to include pain, analgesic use, quality of life, adverse events or overall survival

With the exception of the Smeland et al (2003) study, all patients included had metastatic prostate cancer.

Exclusion criteria Trials with less 20 patients, non-English language

Population -

Interventions Strontium 89 vs. placebo (2 trials)

Strontium 89 vs. placebo (adjuvant to external radiotherapy) (2 trials)

Strontium 89 vs. placebo (adjuvant to chemotherapy) (1 trial)

Strontium 89 vs. strontium 89 + cisplatin (1 trial)

Strontium 89 vs. external radiotherapy (2 trials)

Samarium 153 vs. different dose of Samarium 153 (3 trials)

Samarium 153 vs. placebo (2 trials)

Rhenium 186 vs. placebo (1 trial)

Outcomes Pain rating, Analgesic use, Adverse effects and Overall survival

Results Strontium results

A randomized phase III trial comparing strontium-89 plus cisplatin with strontium-89 plus placebo reported a significantly higher proportion of patients experiencing pain relief for a significantly longer duration with strontium-89 plus cisplatin.

A randomized phase III trial comparing adjuvant strontium-89 with placebo following radiotherapy reported a higher proportion of pain-free patients with strontium-89. Patients who received strontium-89 also experienced fewer new sites of bone pain. A second, but underpowered study failed to confirm these results.

In one randomized trial of strontium-89 versus radiotherapy (hemi body or local), patients treated with strontium-89 developed fewer new sites of pain. In a second trial comparing strontium-89 versus local radiotherapy, median overall survival was improved with radiotherapy, while pain response and time-to-progression were similar in the two groups. One randomized phase III trial reported no difference in pain relief between strontium-89 and placebo.

Samarium results

Two phase III RCTs compared 37 MBq/kg samarium-153 with placebo (Sartor 1997; Serafini 1998). The Sartor trial included only men with metastatic prostate cancer, whereas 68% of the patients in Serafini trial had metastatic prostate cancer (the remainder having other metastatic cancers).

Pain relief

Analgesic use was significantly lower in the samarium treatment group of the Sartor trial. In the Sera trial, more patients treated with samarium-153 experienced complete pain response (34%) than those in the placebo group (14%).

Overall survival

There was no statistically significant difference in overall survival of the two treatment groups in the Sartor trial.

Adverse effects

Both Serafini et al (1998) and Sartor et al (1997) noted mild and transient myelosuppression as the only treatment related toxicity associated with samarium-153.

Rhenium-186 results

One randomised controlled trial compared rhenium-186 to placebo in men with metastatic prostate cancer. A large number of patients were not included in the analysis, however, due to study withdrawal, missing data or loss to follow-up.

Pain relief

A greater pain response was reported in the rhenium-186 group than in the placebo group (65% and 36% respectively, p=0.01).

Overall survival

There was no difference in the overall survival of the two treatment groups

General comments 27 non-randomised (single-arm) trials of strontium were also included in an evidence table.

(Finlay *et al.* 2005)
Design: Systematic review of RCTs (therapy), evidence level: 1++ County: United Kingdom, setting: Tertiary care **Inclusion criteria** Studies of radioisotopes for the palliation of bone metastases. Most of the included studies involved patients with prostate cancer. **Exclusion criteria** No language or location restrictions **Interventions** strontium 89 in addition to standard care, strontium-89 in comparison to radiotherapy, strontium-89 in comparison to other radioisotopes (153Sm, 32P, 186Re and 188Re) **Outcomes** Pain rating, analgesic use, adverse effects, tumour markers (PSA), hot spots on bone scintigraphy, survival **Results** Placebo-controlled studies suggest there is a therapeutic benefit of strontium 89 in the control of pain from bone metastases, although the evidence comes from small studies. The evidence for the use of strontium 89 as an adjuvant to radiotherapy is inconsistent. Comparisons of strontium 89 and external radiotherapy suggest similar subjective response rates. The adverse effects most commonly associated with strontium-89 are thrombocytopenia and neutropenia, but these are usually mild and reversible. Strontium-89 versus other radioisotopes review considered evidence from two randomised trials and two non-randomised studies comparing strontium with other radioisotopes. These studies reported no difference in the pain response rate or treatment toxicity. The authors concluded that the choice of radioisotope can be made on the basis of availability, cost and clinical preference or experience.

Randomized controlled trial

(Nilsson *et al.* 2007)
Design: Randomized controlled trial, evidence level: 1++ Country: , setting: Tertiary care **Inclusion criteria** Men with hormone refractory prostate cancer due to receive EBRT for painful bone metastases. Consecutive rising PSA measurements, ECOG performance status 0 to

2, life expectancy at least 3 months.

Exclusion criteria Other active malignancy, prior chemotherapy, immunotherapy or EBRT within the last 6 months

Population -64 men, aged between 57 and 88 years.

Interventions Men were randomised to receive either radium-223 (50 kBr/kg in 4 IV injections) or placebo. All men received EBRT to the most painful site, with margins and to an area not more than 400 cubic centimetres. Either one fraction of 8 Gy, or 20 Gy in 5 fractions or 30 Gy in 10 fractions was given.

Outcomes Skeletal related events (composite outcome including: 25% increased pain, increased analgesic use, neurological symptoms of bone metastases, pathological fractures or palliative interventions for the bone metastases). Bone alkaline phosphatase.

Secondary outcomes were: toxic effects, time to PSA progression and overall survival.

Follow up Men were monitored every 2 weeks until 4 weeks after the last radioisotope injection, and then again at 6, 9 and 12 months. Men were followed for survival and long-term toxic effects at 18 and 24 months.

Results Multivariate overall survival analysis, adjusted for baseline covariates, showed a HR of 2.12 (95% CI 1.13 to 3.98, p=0.20), indicating increased risk of death in the placebo group.

Apart from constipation, there was no statistically significant difference between the rates of adverse effects in the two groups.

COMPARISON IN MEN WITH PROSTATE CANCER, RECEIVING EBRT FOR BONE METS	RADIUM-223	PLACEBO	OVERALL RESULT
Skeletal-related events	Median time to first SRE was 14 weeks (95% CI 9 to 30 weeks)	Median time to first SRE was 11 weeks (95% CI 5 to 25 weeks)	No sig. difference, p=0.2457 (log rank test)
Change in bone-ALP	Median relative change from baseline to 4 weeks, -65.6% (95% CI -69.5% to -57.7%)	Median relative change from baseline to 4 weeks, 9.3% (95% CI 3.8% to 60.9%)	p<0.0001 (Wilcoxon test)
Overall survival	Median OS was 65.3 weeks (95% CI 48.7 to infinity)	Median OS was 46.4 weeks (95% CI 32.1 to 77.4 weeks)	p=0.066 (log rank test).
Serious adverse events	12 events in 8 patients	19 events in 14 patients	
Haematological adverse events			No substantial difference between groups

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

Study	Comments
(Buchali *et al.* 1988)	RCT included in the systematic reviews
(Lewington *et al.* 1991)	RCT included in systematic review
(Oosterhof *et al.* 2003)	RCT(Sr89 vs. EBRT) included in systematic reviews
(Porter *et al.* 1993)	RCT included in systematic reviews
(Quilty *et al.* 1994)	RCT(Sr89 vs. EBRT) included in systematic reviews
(Smeland *et al.* 2003)	RCT included in systematic reviews
(Tu *et al.* 2001)	RCT included in the systematic review

Health Economic Short Summary

The literature review on Sr-89 identified 50 potentially relevant papers. Nineteen of these papers were obtained for appraisal of which 2 were identified and reviewed (McEwan et al 1994; Malmberg 1997). None contained full economic evaluations, only cost comparisons. All three evaluations compared the costs of providing Sr-89 as an adjunct to radiotherapy to patients with HRPC and bone metastases compared with radiotherapy alone.

The study by McEwan et al. (1994) was based on a small Canadian (CAN$) RCT (n=29), although the costing was undertaken retrospectively. All patients were followed-up until death, which was at a median of 30-34 weeks depending on the treatment arm. The study demonstrated a number of clinical benefits including an improvement in quality of life indices. No price year for the costing was provided. The authors stated that the mean treatment cost per patient for the strontium group was Can$16,570 and Can$23,688 for placebo (approximately £7,700-£11,000). However, evidence from within the manuscript suggests that these costs are incorrect, and that the placebo arm was less costly than the strontium-89 arm. No sensitivity analysis was performed, and the evaluation was generally considered to be of poor quality.

The evaluation by Malmberg et al. (1997) also evaluated the costs of external radiotherapy alone versus external radiotherapy with Sr-89, from a Swedish societal perspective (that is, both direct healthcare and indirect costs were included). The analysis was based on a single RCT, but longer terms costs were estimated. That is, the time horizon for the analysis was a patient's lifetime. The costs relating to radiotherapy included the costs of skeletal scintigraphy, outpatient visits, inpatients days, and travel to the treatment centre. The costs for Sr-89 included the costs of its administration. Costs were reported in 1993 Swedish prices.

The authors reported that the total additional lifetime cost of Sr-89 treatment were more than offset by cost savings from the postponed external radiotherapy treatments. Reported cost savings were approximately between SEK 3,000-11,000 (approximately £200-£800). However, the main limitation with the analysis was that very few details of the methods were reported. Thus it was difficult to determine the quality of the study. In summary, the overall evidence base to support the use of Sr-89 in this setting was considered to be weak.

Health Economic Summary

Overview

All included studies examined population sample of patients with hormone refractory prostate cancer. Common objective was to estimate the cost-effectiveness of a standard care versus standard care plus stronium-89.

McEwan et al. (McEwan *et al.* 1994) compared the costs of radiotherapy plus Metastron (strontium-89) treatment with radiotherapy plus placebo.

Malmberg et al. (Malmberg *et al.* 1997) evaluated the costs external radiotherapy alone versus external radiotherapy with strontium-89.

The relevant evidence from the included studies (McEwan *et al.* 1994; Malmberg *et al.* 1997) are summarised below.

Comparison(s)

All three studies examined the addition of strontium-89 to standard care and its effect on costs of the treatment. McEwan et al. (McEwan *et al.* 1994) and Malmberg et al. (Malmberg *et al.* 1997) identified radiotherapy as a standard care treatment.

Population Sample

The population sample in the study by McEwan et al. was a subset of the participants described in the study of Porter et al., as reported in the clinical evidence table, of the Trans Canada Collaborative Study of 29 patients with hormone refractory prostate cancer and mean age of 73 years. Malmberg et al. used a Canadian sample with two additional sub samples that included data on total direct costs and survival rate from Sweden. No mean for the age of the participants was given. The population sample used by Sherman et al. was from a Phase II trial conducted at the Memorial Sloan-Kettering Cancer Centre and consisted of patients with Androgen Independent Prostate Carcinoma (AIPC) and mean age of 67years.

Both studies included patients with hormone refractory prostate cancer.

Costs

McEwan et al. considered only health service costs which included radiotherapy, drugs costs, outpatient and day care visits, radiology and laboratory investigations, nuclear medicine and tertiary in-patient costs. The costs for the initial radiotherapy with strontium-89 or placebo were not included. All costs are quoted in Canadian dollars (Can $), but price year was not given.

Malmberg et al. included the average unit costs of resources – bone scan, clinical examination treatments and hospitalization. These costs were obtained from an official price list of regional hospital fees for the Southern Sweden. All amounts are quoted in Swedish currency (SEK) for 1993.

Clinical Effectiveness

McEwan et al. report that Porter et al. found, patients in the Metastron (strontium-89) arm demonstrated a significant improvement in quality of life indices, reduction in time to further metastases, reduction in pain and analgesic intake and a significant fall in requirements for additional radiotherapy compared with patients in the placebo arm. There was no significant alteration in

survival (median survival weeks 34 versus 30) or in haematological toxicity. However, no further detail and confidence intervals were reported.

Citing Porter et al., Malmberg et al. state that, though statistically not significant, addition of strontium-89 to radiotherapy treatment prolonged survival. A quality of life analysis demonstrated with statistical significance that addition of strontium-89 reduces pain and improves physical ability. Addition of strontium-89 prolonged the time to further external radiotherapy by 15 weeks (35 weeks versus 20, *P*=0.006); no confidence interval was reported.

Results

The results of the McEwan et al. study found that addition of strontium-89 to standard care proves to be less costly than standard care plus placebo. The authors report that the intervention arm incurred lower overall costs (Can$ 16,570) than the placebo arm (Can$ 23,688), however the cost of strontium-89 was not included.

Mamlberg et al. found that the total additional cost of strontium-89 treatment (SEK 12,400) can be offset by cost savings from the postponed external radiotherapy treatments, reporting total average cost for one relapse treated with external radiotherapy to be SEK 48,600.

Sensitivity Analysis

Study by Malmberg et al. conducted sensitivity analyses by considering following: (a) total direct costs for one relapse treated with radiotherapy, (b) time between relapse, (c) the length of the extended pain-free period with Strontium-89, (d) survival probability and (e) discount rate (varied to 0%). The authors state that the results were sensitive to total direct cost for one relapse and change in time between relapses. The results were not sensitive to different survival probabilities or change in discount rate.

The studies by McEwen et al. did not include sensitivity analyses.

Reviewer Comments

This review of McEwan et al's study is based on the NHS EED review and the original article. This study fails to present a well supported evidence of the effect of strontium-89 on the quality of life of patients. An ideal study design would have been a cost-effectiveness analysis, as quality of life is foremost in palliation.

The study by Malmberg et al. points out the benefit of adding strontium-89 treatment to external radiotherapy. Although, the authors conducted a cost study with thorough sensitivity analysis, the cost-effectiveness analysis was not performed. The title states that economic evaluation between strontium-89 versus external radiotherapy was conducted, however these findings were not reported.

In both studies, no health economic analysis was undertaken to enable conclusions to be drawn concerning the cost-effectiveness of the intervention. Moreover, the studyby Mamlberg et al. was conducted form a societal perspective.

Health Economics Evidence Table

Question: What is the cost-effectiveness of Strontium-89 in patients with hormone refractory prostate cancer (HRPC) and bone metastases?

By: Eugenia Priedane, Pat Linck, Dyfrig Hughes and Rhiannon Tudor Edwards
Date: 14/02/2006

Bibliographic reference	McEwan, A.J., et al., A *Retrospective analysis of the cost effectiveness of treatment with Metastron (89Sr-chloride) in patients with prostate cancer metastatic to bone.* Nuclear Medicine Communications, 1994. 15(7): p. 499-504. Evidence review was based on NHS EED review and original article.	Malmberg, I., et al., *Painful bone metastases in hormone-refractory prostate cancer: Economic costs of strontium-89 and/or external radiotherapy.* Urology, 1997. 50(5): p. 747-753.
Source of funding	Alberta Cancer Board Research Institute Programme.	Not stated.
Economic study type	Retrospective cost study of patients from one arm of a multi-centred RCT as reported by Porter et al. (1993). The study assesses the differences in management costs of administering strontium-89 on the cost of managing patients with bone metastatic prostate cancer. However the costs of the strontium-89 or the radiotherapy given on admission to the trail were not included.	Cost study. Compares the costs of external radiotherapy alone versus external radiotherapy plus strontium-89.
Population, country & perspective	Patients with bone metastatic prostate cancer. All patients deceased at the time of the study (n=29). Mean age for placebo patients was 72.4 years and for strontium patients 73.9 years. The study was conducted from health service costs perspective in Canada.	Population sample of patients with hormone refractory prostate cancer. The authors used a Canadian sample with two additional sub samples that included data on total direct costs and survival rate from Sweden. The Canadian study population is the same population as McEwan et al (1993) Patients included in the analysis were divided into two groups based on the geographic location (a group living within 40 km of the hospital in the county of Malmoehuslaen – "within county"; the other group of patients living 100 to 300 km from the hospital – "outside county" The study was conducted from Societal lifetime cost perspective in Sweden.
Comparison(s)	Radiotherapy plus strontium-89 compared with radiotherapy plus placebo in patients receiving palliative. care in outpatient department.	External radiotherapy alone versus external radiotherapy with strontium-89.
Source of effectiveness data	Effectiveness data is from a multicentre RCT (8 centres) Porter at el. The cost study is from one of the centres.	Efficacy results were obtained from Porter et al. (1993) study.
Cost components included and health care resource utilization	Only health service costs were considered. Resources were retrospectively calculated from case-notes and trial records for the following items. Details of quanti-	Resource use data included investigations (bone scan), outpatient visits, external radiotherapy hospitalization (on-

(HCRU)	ties were not reported. (Sources of the unit costs used in the calculations are given in brackets): Radiotherapy; Drugs costs (provided by a cancer clinic pharmacy); Outpatient and day care visits (from the Alberta Cancer Board); Radiology and laboratory investigations (from the Alberta Health Care Insurance Plan); Nuclear Medicine; Tertiary in-patient costs (Alberta Government Department of Health). The costs for the initial radiotherapy with Metastron or placebo were not included.	cology ward, urology ward and patient hotel), and travelling; no HCRU reported. Costs of one relapse and lifetime costs were estimated.
Results – cost per patient per alternative	Overall the mean treatment cost per patient for the strontium-89 group was Can$ 16,570 and Can$ 23,688 for patients in the placebo group. The total costs per week of survival are Can$ 351 for the strontium group and Can$ 560 for placebo group. The 1991 cost of a standard dose of Metastron was Can$ 1600. The costs of strontium were excluded.	Total additional cost of strontium-89 treatment was estimated at about SEK 12,400. The average total cost for one relapse treated with radiotherapy was estimated at about SEK 31,011 for patient "within county" and SEK 48,600 "outside county".
Results – effectiveness per patient per alternative	The study reports that the RCT, from which this is a sub-set, demonstrated a significant improvement in QoL indices, reduction in time to further metastases, reduction in pain and analgesic intake and a significant fall in requirements for additional radiotherapy. There was no significant alteration in survival (median survival weeks 34 vs. 30) or in haematological toxicity. The magnitude of improvement and confidence intervals were not reported.	Reference to Porter et al. study - although statistically not significant, addition of Strontium-89 to radiotherapy treatment prolonged survival rate. A QoL analysis showed that addition of strontium-89 reduces pain and improves physical ability. Addition of strontium-89 prolonged the time to further external radiotherapy by 15 weeks (35 weeks versus 20, *P*=0.006). The magnitude of improvement and confidence intervals were not reported
Results-uncertainty	No sensitivity analyses carried out.	Sensitivity analyses were performed considering the following: total direct costs for one relapse treated with radiotherapy, time between relapse, the length of the extended pain-free period with strontium-89, Survival probability and discount rate to 0%. The results were sensitive to total direct cost for one relapse and change in time between relapses. The results were not sensitive to different survival probabilities or change in discount rate.
Time horizon, discount rate	Time horizon/discount rate - Not stated.	Time horizon - January 1993-February 1994.

Comments	a) This study fails to present a well supported evidence of the effect of Metastron on the quality of life of patients. An ideal study design would have been a cost-utility analysis, as quality of life is foremost in palliation. b) The quoted cost per week survival may be a misleading concept, as it suggests that the drug has produced a certain number of weeks of survival. The figures in fact reflect cost of palliation per week of survival in the two patient groups. c) Calculation of the final costs is unsound. If we use the results given in table 5, placebo cost per patient is cheaper than strontium. d) Some costs which are normally classified as direct costs in the standard methodology have been termed by the authors as indirect costs. e) The study suffers from not giving price date.	The study by Malmberg et al. points out the benefit of adding strontium-89 treatment to external radiotherapy. Although, the authors conducted a cost study with thorough sensitivity analysis, the cost-effectiveness analysis was not performed

Health Economic Quality Checklist

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

Scoring - yes, no, not clear and not appropriate	Study ID	McEwan et al. (1994)	Malmberg et al. (1997)
	Checklist completed by	PL	EP
Study design	Was a research question stated?	Yes, not clearly	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?)?	No	Yes
	Was the form of economic evaluation used, clearly stated?	No	Yes
	Is the choice of the economic evaluation justified in relation to the questions addressed?	No	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)	Yes	Yes
	Were the details of the synthesis or meta-analysis of estimates given? (If based on an overview of a number of effectiveness studies)	Not applicable	Not applicable
	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?	No	
	Were the details of the subjects from whom valuations were obtained given?	Yes	Yes
	Were any productivity changes (if included) reported separately?	Not applicable	Not applicable
	Was the relevance of any productivity changes to the study questions discussed?	Not applicable	Not applicable
	Were the quantities of resources reported separately from their unit costs?	No	Not Clear
	Were the methods for estimation of quantities and unit costs described?	Not clear	Partly
	Was the currency and price data recorded?	Yes	Yes
	Were the details of currency of price adjustments for inflation or currency conversion given?	In part	In part
Modelling	Were the details of any model used given?	Not applicable	Not applicable
	Was the choice of model and the key parameters on which it was based justified?	Not applicable	Not applicable
Analysis and interpretation of results	Was the time horizon of costs and benefits stated?	No	Yes
	Was the discount rate stated?	No	No
	Was the choice of discount rate justified?		Not applicable
	Was an explanations given if costs or benefits were not discounted?	No	No
	Were the details of statistical tests and confidence rates given for stochastic data?	None done	No
	Was the approach to sensitivity analysis given?	No sensitivity analysis	Yes
	Was the choice of variables for sensitivity analysis justified?	Not applicable	Yes
	Were the ranges over which the variables are varied stated?	Yes	No
	Were relevant alternatives compared?	Yes	Yes
	Was the incremental analysis reported?	No	No
	Were the major outcomes presented in a disaggregated as well as aggregated form?	No	Not applicable

	Was the answer to the study question given?	No	Yes
	Did the conclusions follow from the data reported?	Yes	Yes
	Were the conclusions accompanied by the appropriate caveats?	Caveats given	Caveats given
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)?	No	No
	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
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?	Poor health economic study, not all the costs were included and these was no economic analysis using effectiveness data from the RCT	Partly

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7.5 Pelvic-targeted therapies

7.5.1 Management of obstructive uropathy

What is the most effective way to manage obstructive uropathy in men with hormone refractory prostate cancer?

Short Summary

Evidence about urinary tract decompression in men with ureteric obstruction and hormone refractory prostate cancer came from case series. Most studies concluded that urinary tract decompression, with nephrostomy or ureteral stents, should be considered (Harris & Speakman 2006)(Bordinazzo *et al.* 1994; Chiou *et al.* ; Sandhu *et al.* 1992; Fallon *et al.* 1980). Some however concluded that, despite any survival benefit, urinary tract decompression was usually not appropriate in this group (Dowling *et al.* 1991; Paul *et al.* 1994). There was insufficient evidence about the relative effectiveness of nephrostomy and ureteral stents: no series directly compared different interventions.

PICO question

POPULATION	INTERVENTIONS	COMPARISONS	OUTCOMES
Men with obstructive uropathy and hormone refractory prostate cancer	Treatment for renal failure (dialysis, stents, nephrostomy)	No treatment	• Overall survival • Quality of life

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

Evidence summary

Use of urinary tract decompression for men with hormone refractory prostate cancer patients

Evidence about urinary tract decompression in men with ureteric obstruction and hormone refractory prostate cancer came from case series. Most studies concluded that urinary tract decompression, with nephrostomy or ureteral stents, should be considered (Harris & Speakman 2006)(Bordinazzo *et al.* 1994; Chiou *et al.* ; Sandhu *et al.* 1992; Fallon *et al.* 1980). Some however concluded that, despite any survival benefit, urinary tract decompression was usually not appropriate in this group (Dowling *et al.* 1991; Paul *et al.* 1994). There was insufficient evidence about the relative effectiveness of nephrostomy and ureteral stents: no series directly compared different interventions.

Nephrostomy

Evidence from case series suggests percutaneous nephrostomy is safe and effective in relieving ureteral obstruction in patients with hormone refractory prostate cancer. A series of 21 HRPCa patients (Harris & Speakman 2006) showed a mean survival of 100 days and concluded that nephrostomy should be considered for all patients despite their hormone status; some patients had also received stents. A case series that included 15 patients previously treated with hormones (Bordinazzo *et al.* 1994) concluded that ureteral obstruction can be treated effectively with percutaneous drainage and the treatment should not be withheld in patients previously treated with hormones as 46% of these patients were still alive one year after

the intervention. One case series (Chiou *et al.* 1990) that included 22 patients treated with hormones concluded the adequate safety and effectiveness of percutaneous nephrostomy and stressed that a reasonable survival can be achieved even in patients with renal failure. A case series that included 4 HRPCa patients also emphasised the safety, low complication rate and the duration of survival it permits even if the malignancy is not curable.

A small case series concluded that patients can be discharged from hospital and followed at home after studying a sample of patients with malignant urogenital neoplasia (Romero *et al.* 2005); however, all 5 included HRPCa patients died in the hospital and were never discharged after the procedure. Another case series that included prostate cancer patients (Pappas *et al.* 2000) came to the same safety and effectiveness conclusion, however it is unclear how many HRPCa patients were studied.

Dowling and co-workers (Dowling *et al.* 1991) interpreted their case series data on HRPCa patients (82% died within a median of 119 days) as an indication that percutaneous nephrostomy should be reserved for only the most unusual situation.

One case series (Fallon *et al.* 1980) showed moderately good long-term survival and quality of life in a sample that included prostate cancer patients of which some appeared to be HRPCa patients but it is unclear which nephrostomic procedures were used; the publication saw percutaneous nephrostomy as a temporary measure. Paul and co-workers (Paul *et al.* 1994) observed better survival in a cohort that comprised 9 percutaneous nephrostomy treatments but concluded that for most the kindest course is not to intervene, however it is unclear whether there were HRPCa patients amongst the percutaneous nephrostomy treatments. Sandhu and co-workers (Sandhu *et al.* 1992) concluded from a prognostic marker study that interventional therapy (including nephrostomies) is justified with a 25% five-year survival of patients with advanced prostate cancer and obstructive uropathy. However, the respective survival rate for the 36 patients with bone metastases and treated with hormones was only 14% and the results were not reported for individual interventions. The prostate cancer patients in (Oefelein 2004) underwent interventions for obstructive uropathy which included percutaneous nephrostomy placement, urinary diversion or Foley catheter and the median survival was seven months for patients who had received androgen deprivation therapy but it was not possible to link the results to individual interventions.

JJ stent

The insertion of double-J ureteral stents may be a safe and effective treatment for obstructive uropathy in patients with hormone refractory prostate cancer (evidence level 3).

One case series of 18 HRPCa patients (Chefchaouni *et al.* 1998) concluded that endoscopic ureteroneocystostomy and pigtail stent placement is an attractive treatment option, prolonging survival and improving quality of life. Another series of three men with prostate cancer (Rotariu *et al.* 2001) concluded that the simultaneous placement of two double-J 7F ureteral stents for the management of ureteral obstruction is safe and effective. A case series in which 2 patients underwent antegrade double-J stent insertion (Little *et al.* 2003) noted no complications or infections; however, it is unlikely that these were HRPCa patients. The case series reported by Pappas and co-workers (Pappas *et al.* 2000) that included some prostate cancer patients reported successful stent placement in 81% of cases, in 5% of these, the stent had to be changed due to obstruction. The case series by Harris and co-workers (Harris & Speakman 2006) reported favourable results for nephrostomy in which some of the patients (not necessarily those with HRPCa) also had a stent inserted.

One case series with 3 HRPCa patients concluded that a metal mesh ureteral stent gives poor palliation in distal strictures and permanent nephrostomy may be more acceptable (Ahmed et al., 1999).

Some of the nephrostomy series (Paul *et al.* 1994; Oefelein 2004; Sandhu *et al.* 1992) included patients treated with stents; the same conclusions as above apply but again it is not possible to link the results to individual interventions for obstructive uropathy.

Evidence tables

Observational studies - Cohort studies:

Paul, Love & Chisholm. The management of bilateral ureteric obstruction and renal failure in advanced prostate cancer. British Journal of Urology, 1994, 74, 642-645.

Design: Cohort study (prospective), evidence level 2-

Country: UK, setting: prostate cancer database, hospital case coding

Inclusion criteria All patients with a plasma urea measurement of >= 15mm at any time and with radiological evidence of bilateral upper tract dilatation

Exclusion criteria Patients with bladder outflow tract obstruction

Population number of patients = 36 (24 patients had undergone androgen depletion therapy before ureteric obstruction was diagnosed)

Interventions decompression of the obstructed upper tract (2 open ureteroneocystostomies, 9 percutaneous nephrostomies, 5 ureteric stents) or no decompression; androgen depletion

Outcomes maintenance, complication, survival, hospitalisation

Follow up over 800 days

Results

OUTCOME	Decompression INTERVENTION	COMPARISON No decompression	OVERALL RESULT
Complications and maintenance	2/16 patients developed nephrostomy related Gram-negative infections (1 died), 1 patient needed 3 replacement nephrostomies, 3 patients needed stent replacement (1 twice); 2 nephrostomies and 1 stent were removed after ureteric drainage was re-established following androgen depletion	-	For some patients the small increase in time at home may be valuable but for most the kindest course is not to intervene.
Hospitalisation	8 Patients with previous androgen depletion therapy spent 53% of their surviving time as in-patients; 8 patients without previous therapy 20%	16 Patients with previous androgen depletion therapy spent 80% of their surviving time as in-patients; 4 patients without previous therapy 40%	No statistical significant difference between decompressed and no decompression groups
Survival	The mean survival of 8 patients who had undergone androgen depletion before was 92 days (SD = 80); the mean survival of	The mean survival of 16 patients who had undergone androgen depletion before was 74	No statistical significant difference between decompressed and no de-

	8 patients without previous therapy was 839 days (SD = 901)	days (SD = 92); the mean survival of 4 patients without previous therapy was 261 (SD = 269)	compression groups

General comments Subgroups probably too small to show statistically significant effects; it was not described why some patients received androgen depletion therapy and others did not, nor why some patients underwent upper tract decompression and others did not

Oefelein. Prognostic significance of obstructive uropathy in advanced prostate cancer. Urology, 2004, 63(6), 1117-1121.

Design: Prognostic study combining cohort and case-control elements, evidence level 2-

Country: USA, setting: Urology department

Inclusion criteria Patients with pathologic diagnosis of adenocarcinoma of the prostate treated with androgen deprivation therapy (ADT) for advanced-stage (evidence of metastatic disease or biochemical recurrence after primary local therapy) prostate cancer

Exclusion criteria -

Population number of patients = 260 (39 patients developed bladder neck obstruction, 16 ureteral obstruction; 35 of these had received ADT treatment before as primary therapy)

Interventions transurethral resection of the prostate (TURP, n = 23), indwelling ureteral stent placement (n = 8), TURP and ureteral stent (n = 5), percutaneous nephrostomy placement (n = 8), urinary diversion (n = 1), Foley catheter placement (n = 14)

Outcomes frequency of obstructive uropathy (OU), impact of OU on survival, necessity to repeat procedure

Follow up every 3 to 6 months

Results

OUTCOME	EFFECT OF INTERVENTION	OVERALL RESULT
Complications	Repeated stent changes were performed in 6/13 patients; repeated TURP was performed in 6/23 patients	Obstructive uropathy results in significantly reduced survival in patients with prostate cancer.
Survival	The median overall survival was 42 months for patients with OU (59 for patients without); the median survival for patients with ureteral obstruction was 9.2 months (not reported for bladder neck obstruction patients); the median survival of patients who developed OU during ADT was 7 months (significantly shorter (p = 0.02) than for hormonally naïve patients (median 24 months))	

General comments The results were not reported separately for the different interventions; the focus of the study was the incidence of OU and the impact of primary therapy, not interventions for OU; the publication does not explicitly state that the patients previously treated with ADT were hormone refractory (HRPCa)

Observational studies – Prognostic study

Sandhu, Mayor, Sambrook & George. Outcome and prognostic factors in patients with advanced prostate cancer and obstructive uropathy. British Journal of Urology, 1992, 70, 412-416.

Design: Prognostic marker study (no actual case-control data); evidence level: 3

Country: UK, setting: Urology department and Radiology department

Inclusion criteria All patients with histologically proven prostate cancer with obstructive uropathy (unilateral or bilateral hydroureteronephrosis as seen on IVU, US or CT)

Exclusion criteria -

Population number of patients = 51 (of these, 36 had bone metastases and were treated by hormonal manipulation)

Interventions hormone manipulation (n = 36), transurethral resection of the prostate (TURP, n = 43), nephrostomy (n = 5), re-implantation of the ureter (n = 1), cystoprostatectomy and formation of an ileal conduit (n = 1), permanent suprapubic or urethral catheterisation (n = 4), radiotherapy (n = 4)

Outcomes success, improvement (creatinine), survival

Follow up every 3 to 6 months until death

Results

OUTCOME	EFFECT OF INTERVENTION	OVERALL RESULT
Success	16/43 patients required two TURPS, 9/43 required three or four	Prostate cancer and obstructive uropathy should not uniformly imply a terminal event and interventions are justified with a 25% five-year survival rate.
Renal function	TURP, nephrostomy and ureteric re-implantation lowered serum creatinine Before: mean 0.32 mmol/l, After: mean 0.16 mmol/l within one month	
Survival	Actuarial survival was 57% at two and 25% at five years; the patients with bone metastases had a five-year survival rate of 14% (58% for other patients, significantly different: p = 0.002)	

General comments The results were not reported separately for the different interventions; the focus of the study were prognostic patient characteristics, not effects of specific interventions; publication does not explicitly state that patients with bone metastasis and treated with hormones were hormone refractory (HRPCa); overall result regarding the 25% survival rate

does not apply to HRPCa patients

Observational Studies - Case series:

Dowling, Carrasco & Babaian. Percutaneous urinary diversion in patients with hormone-refractory prostate cancer. Urology, 1991, 37(2), 89-91.

Design: Case series, evidence level: 3

Country: USA, setting: Urology and diagnostic radiology department

Inclusion criteria patients with adenocarcinoma of the prostate and ureteral obstruction who underwent percutaneous urinary diversion and in whom hormonal therapy had failed (HRPCa; sample drawn from all percutaneous urinary diversion cases and where data were available)

Exclusion criteria -

Population number of patients = 22

Interventions unilateral or bilateral percutaneous urinary diversion; some patients received post-nephrostomy therapy: chemotherapy (n = 8), radiation (n = 2), additional hormonal therapy (n = 4), more than one modality (n = 3)

Outcomes success, complications, hospitalisation, survival

Follow up at least 1167 days

Results

OUTCOME	EFFECT OF INTERVENTION	OVERALL RESULT
Success	Hydronephrosis resolved in 1 patient (also received chemotherapy and additional hormone treatment)	It appears that percutaneous urinary diversion does not improve the quality of life of HRPCa patients.
Complications	1/22 (4.5%) due to large perirenal haematoma, 2/22 required hospitalisation to treat a febrile urinary tract infection; 4/22 needed nephrostomy tube changes (ranging from 2 to 6 times) due to occlusion or dislodgement	
Hospitalisation	73% of patients left the hospital, 27% never left and died of the disease in the hospital; 10/16 patients required subsequent rehospitalisation (due to further therapy, complications of therapy or disease progression); the mean number of in-hospital days for the 10 patients was 44 days (range: 5 – 118 days; 31% of their remaining lifetime); the median number of days spent outside the hospital was 139 days (range: 19 – 1116 days) for the 10 patients; all patients that were initially discharged spent an average of 57% of their remaining lifetime in hospital	

Survival	82% of the patients died within a median of 119 days (range: 15 – 1167 days) after the intervention; 78% of these patients died in hospital (sepsis, renal failure, cardiac failure, bowel obstruction or unspecified)	

General comments No information on survival of 4/22 patients that did not die between 15 and 1167 days

Harris & Speakman. Nephrostomies in obstructive uropathy; how should hormone resistant prostate cancer patients be managed and can we predict who will benefit? Prostate Cancer and Prostatic Diseases, 2006, 9, 42-44.

Design: Case series (retrospective), evidence level: 3

Country: UK, setting: Radiology department

Inclusion criteria All patients undergoing nephrostomy

Exclusion criteria -

Population number of patients = 112 (26 with uteric obstruction secondary to prostate cancer (PCa), of which 21 were hormone refractory patients (HRPCa)

Interventions unilateral or bilateral nephrostomy tube insertions; some patients had also a stent inserted when they were well enough and renal function improved after the nephrostomy

Outcomes urea, creatinine, survival, hospitalisation

Follow up: up to 453 days

Results

OUTCOME	EFFECT OF INTERVENTION	OVERALL RESULT
Renal function	The mean uria improvement was 44% for hormone naïve patients, 63% for hormone responding patients and 36% for HRPCa patients; the respective creatinine improvements were 63%, 60% and 48%.	All patients should be considered for nephrostomy despite their hormone status.
Hospitalisation	The mean time spent in hospital was 83 days for the first group, 45 days for the second and 27 for the HRPCa patients; 38% of all patients with uteric obstruction never left hospital care, 8/21 HRPCa patients never left hospital care	
Survival	The mean survival was 227 days for group 1, 114 days for group 2 (median 67 days) and 100 for HRPCa patients (median 53 days); if the urea and creatinine level fell below 15 mmol/l and 250mymol/l, the mean survival was 196 and 188 days respectively for HRPCa patients, if not, the mean survival was 31 and 24 days	

General comments -

Chefchaouni, Flam, Pacha, Thiounn, Zerbib & Debre. Endoscopic ureteroneocystostomy: palliative urinary diversion in advanced prostatic cancer. Techniques in Urology, 1998, 4(1), 46-50.

Design: Case series, evidence level: 3

Country: France, setting: Urology department

Inclusion criteria All patients with obstruction of the ureterovesical junction due to advanced prostatic cancer

Exclusion criteria -

Population number of patients = 31 (18 patients had a biological and / or clinical hormonal refractory disease (HRPCa))

Interventions endoscopic ureteroneocystostomy (resection of trigone to restore continuity of the ureteral orifice and to place a double 7F pigtail ureteral stent), percutaneous nephrostomy, nephrostomy tube was removed in case of normalisation or stabilisation of renal function, stent change scheduled every 6 months

Outcomes technical success, complications, hospitalisation, survival

Follow up 27.5 months

Results

OUTCOME	EFFECT OF INTERVENTION	OVERALL RESULT
Success	The success rate was 76%; 12 patients remained with permanent percutaneous nephrostomy; 1 patient had a ureterovesical re-implantation	Ureteroneocystostomy is an attractive treatment option, prolonging survival and improving quality of life.
Complications and maintenance	No specific complications occurred, in 1 patient the ureteral catheter moved and was changed; 34% of patients had their stent changed (average 1.6 times)	
Hospitalisation	The average hospital stay was reduced from 27.5 (1990-1992) to 6.8 days (1993-1997)	
Survival	The median overall survival was 8 months (0.25 – 27.5, average: 10.2); the median survival of HRPCa patients was 7.8 months; for patients with permanent percutaneous nephrostomy, median survival was 7.5 months, for patients with double pigtail ureteral catheter 10 months	

General comments -

Ahmed, Bishop, Bates & Manhire. Metal mesh stents for ureteral obstruction caused by hormone-resistant carcinoma of prostate. Journal of Endourology, 1999, 13 (3), 211-224.

Design: Case series, evidence level: 3

Country: UK, setting: Urology department and radiology department

Inclusion criteria The sample consisted of patients with hormone refractory carcinoma of the prostate (HRPCa) who presented with renal failure from bilateral ureteral obstruction as a result of long distal strictures, treated with nephrostomy drainage

Exclusion criteria -

Population number of patients = 3

Interventions insertion of a self-expandable endoluminal metal mesh stent projecting into the bladder

Outcomes technical success, maintenance of improvement in renal function, reobstruction, complications, rehospitalisation, quality of life, survival

Follow up was up to 5 months

Results

OUTCOME	EFFECT OF INTERVENTION	OVERALL RESULT
Success	All stents were placed without complications and showed patency	Metal mesh ureteral stents give poor palliation in distal strictures.
Complications and maintenance	1st patient presented with recurring haematuria, and urinary retention (necessitating a suprapubic catheter) and stent gradually obstructed within 3 months, 2nd patient presented with recurrent haematuria, anaemia and gradually obstructing stent, in the 3rd patient presented with haematuria, anaemia and bone pain and the stent obstructed gradually over 5 months (necessitating replacement of a nephrostomy tube)	
Hospitalisation	All patients had multiple hospital admissions for stent-related complications and other symptoms of the disease	

Quality of life	The overall quality of life was very poor for all 3 patients; 1 patient refused further interventions and died	
Survival	2 patients died within 3 months, the 3rd patient was presumably still alive after 5 months post-intervention	

General comments -

Hamdy & Williams. Use of dexamethasone for ureteric obstruction in advanced prostate cancer: percutaneous nephrostomies can be avoided. British Journal of Urology, 1995, 75, 782-785

Design: Case series, evidence level: 3

Country: UK, setting: Urology department

Inclusion criteria The sample consisted of men with advanced prostate cancer, bilateral ureteric obstruction and renal failure

Exclusion criteria -

Population number of patients = 11 (2 had previously been treated with hormones, 2 with external beam irradiation (EBRT))

Interventions 8 mg dexamethasone intravenously followed by daily dose of 2 to 84 mg given every 6 to 24 hours either intravenously or orally; the patients received also individual treatment such as orchidectomy or EBRT

Outcomes renal function (incl. creatinine, urinary output), diuresis, side effects, survival

Follow up varied across patients, up to 59 months

Results

OUTCOME	EFFECT OF INTERVENTION	OVERALL RESULT
Renal function	10/11 patients showed improvement and an induced diuresis within 72h; 6 patients showed a sustained response to definitive therapy after the cessation of steroids	Dexamethasone may obviate the need for urinary diversion in patients with bilateral ureteric obstruction, particularly in men who will not respond to available forms of therapy.
Side effects	No apparent side-effects occurred	
Survival	4 patients (including the 2 previously treated with hormones) whose renal function initially improved did not respond to definitive therapy and died 3 to 4 weeks after steroid cessation; 6 patients were still alive and well at individual follow ups	

	of 28 to 59 months

General comments The publication does not explicitly state that the patients previously treated with hormones were hormone refractory (HRPCa)

Little, Ho, Gawley & Young. Use of nephrostomy tubes in ureteric obstruction from incurable malignancy. International J of Clinical Practice, 2003, 57(3), 180-181.

Design: Case series (retrospective), evidence level: 3

Country: UK, setting: Urology department

Inclusion criteria All patients who had a nephrostomy tube inserted for ureteric obstruction secondary to a malignancy

Exclusion criteria -

Population number of patients = 31 (8 with prostate cancer, of which 4 were hormone refractory (HRPCa) patients)

Interventions insertion of a nephrostomy tube in one or both kidneys; a subgroup underwent antegrade double-J stent insertion via the nephrostomy tube, the tube was subsequently removed

Outcomes pain, survival

Follow up at least up to 414 days

Results Subgroup analyses differentiated curative and palliative patients; the patients not suitable for surgery, chemotherapy or hormonal manipulation (palliative group) included the 4 HRPCa patients

OUTCOME	EFFECT OF nephrostomy tube INTERVENTION	OVERALL RESULT
Complications	The complication rate was 13% (blockage or dislodgement of the tube), there were no life-threatening complications	Percutaneous nephrostomy should be considered in all cases of malignant ureteric obstruction, even if the malignancy is not curable, due to its safety, low complication rate and the duration of survival it permits.
Renal function	the mean creatinine levels were for patients with renal failure Before: 481 mymol/l, After: 170, the difference was significant ($p < 0.01$); the palliative and curative patients did not differ in this outcome ($p = 0.4$)	
Hospitalisation	The palliative group spent more time as inpatients (46% versus 31%, n.s.: $p = 0.1$); patients requiring opiates spent more time as inpatients than those not	

	receiving opiates (p = 0.04)	
Pain	8 patients required daily opiates (> 10mg morphine or 5mg diamorphine)	
Survival	The mean survival in the curative patients was 414 days including ongoing survivors at study end, the mean survival of palliative patients was 232 days, the two groups differed significantly (p = 0.01)	
OUTCOME	EFFECT OF stent INTERVENTION	OVERALL RESULT
Complications	No complications, no infection	

Chiou, Chang & Horan. Ureteral obstruction associated with prostate cancer: The outcome after percutaneous nephrostomy. Journal of Urology, 1990, 143(5), 957-959.

Design: Case series (retrospective), evidence level: 3

Country: USA, setting: Urologic Surgery Department

Inclusion criteria Consecutive patients undergoing percutaneous nephrostomy for ureteral obstruction associated with prostate cancer

Exclusion criteria -

Population number of patients = 37 (22 had previously received hormonal therapy)

Interventions percutaneous nephrostomy tube placement

Outcomes complications, survival, renal function (creatinine level, resolution of obstruction)

Follow up was up to 116 months

Results The administration of intravenous diethylstilbestrol diphosphate and oral diethylstilbestrol in 2 patients did not result in significant improvement of ureteral obstruction within 2 weeks before the interventions; none of 4 patients treated with radiation therapy before the intervention showed an obstruction resolution

OUTCOME	EFFECT OF INTERVENTION	OVERALL RESULT
Complications	None regarding the placement of the tube	Percutaneous nephrostomy is safe and effective in relieving ureteral obstruction and reasonable survival can be seen even in patients with renal failure.
Renal function	Before: creatinine levels ranged from 6.9 to 17.6, After: 0.9 to 12.0; 9/12 patients with severe renal failure had an adequate return of renal function, renal failure was not relieved in 1 patient (died 6 weeks after intervention); in 2 patients the drainage tubes were removed after complete resolution of obstruction following hormonal therapy	

Survival	The median survival was 21 months (range: 1.5 – 116); there was no significant difference in survival between patients presenting with unilateral or bilateral obstruction (p = 0.24); the median survival for patients previously treated with hormones was 12 months (range: 1.5 – 80) ; there was no significant difference between the hormone naïve and treated patients (p = 0.15)	

General comments The publication does not explicitly state that the patients previously treated with hormones were hormone refractory (HRPCa)

Bordinazzo, Benecchi, Cazzaniga, Vercesi & Privitera. Ureteral obstruction associated with prostate cancer: the outcome after ultrasonographic percutaneous nephrostomy. Archivio Italiano di Urologia, Andrologiea, 1994, 66 (4 Suppl.), 101-106.

Design: Case series (retrospective), evidence level: 3

Country: Italy, setting: Urologic Surgery Department

Inclusion criteria Consecutive patients undergoing percutaneous nephrostomy for ureteral obstruction associated with prostate cancer

Exclusion criteria -

Population number of patients = 28 (22 had previously received hormonal therapy)

Interventions unilateral or bilateral percutaneous nephrostomy

Outcomes complications, survival, renal function

Follow up 60 months

Results

OUTCOME	EFFECT OF INTERVENTION	OVERALL RESULT
Complications	None regarding the placement of the tube	Ureteral obstruction can be treated effectively with percutaneous drainage; treatment should not be withheld in patients previously treated with hormones.
Renal function	For 10 patients with renal failure the creatinine levels were Before: 11.9 (SD: 3.83), After: 3.34 (SD: 3.31), 7 had an adequate return of renal function, 2 patients showed a significant decrease in creatinine levels, renal failure was not relieved in 1 patient (died 5 weeks after intervention)	
Survival	The median survival was 22 months, the overall survival rates at one year were 60%, 32% at two years and 15% at three years; there was no significant difference in survival between patients presenting with unilateral or bilateral obstruction (p = 0.24); the sur-	

	vival rates for patients previously treated with hormones was 46% at one year, 17% at two years and 7% at three years	

General comments The publication does not explicitly state that the patients previously treated with hormones were hormone refractory (HRPCa)

Fallon, Olney & Culp. Nephrostomy in cancer patients: To do or not to do? British Journal of Urology, 1980, 52, 237-242.

Design: Case series (retrospective), evidence level: 3

Country: USA, setting: Urology department charts

Inclusion criteria All patients with nephrostomies for upper urinary tract obstruction associated with invasive incurable cancer

Exclusion criteria -

Population number of patients = 100 (37 with prostate cancer (PCa), 28 of these had been treated with chemotherapy including orchiectomy, amongst these were 19 with bilateral orchiectomy prior to nephrostomy)

Interventions unilateral or bilateral nephrostomy; prior to this 80 patients had received surgery, radiation therapy or chemotherapy including orchiectomy; post nephrostomy about 60% of patients were treated with surgery, radiation therapy or chemotherapy including orchiectomy

Outcomes success, complications, hospitalisation, quality of survival, survival

Follow up was up to 70 months

Results

OUTCOME	EFFECT OF INTERVENTION	OVERALL RESULT
Success	59 patients survived well enough to receive neoplasm therapy; 6 had resolution sufficient to remove nephrostomy tubes (1 required diversion later)	Patients with prostate cancer had a moderately good long-term survival and quality of life.
Complications	No intra-operative deaths occurred, 2 patients developed intra-operative haemorrhage and hypotension; there were 31 post-operative complications (septicaemia (n = 10), wound infection (n = 2), pneumonia (n = 2), haemorrhage (n = 5), pulmonary embolus (n = 2), pulmonary oedema, cardiac arrhythmia, thrombophlebitis, cerebral infarction, bowel obstruction (n = 3), GI haemorrhage, perforated ulcer, intestinal fistula) in 27 patients	
Hospitalisation	18 patients died in hospital, 7 were PCa patients; the aver-	

	age time in hospital was 32 days; 2 patients exceeded 100 days, 4 exceeded 40 days; the average stay for survivors was 31 days (some patients stayed for radiation therapy), for PCa patients the average stay for survivors was 23 days	
Quality of life	11 of 37 PCa patients were classified as discharged home with little or no pain, a survival of at least two months and generally ambulatory, alert and able to participate in family life or work, 16/37 were discharged home or to a minimal care institution, pain was controlled with analgesics and there was at least moderate limitation of activities; 10/37 were confined to hospital with pain requiring narcotics or a continuing decline in status	
Survival	The average survival of PCa patients was 12.2 months after nephrostomy (median: 7 months); 18/37 patients survived longer than six months, 14 survived longer than 12 months and 6 longer than 24 months; of the patients with bilateral orchiectomy prior to nephrostomy 7/37 survived longer than one year, of 9/37 patients with bilateral orchiectomy after nephrostomy 2 died in the early post-operative period (sepsis, gastrointestinal haemorrhage) and 7 survived more than one year	

Romero, Broglio, Pires, Roca, Guibu & Perez. Indications for percutaneous nephrostomy in patients with obstructive uropathy due to malignant urogenital neoplasias. Intervantioal Braz J Urol, 2005, 31(2), 117-124.

Design: Case series (retrospective); evidence level: 3

Country: Brazil, setting: Urology department

Inclusion criteria The sample consisted of patients with malignant urogenital neoplasias undergoing percutaneous nephrostomy

Exclusion criteria -

Population number of patients = 43 (5 with hormone refractory prostate cancer (HRPCa))

Interventions unilateral or bilateral percutaneous nephrostomy

Outcomes improvement, survival, hospitalisation, complications, blood urea nitrogen (BUN), creatinine

Follow up 6 and 12 months, varied across patients ranging from 3 to 54 months

Results The results for the HRPCa patients were not reported separately but it is clear that they never left the hospital alive after the procedure

OUTCOME	EFFECT OF INTERVENTION	OVERALL RESULT
Improvement	Significant improvement occurred in 65% of patients; 40%	Morbidity is high in

	showed normalisation of BUN and creatinine levels	this patient group, but the majority can be discharged from hospital and followed at home.
Complications	Postoperative complications occurred in 42% of patients (8 loss of catheter, 5 urinary tract infection, 1 skin infection, 1 haematuria); 3 patients required a new procedure, 5 needed repositioning of the nephrostomy stent in the renal pelvis; there was no procedure related death	
Hospitalisation	The mean percentage of survival time spent in hospitalisation was 17.7%; no data for PCa	
Survival	40% of patients died during hospitalisation due to advanced neoplasia; the mortality rate was higher in PCa patients (p = 0.006), in patients over 52 years of age (p = 0.03) and in patients requiring haemodialysis before the procedure (p = 0.02). 32% survived long enough to undergo primary tumour treatment. The survival rate at six month was 40% and 24% at one year, the rates were higher in patients with uterine cervix neoplasia (p = 0.007) and in patients 52 years or younger (p = 0.008); HRPCa patients died within six months (no other info)	

General comments Overall result regarding discharge does not apply to HRPCa patients

Rotariu, Yohannes, Alexianu, Rosner, Lee, Lucan & Smith. Management of malignant extrinsic compression of the ureter by simultaneous placement of two ipsilateral ureteral stents. Journal of Endourology, 2001, 15(10), 979-983.

Design: Case series, evidence level: 3

Country: USA, setting: Urology department

Inclusion criteria The sample consisted of patients with malignant obstruction of the ureter and in whom a single stent intervention had failed

Exclusion criteria -

Population number of patients = 7 (3 with prostate cancer (PCa), 95, 79 and 68 years old)

Interventions Insertion of two parallel double-J 7F stents in a single ureter

Outcomes insertion success, renal function, hydronephrosis, flank pain, tolerance, survival, alternative urinary diversion necessity

Follow up between 1 to 38 months, mean 16 months

Results

OUTCOME	EFFECT OF INTERVENTION	OVERALL RESULT
Success and	Insertion successful in all cases, stent	Simultaneous placement of 2

maintenance	change every 6 months, none of the patients required an alternative urinary diversion	double-J stents for the management of ureteral obstruction secondary to a malignancy is a safe and effective technique.
Renal function	Before: mean creatinine level 3.12, After: mean 1.48, renal function improved, creatinine level dropped in all patients with elevated level	
Hydronephrosis	Marked improvement, Before: ranging from mild to severe, After: ranging from normal to mild	
Tolerance	Tolerated by all patients without significant discomfort; no increase in irritative symptoms compared with single stent	
Flank pain	Relief noted in all patients	
Survival	3 patients died (of with 2 were PCa patients), others still alive at individual follow ups (ranging from 12 to 39 months); 2 PCa patients died 1 and 3 months after intervention, 1 still alive at 20 month follow up	

General comments Publication does not explicitly state that PCa patients were hormone refractory (HRPCa)

Pappas, Stravodimos, Mitropoulos, Kontopoulou, Haramoglis, Giannopoulou, Tzortzis & Giannopoulos. Role of percutaneous urinary diversion in malignant and benign obstructive uropathy. Journal of Endourology, 2000, 14(5), 401-405.

Design: Case series, evidence level: 3

Country: Greece, setting: Radiology department

Inclusion criteria All patients with obstructive uropathy undergoing percutaneous nephrostomy

Exclusion criteria -

Population number of patients = 156 (including 102 men of which some had prostate cancer (PCa))

Interventions unilateral or bilateral percutaneous nephrostomy, in some patients the insertion of a ureteral stent was also attempted

Outcomes insertion success, complications, renal function, time to renal function normalisation, haematologic and biochemical markers, survival

Follow up was up to 685 days

Results

OUTCOME	EFFECT OF INTERVENTION	OVERALL RESULT
Success	Percutaneous nephrostomy was successful in all but 1 patients; ureteral stent insertion was successful in 81% of patients	Percutaneous urinary diversion under radiologic guidance is a safe and effective procedure for patients with obstructive uropathy.
Renal function	Urea and creatinine levels decreased significantly ($p < 0.001$); within 15 days normalisation of renal function was observed in 66% of patients, dialysis became unnecessary in 28% of patients, 6% showed no improvement; the mean number of days needed for normalisation was 7.7 (range 1 – 15 days); malignancy as the cause of obstruction (rather than benign causes), especially prostate cancer, was highly correlated with stagnation of renal function indices	
Hematologic	No difference in haematocrit values ($p = 0.239$) or white blood cell counts ($p = 0.54$) Before / After intervention	
Complications	Mild haematuria (one day) occurred in most patients, 3 patients needed transfusion, 1 urinoma, 1 hemorrhagic cystitis, 6 minor technical complications, 9 dislodgements of tube, 6 obstructions of tube, 2 obstructions of stent	
Survival	The mean survival was 227.6 days (range: 2 – 685), the median survival was 153 days; patients with prostate cancer had the shortest median survival (80 days, mean: 143.9 days)	

General comments Publication does not explicitly state that PCa patients were hormone refractory (HRPCa); number of patients with PCa unclear

Observational Studies - Case study:

Biers, Sullivan, Roberts & Nobel. Thrombotic microangiopathy in advanced prostatic carcinoma. Urology, 2004, 63(2), 380-382.

Design: Case study; evidence level: 3

Country: UK, setting: Urology department

Inclusion criteria Case report of a 76 year old man with acute renal failure; patient had advanced prostate carcinoma, treated with goserelin but PSA level of 76 myg/mL; CT diagnosis of renal tract obstruction

Exclusion criteria -

Population number of patients = 1

Interventions Bilateral nephrostomy insertion; dialysis

Outcomes survival; post-mortem findings (not treatment related)

Follow up Patient died during surgery

Results

OUTCOME	EFFECT OF INTER-VENTION	OVERALL RESULT
Post-mortem findings	Renal failure appear to have been due to severe thrombotic microangiopathy	Thrombotic microangiopathy is a potentially treatable complication and the presence of thrombocytopenia and anaemia should not be attributed to malignancy associated marrow suppression without additional investigation.
Survival	Patient died of cardio-respiratory arrest during surgery	

General comments -

Expert opinion, unsystematic reviews, formal consensus, clinical guidelines:

Colombel, Mallame & Abbou. Influence of urological complications on the prognosis of prostate cancer. European Urology, 1997; 31(suppl. 3), 21-24.

Design: Review (unsystematic), evidence level: 4

Country: France, setting: Primary to tertiary care

Inclusion criteria The review addressed the influence of urological complications on the prognosis of prostate cancer

Exclusion criteria -

Population 3 studies cited (Paul et al., 1994; Hamdy et al., 1995; Dowling, 1991) on the topic of hormone refractory prostate cancer (HRPCa) patients

Interventions upper urinary tract decompression mentioned for HRPCa

Outcomes survival, quality of life (length of stay in hospital)

Results

OUTCOME	EFFECT OF INTERVENTION	OVERALL RESULT
Quality of Life	Urinary tract decompression will increase the patient's quality of life by reducing their length of	A decision has to be made about whether

	stay in hospital	urinary diversion is necessary.
Survival	Urinary tract decompression does not significantly improve survival	

General comments The results of the cited studies are extracted elsewhere

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.

Reference List

Bordinazzo, R., Benecchi, L., Cazzaniga, A., Vercesi, A. & Privitera, O. (1994) Ureteral obstruction associated with prostate cancer: the outcome after ultrasonographic percutaneous nephrostomy. *Arch Ital. Urol Androl,* 66: 101-106.

Chefchaouni, M. C., Flam, T. A., Pacha, K., Thiounn, N., Zerbib, M. & Debre, B. (1998) Endoscopic ureteroneocystostomy: palliative urinary diversion in advanced prostatic cancer. *Tech. Urol,* 4: 46-50.

Chiou, R. K., Chang, W. Y. & Horan, J. J. Ureteral obstruction associated with prostate cancer: the outcome after percutaneous nephrostomy.

Dowling, R. A., Carrasco, C. H. & Babaian, R. J. (1991) Percutaneous urinary diversion in patients with hormone-refractory prostate cancer.[see comment]. *Urology,* 37: 89-91.

Fallon, B., Olney, L. & Culp, D. A. (1980) Nephrostomy in cancer patients: To do or not to do? *Br J Urol,* 52: 237-242.

Harris, M. R. & Speakman, M. J. (2006) Nephrostomies in obstructive uropathy; how should hormone resistant prostate cancer patients be managed and can we predict who will benefit? *Prostate Cancer & Prostatic Diseases,* 9: 42-44.

Little, B., Ho, K. J., Gawley, S. & Young, M. (2003) Use of nephrostomy tubes in ureteric obstruction from incurable malignancy. *Int J Clin Pract,* 57: 180-181.

Oefelein, M. G. (2004) Prognostic significance of obstructive uropathy in advanced prostate cancer. *Urology,* 63: 1117-1121.

Pappas, P., Stravodimos, K. G., Mitropoulos, D., Kontopoulou, C., Haramoglis, S., Giannopoulou, M., Tzortzis, G. & Giannopoulos, A. (2000) Role of percutaneous urinary diversion in malignant and benign obstructive uropathy. *J Endourol.,* 14: 401-405.

Paul, A. B., Love, C. & Chisholm, G. D. (1994) The management of bilateral ureteric obstruction and renal failure in advanced prostate cancer. *Br J Urol,* 74: 642-645.

Romero, F. R., Broglio, M., Pires, S. R., Roca, R. F., Guibu, I. A. & Perez, M. D. (2005) Indications for percutaneous nephrostomy in patients with obstructive uropathy due to malignant urogenital neoplasias. *International Braz J Urol,* 31: 117-124.

Rotariu, P., Yohannes, P., Alexianu, M., Rosner, D., Lee, B. R., Lucan, M. & Smith, A. D. (2001) Management of malignant extrinsic compression of the ureter by simultaneous placement of two ipsilateral ureteral stents. *J Endourol.,* 15: 979-983.

Sandhu, D. P. S., Mayor, P. E., Sambrook, P. A. & George, N. J. R. (1992) Outcome and prognostic factors in patients with advanced prostate cancer and obstructive uropathy. *Br J Urol,* 70: 412-416.

7.6 Palliative care

What is the most effective model for the delivery of palliative care for men with prostate cancer?

Short Summary

Literature searches did not find any studies that compared palliative care settings or models in prostate cancer. Several observational studies described experiences with palliative care in particular settings. Although this shows that care is possible in such settings, without comparative studies there was no evidence about which palliative care model or setting was best.

Several themes emerged: the need for multidisciplinary delivery of palliative care (Palmieri & Waxman 2005; Pienta *et al.* 1996; Cunliffe 2003; Ok *et al.* 2005) and the integration of curative and palliative treatment (Ok *et al.* 2005; Pienta *et al.* 1996) during the often long course of the disease (Green *et al.* 2002).

PICO question

POPULATION	INTERVENTIONS	COMPARISONS	OUTCOMES
Men with prostate cancer.	Models of palliative care	Other models of palliative care (differing by timing in relation to disease trajectory).	• Symptom control • Management of pain

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

Evidence Summary

None of the studies met all PICO inclusion criteria.

<u>Delivery of palliative care</u>

Multi-disciplinary delivery of palliative care may be effective regarding symptom control and management of pain for men with prostate cancer.

One expert opinion article (Palmieri & Waxman 2005) stated that all patients regardless of their stage should be managed by a multi-disciplinary team which should include oncologists, surgeons, pathologists, radiologists, palliative care and specialist nurses. A case series by Pienta and co-workers (Pienta *et al.* 1996)reported positive experiences with a hospice supportive care programme, that enabled HRPCa patients access to the support of an interdisciplinary team (plus concurrent chemotherapy and in some cases radiotherapy). A case study by Cunliffe (2003) also stressed the importance of collaborative care decisions by all health-care providers. A review on urological malignancies (Ok *et al.* 2005) stated that interdisciplinary teams with physicians, social workers, nurses, pharmacists, psychologists, psychiatrists, occupational, pastoral services, physical, respiratory and dietary therapist work in partnership to determine the best comfort care for the patients and their family; pastoral services and trained volunteers can also support palliative care.

Facilitated access to hospice care may be effective regarding symptom control and management of pain for men with prostate cancer.

The case series by Pienta et al. (Pienta *et al.* 1996) reported that all responding patients and family members felt that all physical and emotional needs were met by a hospice supportive care programme that enabled HRPCa patients access to the support of an interdisciplinary team of health care providers (oncologist and clinical nurse specialist), a hospice nurse and social worker, a programme coordinator providing a link between the conventional care providers and hospice personnel; the patients were also treated with chemotherapy and some also with radiotherapy and 8/20 showed a partial response. The review by Ok and co-workers (Ok *et al.* 2005) stated that hospice programmes can be effective in meeting various needs at the end of life, physicians sometimes refer patients too late to use the hospice care fully and physicians must encourage the terminal patient to transform the goal of living longer to improve the quality of remaining life.

Integration of palliative care

The integration of palliative and curative interventions may be effective regarding symptom control and management of pain for men with prostate cancer rather than considering both as two separate sequences.

The review by Ok and co-workers (Ok *et al.* 2005) mentioned that there should be a smooth transition from mostly curative therapy to mostly palliative care for patients with urological malignancies and that it is unfortunate that regulatory barriers prevent simultaneous hospice care and disease directed therapy. The case series by Pienta and co-workers (Pienta *et al.* 1996)stated that their hospice supportive care programme successfully supported a transitionless system that improves overall health care delivery; the patients had access to hospice support while they were still being treated with chemotherapy and radiotherapy (and 8/20 showed a partial response).

Further issues

The national comprehensive cancer network guidelines for the management of prostate cancer (Scherr *et al.* 2003) stated that treatment plans should be tailored to the patient's value and preferences within the framework of the alternatives considered reasonable by the physician; the statement does not directly cover the specified outcomes symptom control and management of pain nor does it address clinical effectiveness.

The case study published by Cunliffe (Cunliffe 2003) also highlighted the need to respect patient autonomy.

The identified economic evaluations could be used to demonstrate that delivery of palliative care models have to be tailored for patients with prostate cancer to be effective regarding symptom control and management of pain and may differ from care models for patients with other cancer sites or other palliative conditions; however, none of the publications addressed this aspect.

The economic evaluation by Guest et al. (2006) found differences in palliative care treatment patterns amongst different cancer types for patient characteristics such as age of diagnosis, palliative care management, such as lengths of palliative care, resource use, such as hospitalisation, and the NHS cost of resource use for palliative care (3765 Pounds Sterling for prostate cancer; comparator costs ranged from 1816 GBP (colon cancer) to 4789 GBP (ovarian cancer)). Another economic evaluation (Green *et al.* 2002)found that of all compared cancer groups, prostate cancer patients had the third longest survival time from referral (3.8 months), the oldest average age of death and the third highest use of inpatient palliative care services (average number of inpatient spells coupled with the highest average length of stay).

In a German study, Schneider and co-workers (Schneider *et al.* 2007) reported the median number of hospital stays in the 2 years preceding death for men with prostate cancer was 2.00, and the median duration of each stay was 15 days (range 1 to 52 days).

Evidence tables

Case series

Pienta, Esper, Naik, Parzuchowski, Bellefleur & Huber (1996). The hospice supportive care program: A new "transitionless model of palliative care for patients with incurable prostate cancer. Journal of the National Cancer Institute, 88(1), 55.

Design: case series, evidence level: 3

Country: USA, setting: hospital and hospice

Inclusion criteria hormone refractory prostate cancer (HRPCa) who had failed hormone-ablative therapy

Exclusion criteria -

Population n = 20 HRPCa patients plus family members

Interventions and mode of delivery hospice supportive care programme: access to the support from an interdisciplinary team of health care providers (oncologist and clinical nurse specialist), a hospice nurse and social worker, a programme coordinator providing a link between the conventional care providers and hospice personnel; patients also received chemotherapy and some also palliative radiotherapy

Outcomes therapy response, meeting needs

Follow up unclear

Results

OUTCOME	EFFECT OF INTERVENTION	AUTHORS' CONCLUSION
Symptom control	8/20 patients had a partial response to therapy	The programme successfully integrates hospital-based and hospice systems to create a transitionless system that improves overall health care delivery.
Management of pain	all responding patients and family members felt that all physical and emotional needs were met by the programme	

General comments published as a letter

Case studies

Cunliffe (2003). Reflections on pain management: a case study. International Journal of Palliative Nursing, 9(10), 449-453.

Design: Case study, evidence level: 3

Country: UK, setting: Nurse-led community hospital

Inclusion criteria Patient with prostate cancer and bone metastases

Exclusion criteria -

Population n = 1

Interventions and mode of delivery Patient was managed in a nurse-led unit, medical responsibility lay with GP; use of collaborative proactive anticipation of the disease progression by entire health-care team involved; analgesia (transdermal fentanyl, sevredol syrup - alternatives to injections which the patient refused)

Outcomes pain, consciousness, perceived control

Follow up to death

Results

OUTCOME	EFFECT OF INTERVENTION	AUTHORS' CONCLUSION
Management of pain	Patient died peacefully and comfortably, had lost consciousness only a matter of hours before death, there was no evidence of confusion or sedation and the patient was able to take leave of his family as requested – alert and in control	Pain management is complex and individual, only a holistic, flexible partnership between practitioners and patients, supported by existing knowledge, can achieve effectiveness.

General comments

Reviews / expert opinions

Palmieri & Waxman (2005). Prostate cancer is best managed by multidisciplinary teams, Pharmacy in Practice, 15(10, 398-404.

Design: Unsystematic review (expert opinion), evidence level: 4

Country: UK, setting: (authors: Department of cancer medicine)

Inclusion criteria The review addressed the diagnosis and management of prostate cancer

Exclusion criteria -

Population 1 relevant sentence

Interventions management by multi-disciplinary team consisting of oncologists, surgeons, pathologists, radiologist, palliative care and specialist nurses

Outcomes not stated

Follow up -

Results

OUTCOME	EFFECT OF INTERVENTION	AUTHORS' CONCLUSION
Unclear	The authors stated that all patients regardless of their stage should be managed by a multi-disciplinary team as outlined above.	Greater research into all aspects of the disease is required to better understand its biology, natural history and to ultimately to develop new therapeutic interventions

General comments No concrete empirical studies were cited re the extracted statement

Scherr, Swindle & Scardino (2003). National comprehensive cancer network guidelines for the management of prostate cancer. Urology, 61(2 Suppl 1), 14-24.

Design: Unsystematic review (expert opinion), evidence level: 4

Country: USA, setting: National Comprehensive Cancer Network (NCCN)

Inclusion criteria The publication addressed the development of guidelines for the management of prostate cancer

Exclusion criteria -

Population 1 almost relevant sentence

Interventions treatment plan tailored to the patient's value and preferences, within the framework of the alternatives considered reasonable by the physician

Outcomes intervention appropriateness

Follow up -

Results

OUTCOME	EFFECT OF INTERVENTION	AUTHORS' CONCLUSION
appropriateness	The authors stated that the most appropriate treatment plan should be tailored to the patient's value and preferences, within the framework of the alternatives considered reasonable by the physician.	Optimal treatment is risk-adapted to the specific characteristics of the cancer and the expected longevity and personal preferences of patients.

General comments No concrete empirical studies were cited re the extracted statement

OK, Meyers & Evans (2005). Medical and surgical palliative care of patients with urological malignancies. Journal of Urology, 174, 1177-1182.

Design: Unsystematic review, evidence level: 4

Country: USA, setting: (authors: Department of urology, internal medicine and cancer centre)

Inclusion criteria The review addressed the medical and surgical palliative care of patients with urological malignancies

Exclusion criteria -

Population 4 relevant paragraphs concerning the delivery of palliative care circumstances in urological malignancies

Interventions transition from curative to palliative care; hospice programmes; interdisciplinary teams of physicians, social workers, nurses, pharmacists, psychologists, psychiatrists, occupational, pastoral services, physical, respiratory and dietary therapist work in partnership to determine the best comfort care for the patient and family; pastoral services and trained volunteers can also support palliative care

Outcomes physical distress, symptom management, meeting needs, fear, loneliness, availability of services, resistance, quality of life

Follow up -

Results

OUTCOME	EFFECT OF INTERVENTION	AUTHORS' CONCLUSION
Physical distress and symptom management	There should be a smooth transition from mostly curative to mostly palliative care, as disease progresses, emphasis should be on decreasing physical distress and symptom management	Physicians must encourage patients to transform the goal of living longer to improving the quality of remaining life
Other	Hospice programme can be effective for meeting various needs at the end of the life; the interdisciplinary team works in partnership to determine the best comfort care for the patient and family; pastoral services	

	and trained volunteers can lessen the isolation; historically hospice services have been underused; physicians sometimes refer patients too late to hospice care to use services fully; it is unfortunate that regulatory barriers prevent simultaneous hospice care and disease directed therapy payments.	

General comments No concrete empirical studies were cited re the extracted statements; the review reported the searches but no inclusion criteria or details of the included studies; the extracted statements are not prostate cancer specific

Economic evaluations

Guest, Ruiz, Greener & Trotman. Palliative care treatment patterns and associated costs of healthcare resource use for specific advanced cancer patients in the UK. 2005, European Journal of Cancer Care, 15 (1), 65-73.

Design: Economic evaluation (cost study), evidence level: not applicable

Country: UK, setting: NHS

Inclusion criteria Palliative care for different types of advanced cancer patients

Exclusion criteria -

Population Breast, colon, lung, uterus, ovary, stomach/oesophagus and prostate cancer patient groups

Interventions existing services (GP surgery, GP domiciliary visit, district nurse visit, hospital outpatient visit, hospital inpatient stay), care resources (opioids, antidepressant etc.)

Outcomes service use, cost

Follow up -

Results

OUTCOME	EFFECT OF INTERVENTION	AUTHORS' CONCLUSION
Patient characteristics	Differences in palliative care treatment patterns amongst different cancer types for example the age of diagnosis	Data on palliative care resource use can provide useful input when planning local healthcare strategies and service commissioning models.
Palliative care management	Differences for example in lengths of palliative care, range: 180 – 372 days (prostate: 360 days)	

Resource use	Differences for example in hospitalisation, range: 21% - 62% of patients (prostate: 33%)	
Cost	The NHS cost of resource use for palliative care was 3765 GBP for prostate cancer, the comparator costs ranged from GBP 1816 (colon cancer) to GBP 4789 (ovarian cancer)	

General comments the publication does not address the clinical effectiveness of the interventions

Green, Trainer & Hussain. A study of the comparative use of palliative care services by patients with prostate cancer. 2002, Journal of Urology, 167 (4)

Design: Economic evaluation (cost study), evidence level: not applicable

Country: UK, setting: South East England Trust

Inclusion criteria Palliative care services for different types of cancer groups

Exclusion criteria -

Population 9 types of cancer, data for 8573 of patients who died of prostate cancer

Interventions existing services (hospital, home care, day care, hospital unit, hospice, long-term care, private care)

Outcomes service use, cost, death

Follow up -

Results

OUTCOME	EFFECT OF INTERVENTION	AUTHORS' CONCLUSION
Survival	Of all cancer groups, prostate cancer patients had the 3rd longest survival time from referral (3.8 months)	Only by assessing activity coupled with the average length of stay did the study uncover the high use of inpatient services by patients with prostate cancer.
Age	Prostate cancer patients had the oldest average age of death of any group	
Resource use	The average number of inpatient spells coupled with the highest average length of stay sums up to the 3rd highest use of inpatient palliative care services for prostate cancer patients	

General comments published as a poster abstract; the publication does not address the clini-

cal effectiveness of the interventions

(Schneider *et al.* 2007)
Design: Prospective cohort study , evidence level: 3 Country: Germany, setting: Secondary care **Inclusion criteria** Patients who had died from cancer in the year 2004, included in the records of a lower Saxony health insurance company. Only patients with lung, prostate, female breast or colon cancer were included. **Population** number of patients = 355, age range 20 to 99 years, mean age = 69 years, median age = 71 years. **Interventions** Hospitalisation within 5 years preceding death **Outcomes** Number of hospital stays per patient in the 5 or 2 years preceding death. The duration of each stay in days. **Results** 7% of the study population had prostate cancer. The median number of hospital stays in the 2 years preceding death for men with prostate cancer was 2.00. The median duration of each stay was 15 days (range 1 to 52 days). Lung cancer patients had the most frequent and longest stays.

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.

Reference List

Cunliffe, J. (2003) Reflections on pain management: a case study. *Int J Palliative Nursing,* -53.

Green, J. S., Trainer, A. & Hussain, M. (2002) A study of the comparative use of palliative care services by patients with prostate cancer. *J Urol,* 167: 69-70.

Ok, J. H., Meyers, F. J. & Evans, C. P. (2005) Medical and surgical palliative care of patients with urological malignancies. [Review] [48 refs]. *J Urol,* 174: 1177-1182.

Palmieri, C. & Waxman, J. (2005) Prostate cancer is best managed by multidisciplinary teams. *Pharmacy in Practice,* 15: 398-404.

Pienta, K. J., Esper, P. S., Naik, H., Parzuchowski, J., Bellefleur, J. & Huber, M. L. (1996) The hospice supportive care program: A new "transitionless" model of palliative care for patients with incurable prostate cancer. *J Natl Cancer Inst,* 88: 55-56.

Scherr, D., Swindle, P. W., Scardino, P. T. & National Comprehensive, C. N. (2003) National Comprehensive Cancer Network guidelines for the management of prostate cancer. [Review] [101 refs]. *Urology,* 61: 14-24.

Schneider, N., Dreier, M., Amelung, V. E. & Buser, K. (2007) Hospital stay frequency and duration of patients with advanced cancer diseases - differences between the most frequent tumour diagnoses: a secondary data analysis. *European Journal of Cancer Care,* 16: 172-177.

Appendix A - Position Paper: Prostate Cancer and the Effect It May Have On Masculinity

Prostate Cancer And The Effect It May Have On Masculinity

Clare Moynihan

The Institute of Cancer Research.

April 2007.

Introduction

Prostate cancer is the most common male cancer in several developed countries including the United States and northern and western Europe[1]. A higher incidence of prostate cancer in African Americans is recognised[2]. Due to the advances in treatment, many men are known to be living longer with the disease. Any cancer involves family members. Prostate cancer patients are likely to be above the age of 60[4](Ref) although younger men may have the disease[5] Thus, many men will be in or have had relationships and children.

Before looking at the impact that treatment may have on men and masculinity, it is important to address the theory that exists regarding the latter. When theory regarding gender (or men and or women) is not addressed, as is the case in the majority of psychosocial research, 'men' and 'women' present as static entities, 'fixed' in their stereotypical moulds. Men are presented as if they were a homogenous entity, one dimensional, and without a sense of context at least as far as psychosocial factors are concerned.

Theoretical Considerations

A diagnosis of cancer is known to hold connotations that are not only life threatening, but also invoke feelings of self-induced disease, fearfulness, and stigma.[6]. Negative emotional responses go hand in hand with side effects of treatment that not only create adverse physical[7] and psychological side effects, [7,8,9] but may also lead to existential problems such as a loss of identity – a sense of self that is closely linked to a loss of a sense of manhood.[10] It is important that the theoretical elements of 'masculinity' are addressed, both in relation to men in general [11,12] and men who are ill [13] (especially men who have cancer).[10,14,15] Importantly the ways in which 'gender' can apply to the ethos of institutions i8s also an important avenue for enquiry. Thus 'masculinity' here is seen not only as an individualised concept but one that also lends itself to a corporate body.[11,14]

'Hegmonic' masculinity is a central concept held in gender theory. 'Hegmonic' masculinity stands for those masculine ideals that are most commonly subscribed to,[10,16] that include characteristics such as domination, aggressiveness, competitiveness, sexual and athletic prowess, control and stoicism. Hegmonic masculinity also signifies a position of cultural authority and leadership.[11] Although many men are complicit in sustaining hegemonic masculinity as described above, individuals vary.[11,15] Some men may deviate from the stereotype, either completely or in part, and even 'shift' backwards and forwards creating a dynamic and contradictory masculinity, sometimes based on different cultures, periods of history, relations within institutions and other individuals such as women and people in subordinate and/or superior positions.[11, 17]

Men learn to treat their bodies as discrete and separate.[12] For many men, masculinity is demonstrated through the body and by the way it looks. [18,19,20] The idealised one is sexual, muscular,

athletic and disciplined to take control and power.[11,21] A 'real man' is large hard and strong[22] and there can be intense social pressure to be seen as 'masculine.'[18]

Men's sexualities are intricately connected with 'embodied' (of the body) masculinity. Hegmonic male sexuality describes powerful, natural, uncontrollable penis centred characteristics that drive men's insatiable appetite for penetrative sex.[23,24] The presence of the penis and testes signifies distinction from femininity[25] and heterosexual sex is based on erection, penetration and climax. The full and firm erection is generally viewed as the linchpin for this phallocentric model of sex.[15,25]

Sexual function is known to deteriorate with age. There appears to be a widespread acceptance of the biological tradition that decline is a natural consequence of the male ageing process.[26] However, what it is to be 'old' in the sexual arena has recently been contested.[25] Medical treatments for erectile dysfunction have offered alternatives to the so-called essentialist and social limits of how older men's sexuality is expressed. Not withstanding these 'aides' available to men with cancer, the biomedical focus on penis functioning and disregard for the disorders of desire have been criticised for perpetuating phallocentric ideals of male sexuality in men of all ages. [27]

Where emotionality is concerned, men are expected to operate in specific ways that are unemotional, objective and logical [28,12] Emotions are identified with weakness and being 'strong' denotes being in 'control' of emotions[15,17] Strength of mind is revered, rationality and 'being reasonable' are seen as enablers in a quest to occupy distinctive and often privileged places.[29] Interestingly 'expressing emotions' is strongly advocated in the cancer arena; indeed it is thought to prolong life as well as enable 'people' (women for it is they who have put themselves forward for research) to adjust to serious illness, [30,15] Juxtaposed with this 'coping mechanism' is the much applauded and pervasive coping strategy, the 'fighting spirit' where patients have been encouraged to maintain a stoical attitude, even to prolong life.[30] This has been refuted[31] but continues to hold sway in cancer environments.[14]

While some of the 'masculine' characteristics mentioned above may block or enable 'healthy' responses when a man is ill, [14, 30] Nicholas, (2002) [32] has suggested the importance of bearing in mind the distinction between the harmful effects and potential strengths in what he describes as 'traditional gender roles' when men are ill. Some characteristics of hegemonic masculinity may assist men in conceptualising and coping with a serious illness as illustrated in work with relatively young testicular cancer patients who in the majority, 'turned their faces to the wall' in order to cope.[15,33]

It's important to accentuate (again) that not all men 'fit' into the categories stated above. Men in low social classes for example, are often subordinate to others in high social class groups (i.e. medical professionals). But even within social class groups, men are known to be socialised to strive for positions where they can take control.[11] Thus, men who slot into higher social class categories are sometimes likely to feel subordinate at times of illness, when they are confronted with their status as sick people and where they are faced with 'experts' who represent authority and knowledge, reason and control.[11,15]

The older man, by dint of his age, may loose his authoritative aura, becoming subordinate within cultures whether he is ill or not.[34] Illness is directly connected to ageing [10]and according to some can render men vulnerable, passive and dependent – 'the lesser man'– factors traditionally assigned as feminine and in direct opposition to hegemonic masculine constructs of invulnerability, activity and independence.[13] Thus the ill disabled male is often demoted to the realm of the 'abnormal', the 'feminine' and 'not male'. A profound sense of loss and changed identity occurs when the ill body of the present is compared to the body of the past.[13]

Being 'male' brings with it certain so called steadfast characteristics that denote strength (not withstanding that 'maleness' is not a homogeneous entity; that men's health behaviours do not constitute a unitary 'form').[35] However, rather than being innate, it is suggested that they are learned and can change in certain situations such as when a man is ill or in a doctor patient relationship where he may feel subordinate and even emasculated.[14,15] Moreover, all the factors mentioned above may also apply to the way institutions such as hospitals hold within them an

ethos that is 'masculine'[11,14,15]. There is a large body of literature that illustrates the ways in which health personnel represent stereotypical masculine ideals and how they may work within the confines of a strictly biological approach to men and women and the so called 'innate' characteristics of the latter.[11,14,15,17] If this were to be the case, it might be suggested that providers are instrumental in the way men may feel when they are ill, more specifically, when they have prostate cancer.

Metastatic Prostate Cancer

Studies that exist, use (in the vast majority) quantitative methods to 'map' dysfunction in men with metastatic disease who are on treatment including hormone treatments or who are eligible to receive such treatments. Few studies have focused solely on men's experiences of being treated for metastatic prostate cancer with androgen deprivation therapy (ADT) or luteinizing hormone releasing hormone analogues used to interrupt testosterone production (LHRH). Even fewer explore men's sense of masculinity as a result of hormonal therapy or indeed in relation to men with prostate cancer who have to undergo treatments that may on the face of it, sit uneasily with 'hegmonic' masculinity as described above.

Quantitative findings from studies of advanced disease must be cautiously interpreted: many men drop out prior to follow up for reasons that include death and disease progression Thus follow up scores in quantitative surveys often represent only the healthiest men.[38]

Studies[39] have shown that hormone therapy is the only significant predictor of the Quality of Life Index ($p<0.01$)): those on hormone therapy had a significantly worse quality of life including greater pain, fatigue, urinary problems and deteriorating physical functioning.' In the majority, studies point to sexual dysfunction, urinary symptoms, bowel problems, pain, emotional disturbance and reduced overall quality of life, including social and role functioning as a result of treatment for metastatic disease.[38] However the picture is not as simple as it seems.

Sexual function

While men with advanced disease report symptoms such as reduced libido and fatigue, treatments such as androgen deprivation therapy or surgical castration, are particularly known to be associated with diminished libido, impotence, muscle wasting, increased body fat, weight gain, labile mood, reduced concentration and cognitive changes, hot flushes, fatigue and gynaecomastia. [40]

The impact on men will depend on the differing kinds of hormonal treatment received and when they are compared with monitored or population controls[41], or when men are compared with others who have localized disease treated with complete androgen blockade, radical prostatectomy or with orchidectomy. [42,43] Longitudinal studies complicate the picture further. Men on hormone treatment may report worse functioning early after treatment compared to those who deferred [44] and this may persist, while others report that sexual functioning is maintained in those on anti androgens, but decline in those who receive orchidectomy and have been medically castrated.[45,46,47]

Interestingly men taking anti androgen treatment appear to be less effected as far as 'sexual dysfunction' is concerned than those men who have been castrated medically (with LHRH used to interrupt testosterone production) or who have undergone orchidectomy.[45,46,47] Men are known to prefer pharmacological ADT for cosmetic reasons and because it is reversible[48] but this does not altogether explain why men who are offered (or choose) anti androgen treatment, fare better in this domain. In addition it is not entirely clear as to what 'better' actually denotes.

It should be noted that men with sexual problems experience only a moderate level of distress associated with the latter and as measured by standardised questionnaires[42].

Urinary function

While urinary problems are known to exist in men with metastatic disease, [42,43,44] longitudinal studies show that increased quality of life is related to improved urinary symptoms in men receiving both combined androgen blockage or orchiectomy.[43] However, this outcome may relate to age factors.[49]

Bowel function

Bowel function has been shown to be good at baseline and to improve modestly in men treated with combination androgen blockade (CAB) and orchidectomy. [42] Longitudinal studies show a worsening in the CAB group over time and when compared to the orchidectomy group + men taking a placebo. [50]

Pain

The primary symptom of metastatic disease is pain occurring in 50-75% of patients[39] and is more prevalent than in those with non metastatic disease.[51] Pain is reported to improve over time in men receiving CAB[43] who were in remission after a three month treatment time frame; [52] and who had received hormonal therapies after being treated with orchidectomy or estrogen.[53] Improvements are also shown in men with advanced hormone resistant prostate cancer who had been assessed at baseline to 18 weeks after treatment started.[54] However age is shown to relate to experienced pain. Younger men (65 and less) with *lower* rates of metastatic disease have been found to report greater pain when compared to those who were older. [49] Explanations for this may conceivably be due to the ways in which men feel they can respond (and complain) and in the ways that they perceive attention from professionals.[55]

Fatigue

Fatigue is reported in men with metastatic disease[44] A longitudinal study showed that men treated with hormones had greater fatigue and worse physical well being than did an observation group at the six month assessment [44] Others have shown an improvement in fatigue over time.[52, 53]

Psychological distress

31% of men with all stages of prostate cancer have reported levels of distress significant enough to warrant psychiatric evaluation in one study[8] although the condition goes unrecognised by clinicians who refer only 2% of cancer patients with psychiatric problems to psychiatry.[56]

However a study[9] to specifically assess depression in men receiving androgen deprivation therapy reported a prevalence of 12.8% - eight times the national rate of depression in men and 32 times the rate in men over 65 years. Major depression was not associated with worsening disease, treatment types or medical response to ADT. However, a survey study of men diagnosed less than one year and over five years, reported low rates of anxiety and depression, and this did not relate to treatment types[49].

A study by Albertsen et al,[52] like others [45], has shown that mental health improves in men in remission receiving CAB for at least three months. They had a better social well being and better mental health than the group whose disease is progressing and who have received the same treatment for one month only. However hormonally treated patients have been shown to have worse emotional well being than those receiving orchidectomy + placebo at three and six months after treatment commenced.[50]

These differences in psychological status may be a result of differing measures, time assessments and age. Older men are known to have more depression than men with early stage dis-

ease but men under 65 years, experienced more anxiety, more decreased social functioning, greater pain, increased sleep disturbance and greater financial impact than older men regardless of disease state. [49]

The literature suggests that pharmacological hormonal ablation (at least) can improve or decrease health related quality of life in different domains.[41] but little is known as to what it *means* to be a man who is undergoing these treatments. Even less is known about ethnic groups or homosexual men.

The Effect of Advanced Disease on Men's Sense of Masculinity

Qualitative methodology

A few qualitative studies have focused on the impact of hormonal therapy on men's lives.[10,57, 58 ,59] Qualitative work does not concern itself primarily with large numbers or generalisability. Rather the researcher endeavours to explore 'deep' (not 'wide') into the feelings and needs of the participants and particularly the context from which they come. This approach has a long history; namely in the disciplines of anthropology and sociology where people's 'talk' is analysed to represent the meaning they give to aspects of their lives. It is used where the researcher knows little and recognises that 'patient centeredness' and not the assumptions and views of service providers, is of paramount importance. Thus it can provide 'valid' and valuable data in situations where the question requires it – usually 'new' and tricky topics requiring sensitivity, in this case men who had received androgen deprivation therapy (ADT). [60]

Men's narratives are found to be complicated and ambiguous. Work in this area has identified that men treated with ADT have many unique experiences regarding the impact on their bodies and on themselves.[10]

Men's accounts

Men report the ways in which the 'atypical' body becomes a site of transition as a result of hormones. The development of breasts, weight gain, decreased muscle mass [10, 58] and reduced penis and testes size [10] are highlighted by the men as being directly related to ADT, creating uncertainty, surprise and disquiet.[10] Breasts are experienced as feminising; a 'gender duality' sets in as men perceive 'flesh on the chest' as depicting 'femaleness' or femininity. [10,58] Indeed bodies are conceptualised as 'abnormal', undisciplined, less masculine, a 'betwixt and between' state where men do not feel fully male or define themselves as feminine.[61] Body image problems ensue: men are at pains to lose weight and report the ways in which they cease to continue with their out door hobbies such as swimming and golf.

Men have described and compared their body in relation to hegemonic (see above) masculine ideals that are perceived as hugely incompatible with their newly gendered states [10,62] perceived as 'foreign', taking on a 'secret' 'double life' of its own.[10] Importantly, men often feel unable to speak about this perceived state of bodily change, even to their doctors, and they recount a dearth of information giving prior to treatment on side effects.[10]

These changes are coupled with a depletion in energy levels [10,58] following treatment affecting not only physical activities but social and sexual aspects of participants' lives, (including work related activities,[10,58] and a sense of competitiveness[59]) are sidelined or even obliterated from men's lives.[10,58,62] This then can threaten long standing relationships as breadwinner, provider and protector (traditional gender roles).[10,59]

Men recount the ways in which hot flushes are strongly associated with female menopause invoking 'womenhood'. Libido and erectile function, synonymous with hegemonic male sexuality, are reported to be eliminated by ADT.[10,58, 59,61] While regrettable, many men appear to accept this state as being part of prostate cancer treatment. [10,58] Some do not [59] While men experience a profound loss of libido and potency, it is strongly suggested that the latter is acceptable since sexual desire no longer exists. Indeed men are known to point to older age and illness as reasons

for the lack of male sexual performance; a 'biological disconnect' as a result of hormones is seen as a 'fait accompli', the product of science – a cause and effect relationship providing a masculine way of rationalising the inevitability of the changes they experience.[10]

Being unable to keep up with other men (and women) forces men to reformulate and re-locate many previously held practices of 'being men' in the traditional fashion.[10] For example some men redefine their sexuality and preference for penetrative sex when potency is lost, replacing previous traditional practices in diverse ways, [10,58] sometimes stating that the lack of libido in their female partners helps to reconcile their inability to participate in phallocentric ideals of sexual practice.[10] The acceptance of impotence is further evidenced by the fact that men do not seem to resort to counselling for this aspect of their lives [10] and have not attempted to re-establish potency through chemical or mechanical treatments.[10] However, it has also been reported that men express grief and reduced masculinity due to the loss of sexual desire, [57] but men's acceptance of impotence has been reported in other studies and populations.[28,62] This depends however, on whether men are entering new relationships, have poor prognosis and are older. Indeed age is an important variable with regard to all aspects of masculinity and how it is construed and 'acted out' in times of illness.[14,17]

ADT invokes emotions that are strongly linked to femininity: labile mood and altered thought processes - actions that are typified as 'female' hormone induced.[10] Men recount changes in mood; anger, vagueness and a general feeling that the power, control and strength of the masculine mind is altered – reactions that are consistently attributed to hormones [10] rather than to the illness that may be creating emotions of sadness, fear anger and vulnerability. [10] Despite these reactions men are shown to demonstrate the stoicism expected of them,[58] and in turn certain masculine ideals are either re instated or accentuated.[10,58] This stoicism is usually exhibited through the will to fight cancer that is very marked.[58] A focus on 'survivorship', public speaking, political lobbying, media attention, continuing to be the bread winner and family protector are all factors that seem to lend themselves to men's compensating strategies when trying to maintain a sense of a masculine self. [10,58] While masculinity is reformulated by men, there is an underlying suggestion that men are struggling to maintain a sense of masculinity, against all the odds. Men are deeply affected in terms of their bodies and especially by ADT [10].

Localised Disease

Health related quality of life (HRQoL)

At present, there is no consensus about which therapeutic option is best for men with localised disease – non-randomised trials have shown similar survival rates. Little data exists on how QoL is affected among men who have no symptoms related to the tumour let alone how it may affect masculinity. When comparisons were made[63] between men who had chosen hormones and those who had not, the former had more fatigue, loss of energy, emotional distress and lower overall quality of life than men who deferred hormone therapy. CAB had a greater adverse effect on quality of life than monotherapy. The authors concluded by saying 'androgen deprivation therapy may significantly impair the physical and emotional health of asymptomatic patients with non metastatic prostate cancer'.

Other studies point out that merely having localized disease does not seem to affect general domains of (HRQoL). [38,65,66,67] However longitudinal studies reveal that HRQoL is shown to decline over time and then recover. [68,69] Litwin et al [70] found that up to 97% of men who opted for RP regained pre-treatment levels of physical well being, 'role- physical' well being, general health, body pain, energy, 'role emotional' well being, social well being and mental health within one year of treatment. However non whites were less likely than white men to return to pre-treatment levels on physical, 'role physical' and social well being. Unmarried men were less likely than married men to regain pre-treatment levels of general health and social well being. Another found that HRQoL substantially declined in RP patients immediately after treatment but improved by one year.[80]

Longitudinal studies[71] found that the presence of psychiatric co morbidities related to poorer quality over time. Fatigue is also shown to relate to lower global quality of life across three treatment groups – external beam radiotherapy, radical prostatectomy and hormone therapy, and also among diseased men in an observation group.[72] Sexual dysfunction after treatment has been associated with a decline in general health related quality of life. [73] Despite what the authors published papers call 'low reporting of HRQoL' in metastatic patients, specific 'problems' do exist in men with localised disease that may well impinge on men's masculine identities.

Urinary function

Comparison group studies show that men treated for localized prostate cancer have more problems with urinary function than men of the same age without the disease[74,75] especially those who received RP.[74] when compared with a no cancer group and those who had been treated with EBR or EBR + brachytherapy. [74] 90% of the prostatectomy group are shown to resort to absorptive pads on a daily basis.[74] However longitudinal studies have shown that urinary function (in younger men with fewer co morbid conditions)[70], improves one year post RP, [76,77] contrasting with early cross sectional studies.[75,78] Men treated non surgically and those who are observed exhibit few short or long term deficits where urinary function is concerned.[69,76]

Bowel function

Little difference is shown between men treated (by various treatment therapies) and age matched RP group treated 6 to 18 months previously [65] a mean of just over 2 years since treatment,[67] 2 to 4 years since treatment,[78] and 1 to 5 years since treatment.[79] A longitudinal study[80] showed that bowel function was poor in radical prostatectomy and external beam radiotherapy groups at baseline (immediately after treatment) but improved over time. Bowel function was good in hormonally treated and observed groups at baseline one and two years. There is an indication that those treated by EBR fare worse in this domain.

Pain

30% of early stage patient's pain and this is linked to depression.[51] There is a paucity of data that illustrates the way pain may recede as a consequence of treatment. However this may be an indication of its' rarity.

Fatigue

A cross sectional study has shown fatigue to be associated with poor general health related quality of life in men regardless of treatment type.[72] Longitudinal studies have shown that all patients had increased fatigue over time [81] while whole pelvis EBR patients showed the greatest increases in fatigue from pre-treatment time.[81] However it has also been shown that while fatigue is felt early, men recover their energy after 5-6 months post treatment.[82]

Sexual function

'Sexual dysfunction' in this group includes erectile difficulties and an inability to perform penetrative sex. Results from comparison group studies show more sexual problems in this group than men without the disease. [83] However, men who are observed are also known to have sexual problems, suggesting that sexual dysfunction has something to do with the disease itself.[84] Men treated with RP show more sexual problems when compared with those treated with EBR [78] and observed men.[83] Men undergoing androgen deprivation therapy (ADT) and who have localised disease, have more sexual problems than men receiving differing treatments.[64] Longitudinal studies show that sexual problems do not dissipate as rapidly as urinary problems. RP patients

develop severe potency difficulties shortly after treatment and may have great difficulty regaining pre treatment levels of sexual function[70,76,77,80] and this also applies to men treated with radiation and those who are observed up to two years post diagnosis.[76]

Those men who elect to have nerve sparing surgery have reduced sexual dysfunction.[77] However, these men often have better prognoses, less disease, better pre-treatment functional status, and most importantly, better pre treatment sexual function.[38]

Importantly, older age[77] and white Hispanic men [77] have greater difficulty with post treatment sexual dysfunction than younger and African American men. However, Potosky et al (2000) [76] has shown that sexual 'bother' is greater at 2 years post treatment for men treated with radical prostatectomy than those treated with external beam radiotherapy, especially in younger men aged between 55 and 59 years of age.

Emotional states

There is little indication that men's sexual function is linked to emotional distress.[49] However, men who are below 65 years are more anxious, but no more depressed than those over 65. [49] Cross sectional studies have shown that higher psychiatric co morbidity including previous psychiatric history, alcohol abuse and drug abuse after a mean of three and a half years post diagnosis is associated with worse general health related quality of life in men with early stage prostate disease.[71]

Impact on 'masculinity' - men with localised disease

While little has been published regarding 'masculinity' in men with localised disease, two studies were instigated to assess the impact of surgery and subsequent impotence on men's sense of masculinity[59],[84]. Some patients expressed surprise at the unexpected reduction in penis size as a result of surgery and this served to emasculate some participants. Stoicism – a characteristic of 'hegemonic' masculinity, precluded pre-emptive discussion about this factor prior to surgery. However men were seldom informed of this possible side effect.[84]

Erectile function was a significant aspect of many participant's recoveries.[59,84] Men recounted the ways that it had preoccupied their thoughts post surgery[84]. While some men pursued ways such as Viagra to re-establish erectile function, they simultaneously disclaimed their reliance on penetrative sex, 'protecting themselves from yet another point of failure' when such treatments did not restore 'healthy' erections. Potential ridicule surrounding the hope that they were trying to gain erections artificially was avoided by claiming the inappropriateness of treating erectile dysfunction.[84]

Men recounted that 'frequent, spontaneous, natural, rigid erections that reflected virility, desire and manliness' were not met through medical treatments. However when 'aides' were used, they were usually abandoned. Many men re conceptualised their impotency by justifying the latter as a product of older age and the fact that long-term relationships are less reliant on penetrative sex, some claiming that sex was more about intimacy since treatment had commenced.[84]

Like men who have undergone treatments for metastatic disease, most men with localised disease redefined their sense of masculinity as is evidenced in other qualitative studies.[85,86] Intimacy is redefined through activities such as shared interests and physical touch. The authors conclude that men's performances of sexuality and masculinity are highly interwoven; that loss of sexual functioning constitutes a focal disruption for participants and in some instances, poses a significant threat to masculine identities.

Key points here are to avoid assumptions of a fixed relationship between sex and masculinity that will apply to ALL men. The impact of erectile dysfunction is profound but would seem to depend in large part on each man's unique sexual history– 'where sexuality is understood as one aspect

among many of men's pre-illness performances of masculinity.[85,86] However, it is worth remembering that in some cases, men are willing to trade 'cure' with sexual potency.[59] (see below)

Men are shown to avoid expressions of emotionality about their prostate cancer and this was especially the case in relation to other men in an effort to maintain self-sufficiency.[85] A sense of control and a regaining of masculine traits was achieved in advising others. When men did go to support groups, (see below) they preferred to access information or to give it, rather than to elicit support. Few resorted to a change in lifestyle as a result of illness, detaching themselves from their bodies and instead putting work and family ahead of the pursuit of a healthy body. The authors of this study concluded that men's responses, (like their counterparts who have metastatic disease), were indicative of people who were struggling to maintain their sense of masculinity against many odds.

These 'odds' start early. Not withstanding that the very diagnosis of having 'prostate cancer' may undermine men's sense of reality including masculine ideals that may be lived out in every day actions and interactions, the diagnostic tests that men are asked to endure may also have an impact on men's sense of themselves as men. Two qualitative studies [59, 87] reported men's experiences regarding the disease[59] and their attitude towards familial screening.[87] Although men have reported difficulty in disclosing their cancer to others [88,89] such sentiments acted as barriers to recruiting first degree relatives to screening in a research context.[87] Regardless of disease status, men recounted the experience of DRE and biopsy as 'shaming,' 'unpleasant', 'uncomfortable,' reiterating their loathing of the intrusion they represented and this related to DRE [59,87] as well as all transrectal procedures including ultrasound, biopsy[59]; the biopsy sometimes being perceived as particularly shameful and embarrassing.[59] Such interventions raised profound homophobic issues and attitudes[87] in the men and a fear of powerlessness – of emasculation, embarrassment and humiliation.[87,59] even to the point of effecting treatment decisions and this did not depend on stage or treatment type.[59] (see below) There is no data that would throw light on the ways men perceive brachytherapy and how that may impinge on their status as men but we may assume that responses could be similar.

While treatments may have an impact on masculinity, issues surrounding information may impact on men's sense of identity, either in the sense that they receive too much, too little, it may be too incomprehensible or that given information is erroneous. Equally the way men make treatment decisions may also have an effect on masculinity and vice versa. For these reasons I give a brief resume of what is found in the literature pertaining to these two domains.

Information Needs of Men with Localised and Metastatic Prostate Cancer

Studies[90,99] have shown that the majority require information and to share in decision making. Providing sound information provides a sense of control, pain reduction, speedier recovery, increased participation in decision making and improved mental health and better coping skills. [90] Yet men with prostate cancer voice dissatisfaction with the amount of information they receive and with the level of doctor patient communication.[91,92] Importantly, patients in general (including men) report a need to 'pace' what is told to them; some electing to put 'faith' in the doctor and to follow 'doctor's orders'. [93]

One study found that only 13.3% were aware that treatment was concerned with hormonal manipulation and only 34.4% knew the name of their treatment.[94] Knowledge regarding prostate cancer is scant [59,89] but this may relate to age, marital status and social class.[94] However, it is not altogether clear as to whether men are not receiving information or that they simply fail to understand what they are told.[95] Certainly it is said that what and how information is communicated can cause a significant difference in the way individuals with prostate cancer understand the uncertainty of their lives.[90] Staff are known to keep to a rigid biomedical agenda and closed questions, limiting disclosure, even though it is now known that patients prefer information given on their own terms; their needs often being far from stereotypical.[95] Doctors are also known to overestimate patients' understanding of the information they provide.[96] However, when asked to list who the most important source of information was, most men listed their urologist or 'consult-

ant' and most were eager to receive an 'education session' from either the urologist or specialist prostate cancer nurse. [94,106]

The Outpatient Department was the choice of location for 'information sessions', a few preferring such a session to be held in the patient's home.[94] Those receiving hormone therapies were in the main eager to have more education regarding their treatment suggesting videotapes or visual aids of another kind such as leaflets.[92 95,96,97] Educational 'forums',[98] magazines or other print media including internet sites were perceived as yet more ways that men could imagine how information might be imparted or accessed. [92,94,95,99]

More men, preferred not to bring a family member/friend to the education session in one study[94] although others found that men were eager to take family members to a support group.(see below) [98] and most men (69%) receiving androgen deprivation therapy, wanted a family member with them for 'some' or 'all' their medical appointments. [99]

A randomised trial [100] to evaluate the impact of an education package on knowledge of disease and treatment, quality of life, coping and satisfaction on a sample of men on hormonal manipulation therapy, showed that the 'package' had a significant effect on knowledge, quality of life and satisfaction with care but not with 'coping,' advocating further studies to evaluate the latter. Men who 'cope with optimism, are found to want more explanations during diagnosis, treatment and in the post treatment period. ($p<0.05$) [90] Those less in control emotionally and whose mood is less positive require more psychological information in addition to physical information. Men over 70, are said to want more psychological information when they were depressed.[90] It is well to remember, however, that 'coping' (including depression) is a slippery concept, changing over time .[101]

Information needs of men on hormone therapies include the ways in which prostate cancer acts in the body and how the illness might affect men's lives in the few months after the start of treatment and in the future as well as knowing whether there is any cancer in the rest of their bodies. [94] The most prevalent need identified information regarding the investigative tests (especially the meaning of the PSA). [49,94] These are required as soon as it is feasible and do not necessarily rely on treatment groups.[49] Interestingly information regarding psychosocial factors is reported as 'least important', including factors such as where the family or patient might go if they require help to deal with their feelings about illness.[94] While there is a desire for knowledge surrounding treatment generally, the greatest information gap appears to lie in the side effects of hormone treatment and potential methods of easing those side effects.[94] It is important to remember that age may impinge on men's needs. For example Boudioni et al 1999 [102] found that older men with prostate cancer were less likely to seek general written information than younger men, but wanted more treatment specific information. Even when individuals have a strong stated desire for a given type of service, failure to deliver to match patients' preferences may result in underutilization of needed services.[95]

Decision Making

A plethora of studies have investigated the ways in which men make their decisions regarding treatment,[59,103,104, 105]including decision 'aides' to enable men to individualise their choice. There is currently an endeavour to facilitate decision making for prostate cancer patients on an international level through the development of 'decision aides'. (INEPAP – Feldman-Stewart D. et al. Toronto, Canada). Caution is advocated however. Studies on information needs in prostate cancer patients [105] have found a significant variation among men with localised prostate cancer regarding the number of information items necessary to make treatment decisions, and little agreement is shown on most specific items of information. *The authors[105] emphasise the need for doctors not to expect to predict the information needs of every patient and that patients should be specifically asked what information is pertinent to their decisions.*

Studies [94],[103] show that in the main patients chose a treatment on the basis of evidence that it is the best procedure to cure their cancer but this is not necessarily the case[59]. Choosing the treatment with the best side effect profile is one common motivating factor; the risk of urinary inconti-

nence necessitating wearing pads being the most disturbing factor, with erectile dysfunction as the second most disturbing side effect and the fear of experiencing a long recovery after surgery, the third[94].

Men with localised disease do not feel they 'own' their decision; rather it is perceived that the decision is made by the urologist [102] and often patients are not able to recount why a particular treatment has been chosen. These quantitative studies cited here do not explore the impact on men's sense of masculinity although cursory nods are given to a spoiled male identity.[94] There is evidence however that men on hormonal therapies perceive a dearth of information regarding possible side effects of treatment, especially hormonal treatments[94] thus precluding the possibility of making an informed choice. One qualitative study [59] investigated masculinity issues amongst a sample of Australian prostate cancer patients, and found that it was apparent that some men are prepared to trade long-term survival for potency and continence. Indeed men's desire to retain their sense of masculinity was omnipresent during the decision making process and was an important factor in their final treatment decision. Thus their decision did not rest on 'the best cure' principle, but rather one that would allow them to "be a man" and retain the ability to perform sexually. An important point is made by the author: [59] men's attitudes concerning masculinity may differ according to whether they are sought pre or post diagnosis. Men may become less focused on constructions of masculinity and the stigma of tests post diagnosis, focusing more on cure and to other facets of their lives.

Those men with metastatic disease and with regrets (see below) regarding treatment, were less likely to say they were satisfied with the role they played in decision making and were more likely to experience uncertainty about the progress of their disease.[107,108,109] Men who expressed regrets said they did not have much choice and perceived a paucity of information received, stating that there was too much guesswork involved. They were 'bothered' by the knowledge that other men had received treatments very different from their own[107].

Decision-making roles were described in terms of ranging from passivity, being 'out of control' but accepting examinations, diagnoses, decisions and treatments, and vigorously searching for treatment options while dictating strategies to the urologist. However, all spoke about how their decisions were to varying degrees directed by their doctors despite the 'good feeling' some had in involving themselves in the treatment decision.[107]

Caution is required when assessing studies such as the ones cited above. Firstly, few include minority groups, some only focus on surgical treatment for localized disease and often studies evaluate patients after therapy and therefore the exact preferences or thoughts of patients cannot be determined before embarking on a definitive course of action. In addition, the ways that information needs change over time is seldom taken into account. Longitudinal studies are required and more attention should be given to provider's communication processes and patient's needs in the context of decision-making.

Regrets regarding treatment decisions

There is a dearth of literature that throws light on the ways that men appraise their treatment decisions after treatment has been received and those that have been published do not specifically report the link between regret and possible diminished masculinity. There is a suggestion that men are in the main, satisfied with the decision they make regarding treatments. [104,106,107,108,109,110] Dissatisfaction with treatment in one study was attributed to physical complications, including urinary and sexual problems, whereas neither erectile dysfunction nor related problems had a significant effect.[111] However, many cited 'problems' were not included in the response categories.[111] It has been difficult to ascertain whether regretful or satisfied patients perceived themselves as having made their own decision regarding treatment. (see above)

One study that used both quantitative and qualitative methods[107] investigated men's regret regarding their treatment decisions i.e. surgical versus chemical castration and its association with quality of life. Complications included hot flushes, nausea and erectile dysfunction. While most were satisfied, 23% expressed regret, a higher proportion than the 18% who were unsatisfied

with their choice of hormonal therapy in a study by Miles et al,[111] but twice the proportion of men who indicated dissatisfaction with their treatment in a survey conducted by Carvalhal et al.[112]

There was no difference between regretful men and 'non regreters' in terms of demographics including age, race, marital status and education, nor with respect to the number of years since diagnosis.[107] However the two groups did differ with respect to treatment choice: 'Regreters' were more likely to have had castration with surgery but less frequently reported erectile dysfunction, breast enlargement, and hot flushes. However, regretful men indicated poorer scores on every measure of generic and prostate cancer related quality of life especially in the domains of emotional well being, and body awareness indicating greater levels of concern with bodily sensations and functions.

Some men in this study thought that orchidectomy was the most definitive treatment; that medical castration would eliminate the necessity of persistent treatment. Those who lived a considerable distance away from the treatment facility, said it (orchidectomy) avoided repeated inconvenient trips to the doctor and could even eliminate the risk of being unable to pay for expensive injections and iatrogenic risks. However, those receiving monthly leuprolide acetate injections believed that orchidectomy as 'unnecessary' unless that was a 'massive problem'. While less definite than an orchidectomy, the injections were perceived as effective, and avoided the finality of 'cutting anything off.' While orchidectomy brought certain loss of sexual function, injections were perceived as less devastating to sexual activity or at least promised a reversible loss.

Men's Support Needs

Psycho-social support has shown to improve quality of life, and reviews have emphasised the overall positive outcomes of studies examining the effect of psychological care on cancer patients (in the main women.)[113] Yet studies have shown that men with prostate cancer (and men in general) are reluctant to access psychosocial support [99] and when they do their interest is related to younger age and lower quality of life.[99]

A study[49] that took place in a specialist centre found that needs were being well met in the domain of patient care and support. Moreover, a significant number of patients reported having used or desiring support services such as information about their illness. Men especially those who were younger, married or had more advanced disease were found to have increased psychological need and would have liked a series of talks by staff, staffed information service, telephone support services and a library of books and videos on cancer. Those services most utilised were brochures about services and benefits for patients with cancer.

Despite men's seemingly high level of disinterest in services, there are relatively few available to men with prostate cancer.[114,115] This is in spite of an over estimation by health professionals that patients are interested in and use supplementary services.[115] There also appears to be a discrepancy between physician and patient reports as to how many people are referred and patient's recall of such referrals.[115]

Self help groups have been shown to be utilised by men with prostate cancer[117] and have reported benefits which include experiences of being accepted and affirmed; sharing of information; reconstruction of a positive identity; sense of affiliation and community; personal transformation; and opportunities for advocacy and empowerment.[116] A study set out to explore the differences between men and women's perceptions of self help groups.[117] The prostate groups revolved around the need to help men access what they needed to know. This included having expert speakers as the major focus for group meetings and recruiting as many people as possible to meetings. There were opportunities for men to share information with each other in a small group format, but this developed as an adjunct to formal presentations.[117,118]

One to one counselling was a preference amongst patients in a non surgical clinic, although it was not clear as to what form the counselling would take (i.e. information counselling or psychological counselling) .[49]

This latter finding was not found to be the case in an earlier studies[99],[117] in which it was reported that men did not seek intimacy and emotional support[99,117] although this was stated in a group setting[117]. Men with prostate cancer are known not to disclose their prostate cancer status [87, 88] mirroring the gender theorists who have accentuated men's propensity to keep their worries close to their chests for fear of seeming 'feminine.'[15] It also mirrors a randomised trial [119] that tested a psychological intervention with relatively young men who had testicular cancer. The majority refused randomisation and it may be the case that older men may have similar responses. This requires further investigation but as stated there is a seeming reluctance amongst prostate cancer to access psychological services.[99,102]

Interestingly, and unlike women, men are found to perceive prostate cancer as a 'family affair' and spouses are found to participate in meetings in a substantial way. Men with prostate cancer are also keen to invite adult children to meetings.[118] As stated above, while prostate cancer patients are known to have distress, it is also known that they are seldom offered support.[115] The absence of support may be due to the unavailability of services due to a lack of resources.[115] It may also be a result of a 'blindness' in the face of older people, believing them to be 'bolstered' by age, established family networks and stoicism relating to men in general.[13,14]

Partners (and family members) of men with prostate cancer

Various challenges face the partner of a man with prostate cancer, including learning of the diagnosis, helping to deciding among numerous treatment options, dealing with side effects of treatment and possibly facing death in the sick partner. [120] However studies of 'sound quality' are uncommon.[120] Cancer specific measures of distress for partners need to be devised and validated.[120] More longitudinal studies are required.

Such quantitative studies that have been carried out find that female partners are known to be more distressed than patients.[121,122] although patients medical or sexual status did not predict partners' quality of life[123] One cross sectional study[122] found that half the women compared to only one in five male patients manifested difficulties. And yet, the partner has been shown to believe that patients are more distressed than they are themselves,[122] and that the patient is more distressed than he will say,[120] indicating a 'block' in communication between couples and possibly hospital personnel.[120] However, couples relationships have been shown to worsen when the partner (not the patient) reports distress, avoidance, intrusiveness and 'hyper arousal'.[124] The latter predict psychological distress in partners. Couples with high distress report lower levels of family support than couples in which both members report normal levels of distress.[125] 'Couple relationship' research is advocated [120] since discordance in perspectives between patient and partner appears to be common with possible adverse repercussions for their well being.

Domains that cause distress in partners

Urinary difficulties in men are found to be related to partners' distress. [122] Indeed, partners are more concerned about pain and physical limitations arising from treatment than the patient; conversely, patients are more worried about sexual function.[122] While most partners reported at least some dissatisfaction with their current sexual relationship and this may cause distress[59,126] they are also shown to comfort men regarding their impotence.[127]

A longitudinal study found that at baseline, 2 and 4 months, partners of patients with better physical, social and emotional functioning report less distress and caregiver burden.[121] Worsening quality of life in the patient creates the same in the partner.[121] A one year longitudinal, qualitative study [120] reported the diagnosis to be shocking to couples, but this waned over time. The lived experience of the cancer led to a renewed commitment to couple's relationships, a search for information to guide decisions about treatment and facing the question of who and when to share news and how much detail to divulge.[88]

Couples sought a semblance of normality in their lives once treatment decisions had been made but experienced anxiety as surgery loomed. [127,128] While female spouses were perceived by their

sick partners as the major care giver and means of social support, one study showed that at one year post surgery, wives were more reluctant to offer support in case this undermined their husbands' quest for self reliance.[120]

Couper et al[120] advise caution. Ethnicity is rarely examined in this area, although Germino et al [129] investigated coping in white and African American patients and their 'family care providers' (mostly partners). The greater the uncertainty in partners of white patients, but not in African Americans, the greater their doubts about the patient's medical treatment. Uncertainty correlated with poor problem solving and feelings of inadequate support, again in partners of white but not African American patients. The ethnicity of the partners is difficult to ascertain, however. It is also difficult to know whether partners of 'white' men are more able to voice their concerns, or whether health personnel are more able to listen to this group.

Information seeking and decision making (with reference to partners)

According to a literature review [120,131] partners of prostate cancer patients are more active in seeking information and making decisions about treatment, and in general supporting the patients than are partners of breast cancer patients.[117] They are, in any case, in need of comprehensive information about treatment including options should the sick partner relapse.[120] Both partners and patients feel a responsibility to learn as much as possible and many couples are known to make extensive forays into the search for information. This is beneficial although some partners (and patients) find this task overwhelming and confusing in that there is an abundance of conflicting information.[130]

Indeed some partners are known to avoid information in an effort to reduce fear and worry and to maintain a sense of normality.[131] Patient/physician consultations can cause 'disempowerment and partners can feel pressurised.'[131] Importantly information seeking behaviours of partners is shown to change over time and across situations.[131]

O'Rourke and Germino 1998[132] found that at diagnosis, both partners and patients described a pressing need to make a treatment decision due to the distressing nature of their symptoms but reported panic that interfered with their ability to search for information. After the initial shock of diagnosis, patient and partner invest considerable time and energy in seeking information but this may leave both in a state of confusion.

Psychosocial interventions for partners of prostate cancer patients

Relatively few studies have involved the partner of men with prostate cancer although it has been shown that partners and patients who felt supported, were less distressed.[120] Even fewer have used controls or randomisation.[120] There is an indication that men's and women's support needs cannot be assumed to be the same when they have cancer.[117] However this cannot be assumed in a group of women who do not have cancer and who are in the position of being in a relationship with someone who has.

One randomised controlled[133] trial that compared a closed structured psychosocial group intervention against a control group of usual treatment, found that positive reappraisal and growth was higher among the intervention partners. Denial was lower among the 'treated' group compared to controls but the intervention did not result in changes in psychological distress compared to controls. Another[134] found that when they compared partners' psychological distress and decision making before and after an individualised information session, partners reported assuming a more passive role in decision making than originally intended. All patients and partners had lover levels of psychological distress at four months. When partners were randomised to a standardised nursing intervention with controls receiving usual care, it was found that both intervention and control group partners rated themselves as well prepared to take care of physical and emotional needs of patients and this improved at 3 and 6 months post surgery.[135]

There are many limitations that typify the majority of studies in this area (partner studies): Attention has to be paid as to where and how samples were devised and the differing measures used, that may conceivably impact on outcomes. Ethnicity is not addressed, nor the status of same sex partners. Stage of prostate cancer is not always defined and there are excessive ranges in time since diagnosis, a low response rate of partners compared to patients, failure to specify the proportion of participating family member of patients who were spouses and the use of un-validated instruments with adequate description of content is missing. Longitudinal qualitative work 'from which valuable insights into the experience of couples confronted by prostate cancer and its treatment can be found' is advocated .[120]

It appears certain however, that prostate cancer can have marked repercussions on partners and while retrospective and prospective studies suggest that distress may diminish with time, a proportion of partners may remain adversely affected years after the death of the patient.[120]

It is suggested that 'future intervention studies should deal with reluctance to disclose 'news' of the disease to family and friends who are potential sources of support, assist the couple to communicate openly, including about sexual function and intimacy and promote mutual emotional support in couples, discouraging withdrawal and isolation by patient or partner'. [120]

Clinical implications

If we link' the masculinity theory that exists regarding men and men who are ill, we could say with a fair amount of certainty that men (not all) will feel diminished with regard to 'masculinity' having received any one (or more) of the treatments available to prostate cancer patients (including monitored and 'watch and see' patients) and who may have experienced any of the symptoms outlined in this paper. However it would seem that men who have received ADT and have experienced prostatectomies fare worst in terms of feeling emasculated. This does not preclude other men but the latter have experienced sometimes major bodily changes, impotency, loss of libido, incontinence both in terms of urinary and bowel dysfunction, even to the extent that men have had to resort to 'nappies' or pads.

Evidence suggests that both providers and patients considering the use of ADT should be aware of the diverse experiences that can accompany this treatment. Candid discussions (with those who wish to pursue information regarding their treatment related side-effects), and subsequent time to contemplate all potential treatment side effects should precede the initiation of treatment.[10]

Those men who have undergone surgery are equally prone to distressing terms of issues surrounding the concept of masculinity. Potency is not always fully addressed in the decision making process, and can become a major issue for men post treatment. It is crucial that both patients and their clinicians or others who are involved in treatment decision-making process, are aware of the difficulties (as evidenced in this paper) faced by men within that arena. Although not the same for all men, there are some men with prostate cancer who are shown to value quality over quantity of life. 'A non pressurised safe process in which men are able to communicate their values and priorities, rather than a process based on the simple assumption of 'cure' as isolated or uncomplicated, is essential for assisting men in the decision making process'. [59] Furthermore, an increased awareness in all parties involved, regarding the impact that basic testing techniques may have on men's sense of masculinity, is 'vital,'[59] as is privacy, furthering knowledge about procedures and the roles of particular health professionals that may limit the distress experienced by some men.

Even outside the decision making processes and in terms of any of the treatments discussed, the above may apply. This is especially the case with regard to information given and acknowledgment from the clinician of how a man may be feeling as a result of certain interventions.

Linked to this is the obvious need for sound information given to men on their own terms at all junctions of the cancer trajectory. Thus an individualised approach by clinicians and other health personnel is called for.

Last but not least, it must be said that institutions too, could address the ways in which they may subtly or not so subtly, create a certain ethos that may impinge on men's sense of themselves as men. For example clothing given to men who are in the process of prostate biopsy can have an effect on men's sense of masculinity and pride (with which some explicitly link it)[59]. Men perceive their hospital 'gowns' as childlike and feminine, some not covering men's bodies as they expose themselves to hospital staff and other patients.[59] In addition, to what degree we may ask, is the so called 'male approach' to seeking services, a result of a lack of institutional support networks rather than men's desire not to address certain health problems such as support seeking?

It is known that men are though to be 'non-communicative', 'stoical', 'fighters' whereas for many men this is inaccurate. Thus men cannot be seen as a homogenous group. There are many dimensions and ways of being 'masculine' that will depend on the approach taken by health personnel, age, race, ethnicity and social class to name just a few categories.

Partners

The distress caused to partners should be acknowledged and addressed. Like their sick partners they may require comprehensive information and a feeling that they are welcomed into the process of decision-making although they will not necessarily involve themselves in the latter.

Their support is invaluable to the patient and may even ameliorate diminished masculinity but they are only able to provide optimal care if they too feel that they are supported.

More research is required to ascertain the best ways of providing 'support' for this group.

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Gray R, Fitch M, Phillips C, Labrecque M. Klotz L (1999) Presurgery experiences of prostate cancer patients and their spouses. Cancer Practitioner : 130-135.

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Manne S. Babb J. Pinover W. Horwitz E. Ebbert J. (2004) Psycho-educational group ;intervention for wives of men with prostate cancer. Psycho-Oncology 13: 37-46.

Davison B. Goldenberg S. Gleave M. Degner L. (2002) Provision of individualized information to men and their partners to facilitate treatment decision making in prostate cancer. Oncology Nursing forum 30: 107 – 114.

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Appendix B – Search Strategies

Chapter 2: Communication and support

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer Clinical Guideline **Literature search summary**

Question title:

1. How effective are decision aids at informing men with prostate cancer about treatment options?

2. What are the communication methods that effectively inform men with prostate cancer about treatment options?

3. What are the perspectives of partners, wives, carers or family of men who have prostate cancer with regards the information/communication needs about treatment options, decision making processes and influencing factors?

Question no: Topic 6

1. Literature search details

Database name	No of references found	No of references re-trieved	Finish date of search
Medline	708 (20)	338	31/01/06
Premedline	6	3	19/01/06
Embase	1667 (182)	682	01/02/06
Cochrane Library (Wiley)	191	63	01/02/06
Cinahl	443 (24)	295	19/01/06
BNI	11	11	30/01/06
Psychinfo	199 (15)	104	16/01/06
SIGLE	4	2	01/02/06
Web of Science	301	105	01/02/06
Biomed Central	15	1	30/01/06
National Research Register	54	29	01/02/06

Total References retrieved (after de-duplication): 1,240

Medline search strategy *(This search strategy is adapted to each database)*

1. exp Prostatic Neoplasms/

2. Prostatic Intraepithelial Neoplasia/

3. pin.tw.
4. (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.
5. or/1-4
6. Choice Behavior/
7. Decision Making/
8. decision support techniques/
9. decision$.tw.
10. (choic$ or preference$).tw.
11. or/6-10
12. patient compliance/
13. informed consent/
14. treatment refusal/
15. exp consumer satisfaction/
16. exp consumer participation/
17. exp health education/
18. or/12-17
19. 11 and 18
20. ((patient$ or consumer$) adj1 (decision$ or choice$ or prefer$ or participat$)).tw.
21. ((man or men) adj1 (decision$ or choice$ or prefer$ or participat$)).tw.
22. ((personal or interpersonal or individual) adj (decision$ or choice$ or prefer$ or participat$)).tw.
23. or/19-22
24. Pamphlets/
25. pamphlet$.tw.
26. (leaflet$ or diary or diaries or booklet$ or guidebook$).tw.
27. sheet$.tw.
28. cues/
29. cue$.tw.
30. (prompt$ or coach$).tw.
31. (checklist$ or check list$).tw.
32. (written or write).tw.
33. question$.tw.
34. (card$ or helpcard$).tw.
35. (video$ or tape$ or cd$ or film$ or dvd$ or telephone$ or phone$ or computer$ or internet or electronic).tw.
36. *internet/
37. or/24-36
38. communication/

39. communicat$.tw.
40. patient education/
41. ((patient$ or consumer$) adj3 (educat$ or skill$ or teach$ or train$ or coach$)).tw.
42. 38 or 39
43. 40 or 41
44. 42 and 43
45. 37 or 44
46. (preconsultation$ or pre-consultation$).tw.
47. office visits/
48. (office adj3 visit$).tw.
49. consult$.tw.
50. (medical adj3 interview$).tw.
51. waiting room$.tw.
52. scheduled appointment$.tw.
53. ((prior adj3 visit$) or previsit$).tw.
54. "appointments and schedules"/
55. or/46-54
56. 45 and 55
57. (information adj3 need$).tw.
58. information material$.tw.
59. (patient$ adj3 information).tw.
60. (information adj3 web$1).tw.
61. (information adj3 print$).tw.
62. (information adj3 electronic$).tw.
63. or/57-62
64. 56 or 63
65. 23 or 64
66. 5 and 65

2. Health Economics Literature search details

Not required

3. Any further comments:

Although this topic had a number of components, it was felt that one literature search could encompass them all. Part of the search constituted an update of a Cochrane Review [1] which meant re-executing the original Cochrane search, but limited to RCTs and prostate cancer from 2002 onwards. The initial results for this part of the search are detailed in brackets within the literature search details audit box above. For the remainder of the search, no search filters were placed on the main search strategy as qualitative results needed to be retrieved for this topic. In terms of sifting the results, references with regard to carers and families were included but references solely concerned with screening

have been disregarded (apart from background references).

[1] *AM O'Connor, D Stacey, V Entwistle et al Decision aids for people facing health treatment or screening decisions (2003)*

4. Update Search

For the update search, the reviewer required only RCT's and so the search was re-executed using a RCT filter, date limit 2005-2007 and English language only.

Database name	No of references found	No of references re-trieved	Finish date of search
Medline	28	5	21/05/07
Premedline	18 (no filter)	4	21/05/07
Embase	141	6	21/05/07
Cochrane Library (OVID)	45 (Central & DSR)	6	24/05/07
Cinahl	20	1	21/05/07
AMED	1	0	21/05/07
BNI	0	0	21/05/07
Psychinfo	3	1	21/05/07
SIGLE	0	0	21/05/07
Web of Science	170	6	21/05/07
Biomed Central	4	0	21/05/07

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer **Clinical Guideline** **Literature search summary**

Question title: Should men with suspected prostate cancer who have a raised PSA level automatically be referred for biopsy to determine if they have prostate cancer

Question no: 23

5. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline		851	102	25/09/06
Premedline		7	0	26/09/06
Embase		841	47	25/09/06
Cochrane Library		85		27/09/06
Cinahl		19	1	26/09/06
BNI		1	0	26/09/06
Psychinfo		12	0	26/09/06
SIGLE		0	0	26/09/06
Web of Science (SCI & SSCI)		76	12	27/09/06
ISI Proceedings		11	2	27/09/06
Biomed Central		251	0	26/09/06
Current Controlled Trials		-	-	
National Research Register		-	-	
ZETOC		-	-	

Total References retrieved (after de-duplication): 141

Medline search strategy *(This search strategy is adapted to each database.)*

Prostate Cancer AND Biopsy

1 exp Prostatic Neoplasms/

2 prostatic intraepithelial neoplasia/

3 pin.tw.

4 (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.

5 or/1-4
6 exp Biopsy/
7 (transperineal adj4 biops$).tw.
8 (peripheral adj3 biops$).tw.
9 (transrectal adj4 biops$).tw.
10 TRNB.tw.
11 needle biops$.tw.
12 (core biops$ or biopsy core$).tw.
13 (sextant adj3 biops$).tw.
14 biops$ scheme$.tw.
15 prostat$ biops$.tw.
16 biops$ plan$.tw.
17 repeat biops$.tw.
18 (increase adj3 biops$).tw.
19 re-biops$.tw.
20 (immediate adj biops$).tw.
21 (delayed adj biops$).tw.
22 or/6-21
23 5 and 22

RCT and SR filters applied

6. Health Economics Literature search details

(SIGN Health Economics filter added to above search)
[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline		
Premedline		
Embase		
Cochrane Library (except NHSEED)		
NHSEED		
Cinahl		
Psycinfo		
BNI		
EconLit		

Web of Science (SCI & SSCI)		
ISI Proceedings		
SIGLE		
ZETOC		

7. Any further comments:

Sifting Criteria:

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer Clinical Guideline **Literature search summary**

Question title: In men presenting with bone metastases and unknown primary cancer, at what level of PSA does a biopsy become unnecessary?

Question no: Topic 3

8. Literature search details

Database name	No of references found	No of references re-trieved	Finish date of search
Medline	98	18	10/01/06
Premedline	3	1	10/01/06
Embase	157	13	10/01/06
Cochrane Library	12	4	12/01/06
Cinahl	1	0	10/01/06
BNI	0	0	10/01/06
HMIC	0	0	10/01/06
Psychinfo	0	0	10/01/06
SIGLE	0	0	12/01/06
Web of Science	121	15	12/01/06
Biomed Central	39	0	12/01/06
Current Controlled Trials	5	1	12/01/06
National Research Register	8	0	12/01/06
ISI Proceedings	10	4	26/01/06

Total References retrieved (after de-duplication): 49

Medline search strategy *(This search strategy is adapted to each database.)*

Prostate cancer AND Biopsy AND Bone Scan AND PSA

1 exp Biopsy/

2 (transperineal adj4 biops$).tw.

3 (transperineal ultraso$ or tpus).tw.

4 (peripheral adj3 biops$).tw.

5 (transrectal adj4 biops$).tw.

6 TRNB.tw.

7 (transrectal ultraso$ or trus).tw.

8 needle biops$.tw.

9 (core biops$ or biopsy core$).tw.

10 (sextant adj3 biops$).tw.

11 or/1-10

12 eoplasm$ specific antigen.tw.

13 exp prostate-specific antigen/

14 (eoplasm$ adj2 specific adj2 antigen$).tw.

15 PSA.tw.

16 or/12-14

17 exp Prostatic Neoplasms/

18 Prostatic Intraepithelial Neoplasia/

19 pin.tw.

20 (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.

21 or/17-20

22 21 and 11

23 16 and 22

24 exp diagnostic imaging/

25 exp bone/ and bones/

26 24 and 25

27 (bone$ or osseous or osteo$).tw.

28 (scan$ or imaging).tw.

29 (radiograph$ or radiology).tw.

30 scintigra$.tw.

31 ultraso$.tw.

32 urogra$.tw.

33 pyleogra$.tw.

34 cystoscop$.tw.

35 urodynamic$.tw.

36 CT.tw.

37 tomogr$.tw.

38 MRI.tw.

39 SPECT.tw.

40 PET.tw.

41 or/28-40

42 27 and 41

43 26 or 42

44 23 and 43

9. Health Economics Literature search details

(SIGN Health Economics filter added to above search)

[SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline	4	17/01/06
Premedline	0	17/01/06
Embase	7	17/01/06
Cochrane Library (except NHSEED)	0	24/01/06
NHSEED	3	24/01/06
Cinahl	1	19/01/06
Psycinfo	0	19/01/06
BNI	0	19/01/06
EconLit	0	24/01/06
Web of Science	5	24/01/06
ISI Proceedings	2	26/01/06

10. Any further comments:

Encountered several articles discussing whether a bone scan is necessary. These were excluded.

Most articles mentioned that a biopsy and a bone scan were performed, but not if the biopsy was necessary

Articles mentioning negative bone scans were initially excluded from sift, but then included at the request of Angela Melder.

The search also retrieved articles discussing PSA testing and PSA levels where scans and biopsies were also men-

tioned only in passing.

A Google search also produced nothing of obvious value.

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer (Update) Clinical Guideline

Chapter 3 – Diagnosis and Staging **Literature search summary**

Topic 1: Does multiparametric/functional MRI before TRUS biopsy increase diagnostic yield of initial biopsy in men with suspected prostate cancer

11. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2002 – 6/2012	1468	371	11/06/2012
Premedline	2002 – 6/2012	87	65	18/06/2012
Embase	2002 – 6/2012	2483	350	18/06/2012
Cochrane Library	2002 – 6/2012	116	19	11/06/2012
PsycINFO	2002 – 6/2012	4	0	18/06/2012
Web of Science (SCI & SSCI)	2002 – 6/2012	2080	199	18/06/2012
Biomed Central	2002 – 6/2012	108	0	20/06/2012

Total References retrieved (after de-duplication): 670

Medline search strategy *(This search strategy is adapted to each database)*

1. exp Prostatic Neoplasms/
2. exp Prostatic Intraepithelial Neoplasia/
3. PIN.tw.
4. (prostat$ adj3 (cancer$ or carcinoma$ or adeno$ or malignan$ or tum?r$ or neoplas$ or intraepithelial$)).tw.
5. 1 or 2 or 3 or 4
6. (transrectal adj ultrasound*).tw.
7. transrectal ultrasound biops*.tw.
8. (TRUS or TRUSB).tw.
9. (Multi-parametric MRI* or multiparametric*).tw.
10. MP-MRI*.tw.
11. T2-weighted MRI*.tw.
12. dynamic contrast-enhanced MR*.tw.
13. DCE-MRI*.tw.
14. diffusion weighted imag*.tw.
15. DWI*.tw.

16. 1H MR-Spectroscopic Imag*.tw.

17. magnetic spectroscop*.tw.

18. MRSI*.tw.

19. T2W*.tw.

20. T2W TSE*.tw.

21. turbo spin echo*.tw.

22. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 18 or 19 or 20 or 21

23. 5 and 22

24. limit 23 to yr="2002 -Current"

12. Health Economics Literature search details

Database name	No of references found	Finish date of search
Medline	32 (update search: 1)	19/06/2012 (17/05/2013)
Premedline	2 (update search: 8)	19/06/2012 (17/05/2013)
Embase	50 (update search: 5)	19/06/2012 (17/05/2013)
Cochrane Library (except NHSEED)	12 (update search: 0)	19/06/2012 (17/05/2013)
NHSEED	3 (update search: 0)	19/06/2012 (17/05/2013)

Total References retrieved (after de-duplication): 77

13. Any further comments

Cinahl, BNI and AMED were not used for this search as not considered relevant to the topic. The GDG sub-group decided to include search results from 2002 onwards because of the introduction of this technique from 2002 onwards. Basic exclusions filter only used. SIGN Health Economics filter & SCHARR Quality of Life filter was added to the search for the health economics literature search.

14. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit 2012 onwards.

Database name	No of references found	No of references re-trieved	Finish date of search
Medline	259	36	17/05/2013
Premedline	197	46	17/05/2013
Embase	698	103	17/05/2013
Cochrane Library	9	2	17/05/2013
PsycINFO	3	0	17/05/2013
Web of Science (SCI & SSCI)	307	57	17/05/2013

Total References retrieved (after de-duplication): 138

Topic 3: In men who have been referred with suspected prostate cancer, what are the prognostic factors that determine the need for further investigation following a prior negative biopsy(s)?

1. Literature search details

Database name	Dates Covered	No of references found	Finish date of search
Medline	2000 -	1533	07/01/2013
Premedline	7 Jan 2013	67	07/01/2013
Embase	2000 -	3407	08/01/2013
Cochrane Library	2012 issue 12	149	08/01/2013
Amed	2000 -	1	07/01/2013
Web of Science (SCI & SSCI)	2000 -	3843	09/01/2013
Biomed Central	As per database	25	11/01/2013

Total References retrieved (after de-duplication): 3804

Medline search strategy *(This search strategy is adapted to each database)*

1. exp prostatic neoplasms/
2. exp prostatic intraepithelial neoplasia/
3. PIN.tw
4. (prostat$ adj3 (cancer$ or carcinoma$ or adeno$ or malignan$ or tum?r$ or neoplas$ or intraepithelial$)).tw.
5. or/1-4
6. negative.tw.
7. false negative reactions/
8. 6 or 7
9. (rebiops$ or re-biops$).tw.
10. ((repeat$ or review$ or follow-up or followup) adj3 biops$).tw.
11. ((saturat$ or extend$ or template) adj3 biops$).tw.
12. exp biopsy/ or biops.tw
13. 5 and 8 and 12
14. or/9-11
15. 5 and 14
16. 13 or 15
17. limit 16 to yr="2000 -Current"

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on prostate cancer.

3. Any further comments

Limited to year 2000 to present in consultation with GDG.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 07/01/2013 onwards for the first update, and then 25/03/2013 for the second update.

Database name	No of references	Finish date of

	found	search
Medline	28	26/03/2013
Premedline	0	26/03/2013
Embase	133	26/03/2013
Cochrane Library	0	25/03/2013
AMED	1	25/03/2013
Web of Science	112	25/03/2013
Biomed central	5	25/03/2013
Database name	**No of references found**	**Finish date of search**
Medline	33	21/05/2013
Premedline	18	21/05/2013
Embase	181	22/05/2013
Cochrane Library	1	22/05/2013
AMED	0	22/05/2013
Web of Science	78	23/05/2013
Biomed central	2	23/05/2013

Total References retrieved (after de-duplication): 240

Total References retrieved (after de-duplication): 275

Topic 2: In men with suspected prostate cancer whose initial TRUS biopsy is negative what should be the next investigation(s): multiparametric magnetic resonance, 3D ultrasound, template biopsy?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946-	181	101	20/06/2012
Premedline	All	3	2	19/06/2012
Embase	1947-	352	166	20/06/2012
Cochrane Library	All	51	17	26/06/2012
PsycINFO	1806-	0	0	20/06/2012
Web of Science (SCI & SSCI)	1980-	271	113	25/06/2012
Biomed Central	All	56	2	26/06/2012

Total References retrieved (after de-duplication): 267

Medline search strategy *(This search strategy is adapted to each database)*

1. exp prostatic neoplasms/
2. exp Prostatic Intraepithelial Neoplasia/
3. PIN.tw.
4. (prostat$ adj3 (cancer$ or carcinoma$ or adeno$ or malignan$ or tum?r$ or neoplas$ or intraepithelial$)).tw.
5. or/1-4
6. ((transrectal or trans-rectal) adj ultraso$).tw.
7. ((transrectal or trans-rectal) adj3 biops$).tw.
8. (TRUS or TRUSB).tw.
9. or/6-8
10. negative.tw.
11. false negative reactions/
12. 10 or 11
13. 9 and 12
14. 5 and 13
15. ((repeat$ or review$) adj3 biops$).tw.
16. rebiops$.tw.
17. ((saturat$ or extend$ or template) adj3 biops$).tw.
18. exp biopsy/ or biops.tw.
19. Elasticity Imaging Techniques/
20. (elastograph$ or elastogram$).tw.
21. sonoelastogra$.tw.

22. (vibroacoustogra$ or vibro-acoustogra$).tw.
23. (elasticity adj2 imag$).tw.
24. (arfi adj imag$).tw.
25. (acoustic adj2 imag$).tw.
26. *Imaging, Three Dimensional/
27. (3DUS or 3D-US or 3d ultraso$).tw.
28. ((tridimension$ or three dimension$) adj (imag$ or ultraso$).tw.
29. (contrast enhance$ adj2 (imag$ or ultraso$)).tw.
30. (CETRUS or CE-TRUS).tw.
31. (DCE adj (imag$ or ultrso$ or MR$)).tw.
32. ((multi-parametric$ or multiparametric$) adj2 (MR$ or imag$)).tw.
33. (MP-MR$ or MPMR$).tw.
34. T2 weighted MR$.tw.
35. T2W$.tw.
36. (diffusion adj2 (imag$ or MR$)).tw.
37. DWI$.tw.
38. magnetic spectroscop$.tw.
39. MRS*.tw.
40. MR spectroscop$.tw.
41. or/19-40
42. 18 and 41
43. 15 or 16 or 17 or 42
44. 14 and 43

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
Medline	2	14/05/2013
Premedline	0	14/05/2013
Embase	2	14/05/2013
Cochrane Library (except NHSEED)	3	14/05/2013
NHSEED	1	14/05/2013
Web of Science (SCI & SSCI) and ISI Proceedings	2	14/05/2013

Total References retrieved (after de-duplication): 10

3. Any further comments

No date limit was used as not an exact update from the previous guideline. Basic exclusions filter only used. SIGN

Health Economics filter was added to the search for the health economics literature search.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 19/06/2012 onwards.

Database name	No of references found	No of references re-trieved	Finish date of search
Medline	50	26	14/05/2013
Premedline	3	2	14/05/2013
Embase	173	61	14/05/2013
Cochrane Library	2	0	14/05/2013
PsycINFO	3	0	14/05/2013
Web of Science (SCI & SSCI)	42	16	14/05/2013
Biomed Central	12	0	14/05/2013

Total References retrieved (after de-duplication): 66

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer **Clinical Guideline** **Literature search summary**

Question title: 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?

Question no: 13

5. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline		999	44	15/06/06
Premedline		2	0	15/06/06
Embase		847	45	15/06/06
Cochrane Library		1595	15	16/06/06
Cinahl		13	0	15/06/06
BNI		0	0	15/06/06
Psychinfo		22	0	15/06/06
SIGLE		7	0	16/06/06
Web of Science (SCI & SSCI)		1017	59	19/06/06
ISI Proceedings		188	9	19/06/06
Biomed Central		680	1	16/06/06
Current Controlled Trials		243	0	20/06/06
National Research Register		78	2	20/06/06
ZETOC		122	19	20/06/06

Total References retrieved (after de-duplication): 161

Medline search strategy *(This search strategy is adapted to each database.)*

Prostate cancer AND (Radical treatment OR Active Surveillance) AND (MRI OR CT OR Isotope bone scan OR Chest X-Ray)

1. exp Orchiectomy/
2. (orchiectom$ or orchidectom$).tw.
3. castrat$.tw.
4. exp Radiotherapy/
5. radiotherap$.tw.

6. (radical adj radiotherap$).tw.
7. (radical or complete$ or total or en bloc).tw.
8. Radiotherapy, Adjuvant/
9. Brachytherapy/
10. brachytherap$.tw.
11. (interstitial adj (irradiation or radiation)).tw.
12. (radiation adj (therap$ or treatment$)).tw.
13. (three dimensional adj2 radiotherap$).tw.
14. 3D radiotherap$.tw.
15. 3DCRT.tw.
16. external beam radiotherap$.tw.
17. systemic radiotherap$.tw.
18. exp Prostatectomy/
19. (radical adj3 prostatectomy).mp
20. (remov$ adj3 prostate gland).mp.
21. RRP.tw.
22. (Laparoscop$ adj3 prostatectomy).tw.
23. (perineal adj prostatectomy).tw.
24. RPP.tw.
25. or/1-24
26. exp Prostatic Neoplasms/
27. prostatic intraepithelial neoplasia/
28. pin.tw.
29. (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.
30. clinic$ local$ adenocarcinom$.tw.
31. clinic$ local$ prostat$ cancer$.tw.
32. organ$ confined disease$.tw.
33. new$ diagnos$.tw.linic$
34. or/26-33
35. watchful wait$.tw.
36. (watch$ adj2 wait$).tw.
37. watchful observation.tw.
38. watchful surveillance.tw.
39. watchful monitoring.tw.
40. active surveillance.tw.
41. active monitoring.tw.

42. expectant manag$.tw.
43. expectant monitoring.tw.
44. expectant surveillance.tw.
45. deferred treatment$.tw.
46. deferred therap$.tw.
47. delayed treatment$.tw.
48. delayed therap$.tw.
49. conservative monitoring.tw.
50. or/35-49
51. 25 and 34
52. 50 and 34

53. exp magnetic resonance imaging/
54. Magnetic Resonance Spectroscopy/
55. magnetic resonance.tw.
56. MRI$1.tw.
57. NMR$1.tw.
58. MRS$1.tw.
59. MRT.tw.
60. MR imaging.tw.
61. MR scan$.tw.
62. MR spectroscop$.tw.
63. MR elastograph$.tw.
64. (magnet$ adj3 (scan$ or imaging)).tw.
65. (diffusion adj2 (scan$ or imaging)).tw.
66. (planar adj (scan$ or imaging$)).tw.
67. (planar adj tomogra$).tw.
68. (echoplanar adj (scan$ or imaging)).tw.
69. zeugmatogra$.tw.
70. MRE.tw.
71. SPECT$1.tw.
72. FMRI$.tw.
73. (functional adj2 (scan$ or imaging)).tw.
74. or/53-73

75. exp Tomography, X-Ray Computed/
76. (comput$ adj1 tomograph$).tw.
77. ((ct or cat) adj (scan$ or imaging)).tw.
78. cine-ct.tw.
79. electron beam computed tomography$.tw.
80. tomodensitometry$.tw.
81. 3-dimensional computerized tomography$.tw.
82. three four-dimensional medical imaging modalit$.tw.
83. preoperative computed tomogram.mp.
84. or/75-83

85. exp X-Rays/
86. x-ray$.tw.
87. (chest adj3 x-ray$).tw.
88. (x-ray$ or x ray$ or xray$ or radiography$).tw.
89. exp Radiography, Thoracic/
90. (chest adj3 radiograph$).tw.
91. or/85-90

92. exp "Bone and Bones"/
93. isotope bone scan.mp.
94. bone$ scan$.tw.
95. bone$ imag$.tw.
96. or/92-95

97. scintigra$.tw.
98. ultraso$.tw.
99. urogra$.tw.
100. pyleogra$.tw.
101. cystoscop$.tw.
102. urodynamic$.tw.
103. Endorectal coil MR imag$.tw.
104. endorectal ultrasonograph$.tw.
105. exp Ultrasonography/
106. exp Ultrasonic Therapy/
107. or/97-106

108. 74 or 84 or 91 or 96 or 107

109. 51 and 108

110. 52 and 108

111. 109 or 110

6. Health Economics Literature search details

(SIGN Health Economics filter added to above search)
[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline	102	
Premedline	0	
Embase	168	
Cochrane Library (except NHSEED)	212	
NHSEED	141	
Cinahl	9	
Psycinfo	4	
BNI	0	
EconLit	0	
Web of Science (SCI & SSCI)	15	
ISI Proceedings	9	
SIGLE	0	
ZETOC	2	

7. Any further comments:

Sifting Criteria:

Topic 4a and 4b: Does staging with MRI improve outcomes in men with prostate cancer? In which patients with prostate cancer will MRI staging alter treatment?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2008-	921	99	14/08/2012
Premedline	All	117	12	13/08/2012
Embase	2008-	1528	152	05/09/2012
Cochrane Library	2008-	223	3	10/09/2012
PsycINFO	2008-	6	0	14/08/2012
Web of Science (SCI & SSCI)	2008-	963	75	11/09/2012
Biomed Central	2008	95	1	11/09/2012

Total References retrieved (after de-duplication): 208

Medline search strategy (This search strategy is adapted to each database)

1. exp Prostatic Neoplasms/
2. prostatic intraepithelial neoplasia/
3. PIN.tw.
4. (prostat$ adj3 (cancer$ or carcinoma$ or adeno$ or malignan$ or tum?r$ or neoplas$ or intraepithelial$)).tw.
5. or/1-4
6. limit 5 to yr=”2008 –Current”
7. exp Magnetic Resonance Imaging/
8. magnet$ resonance.tw.
9. (MRI or MR$2 or NMR$1).tw.
10. (MP-MR$ or MPMR$).tw.
11. (MR adj (imag$ or scan$)).tw.
12. (magnet$ adj (imag$ or scan$)).tw.
13. ((magnet$ or MR) adj spectroscop$).tw.
14. or/7-13
15. 6 and 14
16. Neoplasm Staging/
17. (staging or stage$1 or classif$ or evaluat$ or tnm).tw.
18. 16 or 17
19. 15 and 18

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on prostate cancer.

3. Any further comments:

Update of previous guideline topic so searched from 2008 onwards. Basic exclusions filter only used.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit 13/08/2012 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	195	15	14/05/2013
Premedline	21	3	14/05/2013
Embase	513	55	14/05/2013
Cochrane Library	11	0	14/05/2013
PsycINFO	2	0	14/05/2013
Web of Science (SCI & SSCI)	220	25	14/05/2013
Biomed Central	17	0	14/05/2013

Total References retrieved (after de-duplication): 62

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer **Clinical Guideline** **Literature search summary**

Question title: Is there a need for radiological imaging in men with prostate cancer who are not intended for curative treatment

Question no: 14

8. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline		629	21	27/06/06
Premedline		13	1	27/06/06
Embase		414	24	27/06/06
Cochrane Library		71	9	27/06/06
Cinahl		10	2	27/06/06
BNI		2	0	27/06/06
Psychinfo		3	0	27/06/06
SIGLE		0	0	28/06/06
Web of Science (SCI & SSCI)		262	7	28/06/06
ISI Proceedings		58	0	28/06/06
Biomed Central		134	1	28/06/06
Current Controlled Trials		34	0	28/06/06
National Research Register		27	0	28/06/06
ZETOC		44	0	28/06/06

Total References retrieved (after de-duplication): 60

Medline search strategy *(This search strategy is adapted to each database.)*

(Prostate cancer) AND (Metastasis OR metastatic) OR (Life Expectancy OR Quality of Life

OR (Treatment Refusal OR Prognosis OR Age Factor OR Morbidity Or Comorbidity) AND (computer tomography OR CT) OR (isotope bone scan OR bone scan OR bone imaging)

1 exp Prostatic Neoplasms/

2 prostatic intraepithelial neoplasia/

3 pin.tw.

4 (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.

5 or/1-4
6 exp Neoplasm Recurrence, Local/
7 exp Neoplasm Metastasis/
8 exp Neoplasm, Residual/
9 biochemical relaps$.tw.
10 exp Lymphatic Metastasis/
11 (lymph$ adj1 involv$).tw.
12 (lymph$ adj3 (status or metastas$ or micrometastas$)).tw.
13 exp Bone Neoplasms/sc [Secondary]
14 (bone$ adj10 metasta$).tw.
15 (bony adj metasta$).tw.
16 (skelet$ adj3 metasta$).tw.
17 ((spine or spinal) adj2 metasta$).tw.
18 (osseous adj3 metasta$).tw.
19 (osteo$ adj3 metasta$).tw.
20 systemic treatment.mp.
21 metastatic.tw.
22 exp Disease Progression/
23 or/6-22
24 exp Survival Analysis/
25 exp Life Expectancy/
26 exp Treatment Outcome/
27 exp Treatment Failure/
28 exp "Outcome and Process Assessment (Health Care)"/ or exp "Outcome Assessment (Health Care
29 exp Disease-Free Survival/
30 exp "Quality of Life"/
31 ((treatment or process$) adj2 (outcome$ or effect$ or efficac$)).tw.
32 disease$ specific mortality.tw.
33 exp Treatment Refusal/
34 exp Morbidity/
35 exp Comorbidity/
36 exp Age Factors
37 exp "Aged, 80 and over"/ or exp Aged/
38 exp Patient Selection/
39 exp Prognosis/
40 exp Life Expectancy/

41 exp Quality-Adjusted Life Years/
42 exp Decision Making/
43 medical decision$ making.tw.
44 exp "Attitude of Health Personnel"/
45 exp Attitude to Health/
46 exp Withholding Treatment/
47 or/24-46
48 exp Tomography, X-Ray Computed/
49 (comput$ adj1 tomograph$).tw.
50 ((ct or cat) adj (scan$ or imaging)).tw.
51 cine-ct.tw.
52 electron beam computed tomography$.tw.
53 tomodensitometry$.tw.
54 3-dimensional computerized tomography$.tw.
55 or/48-54
56 exp "Bone and Bones"/
57 isotope bone scan.mp.
58 bone$ scan$.tw.
59 bone$ imag$.tw.
60 exp Radionuclide Imaging/
61 radioisotope bone scan$.tw.
62 isotope bone scan$.tw.
63 or/56-62
64 5 and 23
65 5 and 47
66 64 or 65
67 55 or 63
68 66 and 67

9. Health Economics Literature search details

(SIGN Health Economics filter added to above search)
[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline	52	28/06/06

Premedline	0	28/06/06
Embase	105	28/06/06
Cochrane Library (except NHSEED)	4	28/06/06
NHSEED	5	28/06/06
Cinahl	4	28/06/06
Psycinfo	0	28/06/06
BNI	0	28/06/06
EconLit	0	28/06/06
Web of Science (SCI & SSCI)	62	28/06/06
ISI Proceedings	10	28/06/06
SIGLE	0	28/06/06
ZETOC	12	28/06/06

10. Any further comments:

Sifting Criteria:

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer Clinical Guideline	**Literature search summary**

Question title: In men with localised prostate cancer, what is the validity of published prostate cancer nomograms?

Question no: Topic 2B

11. Literature search details

Database name	No of references found	No of references re-trieved	Finish date of search
Medline	275	110	17/01/06
Premedline	8	2	17/01/06
Embase	251	78	18/01/06
Cochrane Library	17	1	18/01/06
Cinahl	8	5	18/01/06
BNI	0	0	18/01/06
Psychinfo	0	0	18/01/06
SIGLE	0	0	18/01/06
Web of Science	311	95	18/01/06
Biomed Central	4	0	18/01/06
Current Controlled Trials	0	0	18/01/06
National Research Register	0	0	18/01/06
ISI Proceedings	47	27	26/01/06

Total References retrieved (after de-duplication): 177

Medline search strategy *(This search strategy is adapted to each database.)*

Prostate Cancer AND Nomograms

1 exp Prostatic Neoplasms/

2 Prostatic Intraepithelial Neoplasia/

3 pin.tw.

4 (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.

5 or/1-4

6 Nomograms/

7 nomogram$.tw.

8 nomograph$.tw.
9 (alignment$ adj2 chart$).tw.
10 *"models, statistical"/
11 (predict$ adj (tool$ or instrument$)).tw.
12 Partin.tw.
13 Kattan.tw.
14 Pisansky.tw.
15 Hilabi.tw.
16 (uro adj gramma).tw.
17 or/6-16
18 5 and 17

12. Health Economics Literature search details – NOT REQUIRED FOR THIS QUESTION

(SIGN Health Economics filter added to above search)
[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline		
Premedline		
Embase		
Cochrane Library (except NHSEED)		
NHSEED		
Cinahl		
Psycinfo		
BNI		
EconLit		
Web of Science		

13. Any further comments:

Sifting Criteria:

References were not included where nomograms were mentioned only in passing and do not constitute the majority of the topic.

14. Update searches

Update Search

searched with date limit 2005- 2007 and English language only

Database name	No of references found	No of references retrieved	Finish date of search
Medline	73	32	19/06/07
Premedline	9	4	19/06/07
Embase	112	44	20/06/07
Cochrane Library	2	0	20/06/07
Cinahl	3	1	20/06/07
AMED	0	0	20/06/07
BNI	0	0	20/06/07
Psychinfo	1	0	20/06/07
SIGLE	0	0	20/06/07
Web of Science	141	70	19/06/07
Biomed Central	0	0	20/06/07

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer Clinical Guideline **Literature search summary**

Question title: What do we need to measure to predict a patient's probability of disease specific mortality, lymph node involvement or recurrent disease?

What are the risk factors for:

- disease specific mortality;
- lymph node involvement;
- treatment failure

Limited to systematic reviews and date range of last five years.

Question no: Topic 2A

15. Literature search details

Database name	No of references found	No of references re-trieved	Finish date of search
Medline	724	130	07/02/06
Premedline	0	0	07/02/06
Embase	119	18	07/02/06
Cochrane Library	108	8	07/02/06
Cinahl	36	6	07/02/06
AMED	0	0	07/02/06
BNI	0	0	07/02/06
Psychinfo	41	5	07/02/06
SIGLE	0	0	07/02/06
Web of Science	67	15	08/02/06
Biomed Central	74	1	08/02/06
ISI Proceedings	4	1	08/02/06
ZETOC	15	2	07/02/06

Total References retrieved (after de-duplication): 171

Medline search strategy *(This search strategy is adapted to each database.)*

Prostate Cancer AND Prognostic Factors AND Outcomes AND Systematic Reviews filter

1. exp Prostatic Neoplasms/
2. Prostatic Intraepithelial Neoplasia/
3. pin.tw.
4. (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.
5. or/1-4
6. exp prostate specific antigen/
7. psa.tw.
8. (psa adj density).tw.
9. psad.tw.
10. prostate specific membrane antigen.tw.
11. psma.tw.
12. exp neoplasm staging/
13. (gleason or TNM or WHO or grade$ or grading or stage$1 or staging or score$1 or scoring).tw.
14. exp tumor markers, biological/
15. (tumo?r$ adj marker$).tw.
16. (prognos$ adj marker$).tw.
17. (prognos$ adj indicat$).tw.
18. (prognos$ adj factor$).tw.
19. (predict$ adj factor$).tw.
20. (predict$ adj marker$).tw.
21. (predict$ adj indicat$).tw.
22. (clinical adj predict$).tw.
23. exp proliferating cell nuclear antigen/
24. pena.tw.
25. (proliferat$ adj2 marker$).tw.
26. Neoplasm Invasiveness/
27. perineural invasion.tw.
28. (invas$ adj3 (vascul$ or space or capsul$ or micovascul$)).tw.
29. seminal vesicle involv$.tw.
30. capsular penetration.tw.
31. extraprostatic extension$.tw.
32. (margin$ adj3 (surg$ or positiv$ or negativ$ or extens$)).tw.
33. or/6-32

34. 5 and 33
35. exp survival analysis/
36. exp disease progression/
37. exp neoplasm recurrence, local/
38. exp neoplasm, residual/
39. exp neoplasm metastasis/
40. exp lymphatic metastasis/
41. exp life expectancy/
42. exp treatment outcome/
43. exp treatment failure/
44. exp "outcome assessment (health care)"/
45. exp disease free survival/
46. exp quality of life/
47. ((treatment or process$) adj2 (outcome$ or effect$ or efficac$)).tw.
48. disease$ specific mortality.tw.
49. (lymph$ adj1 involv$).tw.
50. (lymph$ adj3 (status or metastas$ or micrometastas$)).tw.
51. biochemical relaps$.tw.
52. or/35-51
53. 34 and 52

16. Health Economics Literature search details – SEARCH NOT REQUIRED

(SIGN Health Economics filter added to above search)

[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline		
Premedline		
Embase		
Cochrane Library (except NHSEED)		
NHSEED		
Cinahl		
Psycinfo		
BNI		
EconLit		

Web of Science		
ISI Proceedings		

17. Any further comments:

Without filters, results are 7994 in Medline and 12461 in Embase

Due the high volume of results, the search was restricted to systematic reviews only with a timespan of the last five years.

4. Update Searches

Systematic reviews filter, searched with date limit 2005- 2007 and English language only

Database name	No of references found	No of references retrieved	Finish date of search
Medline	233	17	19/06/07
Premedline	5	1	19/06/07
Embase	102	17	19/06/07
Cochrane Library	40	3	19/06/07
Cinahl	6	1	19/06/07
AMED	0	0	19/06/07
BNI	0	0	19/06/07
Psychinfo	20	0	19/06/07
SIGLE	0	0	19/06/07
Web of Science	34	13	19/06/07
Biomed Central	0	0	19/06/07

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer (Update) Clinical Guideline

Chapter 4 – Localised Prostate Cancer **Literature search summary**

Topics 5 and 6: Which men with localised prostate cancer should be offered active surveillance? What is the most effective follow up protocol for men for active surveillance?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2006 -	610 / 143	402 / 21	29/06/2012
Premedline	June 28, 2012	105 / 7	60 / 2	29/06/2012
Embase	2006 -	1280 / 296	759 / 23	29/06/2012
Cochrane Library	2006 -	181	63	29/06/2012
Web of Science (SCI & SSCI)	2006 -	1080	491	29/06/2012
Biomed Central	2006 -	39	0	29/06/2012
PsycINFO	2006 -	32	16	29/06/2012

Total References retrieved (after de-duplication): 976

Medline search strategy *(This search strategy is adapted to each database)*

Active Surveillance Search

1 exp Prostatic Neoplasms/

2 Prostatic Intraepithelial Neoplasia/

3 (prostat$ adj3 (cancer$ or carcinoma$ or adeno$ or malignan$ or tum?r$ or neoplas$ or intraepithelial$)).tw.

4 PIN.tw.

5 1 or 2 or 3 or 4

6 (active adj1 surveillance).tw.

7 (active adj1 monitoring).tw.

8 watchful wait$.tw.

9 (watch$ adj2 wait$).tw.

10 watchful observation.tw.

11 watchful surveillance.tw.

12 watchful monitoring.tw.

13 active surveillance.tw.

14 active monitoring.tw.

15 expectant manag$.tw.

16 expectant monitoring.tw.

17 expectant surveillance.tw.

18 deferred treatment$.tw.

19 deferred therap$.tw.

20 delayed treatment$.tw.

21 delayed therap$.tw.

22 conservative monitoring.tw.

23 Watchful waiting/

24 or/6-23

25 5 and 24

26. limit 25 to yr="2006 -Current"

Prognostic Search

1. prostatic neoplasms/

2. (prostat$adj5 (cancer$ or carcin$ or tumor$ or tumour$ or neoplasm$)).tw.

3. ((carcinoma or neoplasia or neoplasm$ or adenocarcinoma or cancer$ or tumor$ or tumour$ or malignan$) adj3 prostat$).tw.

4. 1 or 2 or 3

5. prognostic methods.mp.

6. predictive factors.mp.

7. (prognos$ adj10 (relapse$ or recurrence$ or survival$ or death$ or mortality or progress$ or disease free or psa failure$ or biochemical failure$)).ti,ab.

8. (predict$ adj10 (relapse$ or recurrence$ or survival$ or death$ or mortality or progress$ or disease free or psa failure$ or biochemical failure$)).ti,ab.

9. (neural network$ adj10 (relapse$ or recurrence$ or survival$ or death$ or mortality or progress$ or disease free or psa failure$ or biochemical failure$)).ti,ab.

10. survival rate/

11. exp prognosis/and (relapse$ or recurrence$ or survival$ or death$ or mortality or progress$ or disease free or psa failure$ or biochemical failure$).ti,ab.

12. disease free survival/

13. mortality/

14. recurrence/

15. neural networks computer/and (relapse$ or recurrence$ or survival$ or death$ or mortality or progress$ or disease free or psa failure$ or biochemical failure$).ti,ab.

16. exp models statistical/and (relapse$ or recurrence$ or survival$ or death$ or mortality or progress$ or disease free or psa failure$ or biochemical failure$).ti,ab.

17. algorithms/and (relapse$ or recurrence$ or survival$ or death$ or mortality or progress$ or disease free or psa failure$ or biochemical failure$).ti,ab.

18. (algorithm$ adj10 (relapse$ or recurrence$ or survival$ or death$ or mortality or progress$ or disease free or psa failure$ or biochemical failure$)).ti,ab.

19. exp survival analysis/

20. nomogram$.mp.

21. ((marker$ or biomarker$) adj10 (prognos$ or predict$)).mp.

22. or/5–21

23. letter.pt.

24. comment.pt.

25. (animal or cell line$ or vitro or invitro or rat or rats or mouse or mice).ti,ab.

26. or/23–25

27. (4 and 22) not 26

28. limit 27 to yr="2006 -Current"

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on prostate cancer.

3. Any further comments

Cinahl, BNI, AMED were checked and no unique references were found.
Basic Active Surveillance search, for Topic 6 requirements, update topic so searched from 2006 onwards with basic exclusions filter only used.
Prognostic search, for Topic 5 requirements, with systematic reviews filter executed in Medline and Embase only.
Update of the following HTA Report from 2006 onwards:
Sutcliffe, P. et al. Use of classical and novel biomarkers as prognostic risk factors for localised prostate cancer: a systematic review. Health Technology Assessment 2009; 13 (5)

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2012 on-wards.

Database name	No of references found	No of references re-trieved	Finish date of search
Medline	301 / 81	48 / 1	20/05/2013
Premedline (17 May, 2013)	144 / 8	71 / 2	20/05/2013
Embase	588 / 155	174 / 4	20/05/2013
Cochrane Library	51	5	20/05/2013
PsycINFO	9	2	20/05/2013
Web of Science (SCI & SSCI)	329	77	20/03/2013
Biomed Central	22	0	20/05/2013

Total References retrieved (after de-duplication): 234

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer **Clinical Guideline**	**Literature search summary**

Question title: Effectiveness of radical prostatectomy

Question no: topic 5

18. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1966-current	1613	371	02/03/06
Premedline	All	9	3	02/03/06
Embase	1980 - current	795	133	03/03/06
Cochrane Library	All dates	440	88	10/03/06
Cinahl	All	44	10	02/03/06
BNI	All	4	1	15/03/06
Psycinfo	1967 - current	32	5	15/03/06
HMIC		5	4	15/03/06
SIGLE	All	0	0	15/03/06
International Pharmaceutical Abstracts	All	23	6	15/03/06
Web of Science (SCI & SSCI)	All	1108	119	14/03/06
ISI Proceedings	All	35	3	14/03/06
Biomed Central	All	47	0	16/03/06
Current Controlled Trials	All	106	9	16/03/06
National Research Register	All	124	18	15/03/06
Research Findings Register	All	8	1	15/03/06

Total References retrieved (after de-duplication):

Medline search strategy *(This search strategy is adapted to each database.)*

Prostate Cancer AND Radical Prostatectomy AND (Systematic Reviews OR RCTs) filters

1 Prostatectomy/

2 prostatectom$.tw.

3 resection.tw.

4 or/1-3

5 (radical or complete$ or total or en bloc).tw.

6 5 and 4

7 (LRP or TLRP or RALRP or RAP or RRP or RPP or EERP).tw.

8 heilbronn technique.tw.

9 7 or 8

10 6 or 9

11 exp Prostatic Neoplasms/

12 Prostatic Intraepithelial Neoplasia/

13 pin.tw.

14 (eoplasm$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or eoplasm$ or intraepithelial$ or adeno$)).tw.

15 or/11-14

16 10 and 15

19. Health Economics Literature search details

(SIGN Health Economics filter added to above search)

[SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline	251	02/03/06
Premedline	2	02/03/06
Embase	238	03/03/06
Cochrane Library (except NHSEED)	6	10/03/06
NHSEED	36	10/03/06
Cinahl	51	02/03/06
Psycinfo	3	15/03/06
BNI	0	15/03/06
HMIC	1	15/03/06
International Pharmaceutical Abstracts	6	15/03/06
EconLit	0	15/03/06
Web of Science (SCI & SSCI)	154	13/03/06
ISI Proceedings	3	13/03/06
SIGLE	4	13/03/06

20. Any further comments:

Original search strategy, which included index and free text surgery terms, generated over 5000 hits (with filters on), so a simplified ‘radical prostatectomy’ only search strategy had to be used.

Removed ‘radical’ terms from health economics search in order to maximise sensitivity of retrieval

Sifting Criteria:

Trans-Urethral Prostatectomy (TURP) excluded in sifts.

Articles discussing other treatments after or before radical prostatectomies have been excluded in sift.

Articles discussing prostatectomy pathology and specimens excluded.

Both monotherapies and comparison to all other therapies (e.g. hormone therapy) included.

21. Update searches:

Search limited to 2005-2007 date range with SR & RCT filters applied.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	342	47	04/07/07
Premedline	18	4	04/07/07
Embase	289	87	09/07/07
Cochrane Library	151	13	10/07/07
Cinahl	15	2	04/07/07
Amed	0	0	04/07/07
BNI	0	0	04/07/07
Psychinfo	17	0	04/07/07
SIGLE	0	0	04/07/07
Web of Science (SCI & SSCI)	402	42	10/07/07

Health Economics Update searches

Database name	No of references found	Finish date of search
Medline	35	11/07/07
Premedline	3	11/07/07
Embase	43	11/07/07
Cochrane Library (except NHSEED)	1	10/07/07
NHSEED	11	10/07/07
Cinahl	5	11/07/07
Psycinfo	0	11/07/07
BNI	0	11/07/07
HMIC	0	11/07/07
EconLit	1	11/07/07
Web of Science (SCI & SSCI)	103	11/07/07
SIGLE	0	11/07/07

Topic 7: Which is the most effective radical prostatectomy method for prostate cancer: retropubic, transperineal, laparoscopic or robot-assisted laparoscopic radical prostatectomy?

1. Literature search details

Database name	Dates Covered	No of references found	Finish date of search
Medline	2010 -	627	10/12/2012
Premedline	All	60	10/12/2012
Embase	2010 -	1392	10/12/2012
Cochrane Library	2010	65	10/12/2012
Web of Science (SCI & SSCI)	2010 -	226	10/12/2012
BIOSIS	2010	252	10/12/2012

Total References retrieved (after de-duplication and sifting): 1220

Medline search strategy *(This search strategy is adapted to each database)*

1. exp Prostatic Neoplasms/su
2. Prostatectomy/
3. (radical adj5 prostatectom$).tw.
4. or/1-3
5. Prostatic Neoplasms/
6. (cancer adj3 (prostate or prostatic)).tw.
7. (carcinoma adj (prostate or prostatic)).tw.
8. (neoplas$ adj3 (prostate or prostatic)).tw.
9. (malignan$ adj3 (prostate or prostatic)).tw.
10. or/5-9
11. Surgical Procedures, Operative/
12. su.fs.
13. (surgery or surgical or surgeon$).tw.
14. (resect$ or operation$ or operat$).tw.
15. or/11-14
16. 10 and 15
17. 4 or 16
18. Laparoscopy/
19. Endoscopy/
20. Video-Assisted Surgery/
21. Surgical Procedures, Minimally Invasive/

22. laparoscop$.tw.
23. endoscop$.tw.
24. (minimal$ adj3 (invasiv$ or access$)).tw.
25. (key hole or keyhole or robot$).tw.
26. video assist$.tw.
27. (trans peritoneal or transperitoneal or extra peritoneal).tw.
28. (montsouris or heilbronn).tw.
29. (da vinci or zeus).tw.
30. or/18-29
31. 17 and 30
32. meta analysis.pt.
33. review.pt.
34. Meta Analysis/
35. exp "Review Literature as Topic"/
36. Randomized Controlled Trial/
37. (controlled or design or evidence or extraction).ab.
38. (sources or studies).ab.
39. or/32-38
40. exp Clinical Trial/
41. randomized controlled trial.pt.
42. controlled clinical trial.pt.
43. randomi?ed.ab.
44. placebo.ab.
45. drug therapy.fs.
46. randomly.ab.
47. trial.ab.
48. groups.ab.
49. or/40-48
50. Comparative Study/
51. Follow-Up Studies/
52. Time Factors/
53. (preoperat$ or pre operat$).mp.
54. (chang$ or evaluat$ or reviewed or baseline).tw.
55. (prospective$ or retrospectiv$).tw.
56. (cohort$ or case series).tw.
57. (compare$ or compara$).tw.

58. or/50-57

59. 31 and (39 or 49 or 58)

60. animals/ not (humans/ and animals/)

61. 59 not 60

62. limit 61 to ed=20100901-20121210

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on prostate cancer.

3. Any further comments

Undertook an update of the following HTA Report from October 2010 onwards:
Ramsey, C. et al Systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of laparoscopic surgery and robotic surgery for removal of the prostate in men with localised prostate cancer Health Technology Assessment 2012; 16 (41)

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 10/12/2012 onwards.

Database name	No of references found	No of references re-trieved	Finish date of search
Medline	94	49	14/05/2013
Premedline	6	3	14/05/2013
Embase	182	81	14/05/2013
Cochrane Library	7	2	14/05/2013
Web of Science (SCI & SSCI)	45	13	14/05/2013
BIOSIS	147	53	14/05/2013

Total References retrieved (after de-duplication): 100

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer **Clinical Guideline**	**Literature search summary**

Question title: Effectiveness of conventional radiotherapy

Question no: topic 5

22. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1966-current	904	904	06/03/06
Premedline	All	4	4	06/03/06
Embase	1980 - current	580	580	07/03/06
Cochrane Library	All dates	82	82	06/03/06
Cinahl	All	23	23	07/03/06
BNI	All	0	0	07/03/06
Psychinfo	1967 - current	0	0	07/03/06
SIGLE	All	0	0	07/03/06
International Pharmaceutical Abstracts	All	5	5	07/03/06
Web of Science (SCI & SSCI)	All	620	620	07/03/06
ISI Proceedings	All	120	120	07/03/06
Biomed Central	All	8	0	09/03/06
Current Controlled Trials	All	13	4	09/03/06
National Research Register	All	290	96	08/03/06
Research Findings Register	All	1	1	09/03/06

Total References retrieved (after de-duplication): 1710

Medline search strategy *(This search strategy is adapted to each database.)*

Prostate Cancer AND Conventional Radiotherapy AND (Systematic Reviews OR RCTs) filters

1 *Radiotherapy/
2 radiotherap$.tw.
3 radiation treatment$.tw.
4 radiation therap$.tw.
5 irradiation.tw.
6 Radiotherapy, adjuvant/

7 (radio$ isotop$ adj2 (therap$ or treatment$)).tw.
8 (hyperfractionated adj2 radiation).tw.
9 (fractionated adj2 radiation).tw.
10 (Radionuclide$ adj2 (therap$ or treatment$)).tw.
11 RT.tw.
12 (radical or standard$ or conventional or curative).tw.
13 or/1-11
14 12 and 13
15 exp Prostatic Neoplasms/
16 Prostatic Intraepithelial Neoplasia/
17 pin.tw.
18 (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.
19 or/14-18
19 14 and 19

23. Health Economics Literature search details

(SIGN Health Economics filter added to above search)
[SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline	116	07/03/06
Premedline	1	07/03/06
Embase	169	07/03/06
Cochrane Library (except NHSEED)	15	09/03/06
NHSEED	7	09/03/06
Cinahl	22	07/03/06
Psycinfo	0	07/03/06
BNI	0	07/03/06
EconLit	0	09/03/06
Web of Science (SCI & SSCI)	78	09/03/06
ISI Proceedings	13	09/03/06
SIGLE	0	07/03/06

24. Any further comments:

Original search strategy, a full and detailed strategy covering most types of radiotherapy, generated a high volume of hits (with filters on). After discussion with Angela M and Fergus, a simplified 'conventional radiotherapy' search strategy (above) was used.

Sifting Criteria:

After deduplication of the database, volunteer GDG members did the sifting. Angela M has a record of the inclusion/exclusion criteria sent.

25. Update search

Search limited to 2005-2007 date range with SR & RCT filters applied.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	215	42	02/07/07
Premedline	10	4	02/07/07
Embase	282	51	02/07/07
Cochrane Library	67	15	02/07/07
Cinahl	17	5	02/07/07
Amed	4	1	02/07/07
BNI	0	0	02/07/07
Psychinfo	0	0	02/07/07
SIGLE	0	0	02/07/07
Web of Science (SCI & SSCI)	248	21	02/07/07

Health Economics Update searches

Database name	No of references found	Finish date of search
Medline	11	10/07/07
Premedline	0	10/07/07
Embase	21	10/07/07
Cochrane Library (except NHSEED)	5	10/07/07
NHSEED	5	10/07/07
Cinahl	1	10/07/07
Psycinfo	0	10/07/07
BNI	0	10/07/07
HMIC	0	10/07/07
EconLit	0	11/07/07
Web of Science (SCI & SSCI)	82	11/07/07
SIGLE	0	11/07/07

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer Clinical Guideline **Literature search summary**

Question title: Effectiveness of Conformal Radiotherapy

Question no: Topic 5

26. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1966-current	402	181	20/03/06
Premedline	All	2	2	20/03/06
Embase	1980 - current	189	93	20/03/06
Cochrane Library	All dates	115	55	22/03/06
Cinahl	All	10	7	20/03/06
BNI	All	0	0	20/03/06
Psychinfo	1967 - current	1	1	20/03/06
SIGLE	All	0	0	22/03/06
International Pharmaceutical Abstracts	All	9	5	23/03/06
Web of Science (SCI & SSCI)	All	313	85	21/03/06
ISI Proceedings	All	60	23	21/03/06
Biomed Central	All	5	1	23/03/06
Current Controlled Trials	All	8	3	23/03/06
National Research Register	All	62	45	23/03/06
Research Findings Register	All	1	1	23/03/06

Total References retrieved (after de-duplication): 345

Medline search strategy *(This search strategy is adapted to each database.)*

Prostate Cancer AND Conformal Radiotherapy AND (Systematic Reviews or RCTs) filters

1 exp Radiotherapy, conformal/
2 conformal radiation therap$.tw.
3 conformal radiation treatment$.tw.
4 conformal radiotherap$.tw.
5 exp Radiotherapy, Computer-Assisted/

6 exp Radiotherapy Planning, computer-assisted/
7 intensity modulated radiotherap$.tw.
8 IMRT.tw.
9 CRT.tw.
10 3DCRT.tw.
11 multileaf.tw.
12 MLC.tw.
13 EPID.tw.
14 electronic portal imaging.tw.
15 or/1-14
16 exp Prostatic Neoplasms/
17 Prostatic Intraepithelial Neoplasia/
18 pin.tw.
19 (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.
20 or/16-19
21 15 and 20

27. Health Economics Literature search details

(SIGN Health Economics filter added to above search)
[SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline	46	22/03/06
Premedline	0	22/03/06
Embase	40	22/03/06
Cochrane Library (except NHSEED)	18	22/03/06
NHSEED	9	22/03/06
Cinahl	5	22/03/06
Psycinfo	0	22/03/06
BNI	0	22/03/06
EconLit	0	23/03/06
Web of Science (SCI & SSCI)	64	21/03/06
ISI Proceedings	14	21/03/06
SIGLE	0	23/03/06
International Pharmaceutical Abstracts	0	23/03/06

28. Any further comments:

Sifting Criteria:

Animal studies excluded.

Included dose and volume studies

29. Update Search

Limited to date range 2005-2007, with SR and RCT filters applied

Database name	No of references found	No of references re-trieved	Finish date of search
Medline	128	43	27/06/07
Premedline	4	3	27/06/07
Embase	78	32	27/06/07
Cochrane Library	28	12	27/06/07
Cinahl	6	1	27/06/07
Psycinfo	0	0	27/06/07
Amed	0	0	27/06/07
BNI	0	0	27/06/07
Web of Science (SCI & SSCI)	78	28	27/06/07
SIGLE	0	0	27/06/07

Health Economics Update searches

Database name	No of references found	Finish date of search
Medline	4	10/07/07
Premedline	0	10/07/07
Embase	13	10/07/07
Cochrane Library (except NHSEED)	1	10/07/07
NHSEED	2	10/07/07
Cinahl	0	10/07/07
Psycinfo	0	10/07/07
BNI	0	10/07/07
HMIC	0	10/07/07
EconLit	0	11/07/07
Web of Science (SCI & SSCI)	20	11/07/07
SIGLE	0	11/07/07

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer Clinical Guideline **Literature search summary**

Question title: Effectiveness of EBRT

Question no: Topic 5

30. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1966-current	648	322	20/02/06
Premedline	All	2	2	20/02/06
Embase	1980 - current	477	199	21/02/06
Cochrane Library	All dates	125	63	23/02/06
Cinahl	All	18	11	20/02/06
BNI	All	0	0	20/02/06
Psychinfo	1967 - current	5	0	20/02/06
SIGLE	All	7	0	23/02/06
International Pharmaceutical Abstracts	All	11	4	24/02/06
Web of Science (SCI & SSCI)	All	403	295	24/02/06
ISI Proceedings	All	74	35	24/02/06
Biomed Central	All	7	0	27/02/06
Current Controlled Trials	All	29	6	27/02/06
National Research Register	All	79	55	27/02/06
Research Findings Register	All	1	0	27/02/06

Total References retrieved (after de-duplication): 678

Medline search strategy *(This search strategy is adapted to each database.)*

Prostate Cancer AND EBRT AND (Systematic Reviews or RCTs) filters

1 external beam radiotherap$.tw.
2 external beam radiation therap$.tw.
3 external beam radiation treatment$.tw.
4 external beam irradiation.tw.
5 external beam therap$.tw.
6 external beam treatment$.tw.

7 EBRT.tw.
8 XRT.tw.
9 Radiotherapy, Conformal/
10 conformal radiotherap$.tw.
11 conformal radiation therap$.tw.
12 conformal radiation treatment$.tw.
13 conformal irradiation.tw.
14 CRT.tw.
15 3DCRT.tw.
16 Radiotherapy, Intensity-Modulated/
17 IMRT.tw.
18 intensity modulated conformal radiotherap$.tw.
19 (intensity modulat$ adj2 radiotherap$).tw.
20 or/1-19
21 exp Prostatic Neoplasms/
22 Prostatic Intraepithelial Neoplasia/
23 pin.tw.
24 (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.
25 or/21-24
26 20 and 25

31. Health Economics Literature search details

(SIGN Health Economics filter added to above search)
[SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline	76	20/02/06
Premedline	0	20/02/06
Embase	112	23/02/06
Cochrane Library (except NHSEED)	11	23/02/06
NHSEED	4	23/02/06
Cinahl	15	20/02/06
Psycinfo	2	23/02/06
BNI	0	20/02/06
EconLit	0	23/02/06
Web of Science (SCI & SSCI)	86	24/02/06
ISI Proceedings	18	24/02/06

SIGLE	0	23/02/06
ZETOC	5	27/02/06
International Pharmaceutical Abstracts	2	24/02/06
National Research Register	0	27/02/06

32. Any further comments:

Sifting Criteria:

Animal studies excluded.

Included dose, volume and toxicity related references

33. Update search

Search limited to 2005-2007 date range with SR & RCT filters applied.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	185	37	03/07/07
Premedline	6	2	03/0707
Embase	173	30	03/07/07
Cochrane Library	39	23	04/03/07
Cinahl	8	1	03/07/07
Amed	0	0	03/07/07
BNI	0	0	03/07/07
Psychinfo	1	0	03/07/07
SIGLE	0	0	03/07/07
Web of Science (SCI & SSCI)	187	46	04/07/07

Health Economics Update searches

Database name	No of references found	Finish date of search
Medline	2	10/07/07
Premedline	0	10/07/07
Embase	24	10/07/07
Cochrane Library (except NHSEED)	1	10/07/07
NHSEED	2	10/07/07
Cinahl	0	10/07/07
Psycinfo	0	10/07/07
BNI	0	10/07/07
HMIC	0	10/07/07
EconLit	0	11/07/07

Web of Science (SCI & SSCI)	19	11/07/07
SIGLE	0	11/07/07

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer Clinical Guideline **Literature search summary**

Question title: Effectiveness of Brachytherapy

Question no: Topic 5

34. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1966-current	513	232	02/02/06
Premedline	All	1	1	03/02/06
Embase	1980 - current	314	81	03/02/06
Cochrane Library	All dates	85	80	03/02/06
Cinahl	All	25	12	03/02/06
BNI	All	0	0	03/02/06
Psychinfo	1967 - current	2	0	03/02/06
SIGLE	All	1	1	10/02/06
Web of Science (SCI & SSCI)	All	183	113	10/02/06
ISI Proceedings	All	41	33	10/02/06
International Pharmaceutical Abstracts	All	10	1	10/02/06
Biomed Central	All	14	1	14/02/06
Current Controlled Trials	All	32	7	14/02/06
National Research Register	All	21	11	14/02/06
Research Findings Register	All	2	2	09/02/06
ZETOC	All	20	7	13/02/06

Total References retrieved (after de-duplication): 392

Medline search strategy *(This search strategy is adapted to each database.)*

Prostate Cancer AND Brachytherapy AND (Systematic Reviews or RCTs) filters

1 Brachytherapy/

2 brachytherap$.tw.

3 (interstitial adj (irradiation or radiation or radiotherap$)).tw.

4 (intracavity adj (irradiation or radiation or radiotherap$)).tw.

5 surface radiotherap$.tw.

6 curietherap$.tw.

7 (implant$ adj (radiotherap$ or irradiation)).tw.

8 or/1-7

9 exp Prostatic Neoplasms/

10 Prostatic Intraepithelial Neoplasia/

11 pin.tw.

12 (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.

13 or/9-12

14 8 and 13

35. Health Economics Literature search details

(SIGN Health Economics filter added to above search)

[SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline	67	14/02/06
Premedline	0	14/02/06
Embase	96	14/02/06
Cochrane Library (except NHSEED)	19	14/02/06
NHSEED	11	14/02/06
Cinahl	8	14/02/06
Psycinfo	1	14/02/06
BNI	0	14/02/06
EconLit	0	14/02/06
Web of Science (SCI & SSCI)	76	10/02/06
ISI Proceedings	14	10/02/06
SIGLE	0	10/02/06
ZETOC	29	14/02/06
International Pharmaceutical Abstracts	1	10/02/06

36. Any further comments:

Sifting Criteria:

Animal studies excluded.

Excluded were articles that only mentioned brachytherapy in passing, and articles studying a treatment only after brachytherapy.

37. Update Search

Search limited to 2005-2007 date range with SR & RCT filters applied.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	156	34	26/06/07
Premedline	1	0	26/06/07
Embase	152	31	26/06/07
Cochrane Library	34	20	26/06/07
Cinahl	13	1	26/06/07
Amed	0	0	26/06/07
BNI	0	0	26/06/07
Psychinfo	3	0	26/06/07
SIGLE	0	0	26/06/07
Web of Science (SCI & SSCI)	60	18	26/06/07

Health Economics Update searches

Database name	No of references found	Finish date of search
Medline	7	10/07/07
Premedline	1	10/07/07
Embase	26	10/07/07
Cochrane Library (except NHSEED)	4	10/07/07
NHSEED	2	10/07/07
Cinahl	10	10/07/07
Psycinfo	0	10/07/07
BNI	0	10/07/07
HMIC	0	10/07/07
EconLit	0	11/07/07
Web of Science (SCI & SSCI)	17	11/07/07
SIGLE	0	11/07/07

Topic 8: Is the combination of brachytherapy with external beam radiotherapy more effective than either method alone for localised or locally advanced non metastatic prostate cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	716	304	19/09/2012
Premedline	Sept 18, 2012	21	9	19/09/2012
Embase	1974 -	1242	545	21/09/2012
Cochrane Library	As per database	194	105	10/09/2012
Web of Science (SCI & SSCI)	1970 -	1596	367	25/09/2012
Biomed Central	As per database	46	5	24/09/2012

Total References retrieved (after de-duplication): 680

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Prostatic Neoplasms/

2 prostatic intraepithelial neoplasia/

3 PIN.tw.

4 (prostat$ adj3 (cancer$ or carcinoma$ or adeno$ or malignan$ or tum?r$ or neoplas$ or intraepithelial$)).tw.

5 1 or 2 or 3 or 4

6 BRACHYTHERAPY/

7 brachytherap$.tw.

8 ((interstitial or intracavity or implant$) adj (irradiation or radiation$ or radiotherap$)).tw.

9 surface radiotherap$.tw.

10 curietherap$.tw.

11 ((seed$ or permanent$) adj implant$).tw.

12 6 or 7 or 8 or 9 or 10 or 11

13 5 and 12

14 (high adj2 dose adj2 rate$).tw.

15 hdr.tw.

16 (low adj2 dose adj2 rate$).tw.

17 ldr.tw.

18 ((high$ or full$ or supplemental or low$) adj2 dose$).tw.

19 14 or 15 or 16 or 17 or 18

20 13 and 19

2. Health Economics Literature search details

This topic was identified as medium priority and further health economics work was undertaken but no additional searches were required. The health economics search undertaken across the population identified any general health economics papers on prostate cancer.

3. Any further comments

Cinahl, BNI, AMED and PsycINFO were not used for this search as not considered relevant to the topic. No date limit was used as not an exact update from the previous guideline. Basic exclusions filter only used.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2012 on-wards.

Database name	No of references found	No of references re-trieved	Finish date of search
Medline	68	4	16/05/2013
Premedline (15 May, 2013)	51	23	16/05/2013
Embase	313	60	16/05/2013
Cochrane Library	21	3	16/05/2013
Web of Science (SCI & SSCI)	232	42	16/05/2013
Biomed Central	20	4	16/05/2013

Total References retrieved (after de-duplication): 99

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer Clinical Guideline **Literature search summary**

Question title: Effectiveness of High Intensity Focused Ultrasound

Question no: Topic 5

38. Literature search details

Database name	No of references found	No of references retrieved	Finish date of search
Medline	40	30	25/01/06
Premedline	1	1	25/01/06
Embase	23	16	25/01/06
Cochrane Library	10	6	26/01/06
Cinahl	2	1	25/01/06
BNI	0	0	25/01/06
Psychinfo	0	0	25/01/06
SIGLE	0	0	27/01/06
Web of Science (SCI & SSCI)	136	66	27/01/06
ISI Proceedings	2	0	27/01/06
Biomed Central	0	0	08/02/06
Current Controlled Trials	0	0	08/02/06
National Research Register	10	2	08/02/06
ZETOC	75		08/02/06
International Pharmaceutical Abstracts	0	0	27/01/06

Total References retrieved (after de-duplication): 49

Medline search strategy *(This search strategy is adapted to each database.)*

Prostate Cancer AND HIFU AND (Systematic Reviews or RCTs) filters

1 exp Prostatic Neoplasms/

2 Prostatic Intraepithelial Neoplasia/

3 pin.tw.

4 (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.

5 or/1-4

6 Ultrasound, High-Intensity Focused, Transrectal/

7 (high intensity adj2 ultraso$).tw.

8 HIFU.tw.

9 or/6-8

10 5 and 9

39. Health Economics Literature search details

(SIGN Health Economics filter added to above search)

[SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline	3	27/01/06
Premedline	1	27/01/06
Embase	3	27/01/06
Cochrane Library (except NHSEED)	1	08/02/06
NHSEED	0	08/02/06
Cinahl	0	27/01/06
Psycinfo	0	27/01/06
BNI	0	27/01/06
EconLit	0	08/02/06
Web of Science (SCI & SSCI)	3	27/01/06
ISI Proceedings	1	27/01/06
SIGLE	0	27/01/06
ZETOC	2	08/02/06
International Pharmaceutical Abstracts	0	27/01/06

40. Any further comments:

Filters applied to Ovid databases, but not to other databases. These were manually sifted to retrieve systematic reviews and rcts.

Sifting Criteria:

Animal studies excluded

41. Update search

Search limited to 2005-2007 date range with SR & RCT filters applied.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	29	10	03/07/07
Premedline	1	1	03/07/07

Embase	45	10	03/07/07
Cochrane Library	8	4	04/07/07
Cinahl	1	0	03/07/07
Amed	0	0	03/07/07
BNI	0	0	03/07/07
Psychinfo	0	0	03/07/07
SIGLE	0	0	03/07/07
Web of Science (SCI & SSCI)	11	3	04/07/07

Health Economics Update searches

Database name	No of references found	Finish date of search
Medline	1	10/07/07
Premedline	0	10/07/07
Embase	2	10/07/07
Cochrane Library (except NHSEED)	0	10/07/07
NHSEED	0	10/07/07
Cinahl	0	10/07/07
Psycinfo	0	10/07/07
BNI	0	10/07/07
HMIC	0	10/07/07
EconLit	0	11/07/07
Web of Science (SCI & SSCI)	2	11/07/07
SIGLE	0	11/07/07

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer Clinical Guideline **Literature search summary**

Question title: Effectiveness of Cryotherapy

Question no: Topic 5

42. Literature search details

Database name	No of references found	No of references re-trieved	Finish date of search
Medline	156	67	26/01/05
Premedline	0	0	26/01/05
Embase	74	35	09/02/06
Cochrane Library	26	18	09/02/06
Cinahl	5	5	09/02/06
BNI	0	0	09/02/06
Psychinfo	1	0	09/02/06
SIGLE	0	0	27/01/06
Web of Science (SCI & SSCI)	38	18	09/02/06
ISI Proceedings	12	2	27/01/06
Biomed Central	8	1	09/02/06
Current Controlled Trials	17	0	09/02/06
National Research Register	10	4	09/02/06
Research Findings Register	2	2	09/02/06
ZETOC	3	2	09/02/06

Total References retrieved (after de-duplication): 124

Medline search strategy *(This search strategy is adapted to each database.)*

Prostate Cancer AND Cryotherapy AND (Systematic Reviews or RCTs) filters

1 Cryotherapy/
2 Cryosurgery/
3 Hypothermia, Induced/
4 cryoablat$.tw.
5 (cryo$ adj ablat$).tw.
6 cryotreatment$.tw.
7 cryotherap$.tw.

8 cryotherm$.tw.
9 (cryo$ adj surgery).tw.
10 or/1-9
11 ((cryo$ or hypotherm$ or freez$) adj5 prostat$).tw.
12 exp Prostatic Neoplasms/
13 prostatic intraepithelial neoplasia/
14 pin.tw.
15 (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.
16 or/12-15
17 10 and 16
18 11 or 17

43. Health Economics Literature search details

(SIGN Health Economics filter added to above search)
[SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline	7	26/01/06
Premedline	0	26/01/06
Embase	10	27/01/06
Cochrane Library (except NHSEED)	2	09/02/06
NHSEED	1	09/02/06
Cinahl	1	27/01/06
Psycinfo	0	27/01/06
BNI	0	27/01/06
EconLit	0	09/02/06
Web of Science (SCI & SSCI)	9	09/02/06
ISI Proceedings	2	09/02/06
SIGLE	0	27/01/06
ZETOC	0	09/02/06
International Pharmaceutical Abstracts	2	27/01/06

44. Any further comments:

Sifting Criteria:

Animal studies excluded.

45. Update searches

Search limited to 2005-2007 date range with SR & RCT filters applied.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	45	28	02/07/07
Premedline	0	0	02/07/07
Embase	38	15	03/07/07
Cochrane Library	11	5	03/07/07
Cinahl	3	0	02/07/07
Amed	0	0	02/07/07
BNI	0	0	02/07/07
Psychinfo	0	0	02/07/07
SIGLE	0	0	02/0707
Web of Science (SCI & SSCI)	11	5	03/07/07

Health Economics Update searches

Database name	No of references found	Finish date of search
Medline	1	10/07/07
Premedline	0	10/07/07
Embase	6	10/07/07
Cochrane Library (except NHSEED)	1	10/07/07
NHSEED	0	10/07/07
Cinahl	1	10/07/07
Psycinfo	0	10/07/07
BNI	0	10/07/07
HMIC	0	11/07/07
EconLit	0	11/07/07
Web of Science (SCI & SSCI)	5	11/07/07
SIGLE	0	11/07/07

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer Clinical Guideline **Literature search summary**

Question title: Effectiveness of Watchful Waiting

Question no: Topic 5

46. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1966-current	215	128	06/02/06
Premedline	All	4	4	06/02/06
Embase	1980 - current	128	70	14/02/06
Cochrane Library	All dates	52	8	15/02/06
Cinahl	All	17	10	06/02/06
BNI	All	3	3	06/02/06
Psychinfo	1967 - current	8	4	06/02/06
SIGLE	All	0	0	15/02/06
International Pharmaceutical Abstracts	All	11	3	15/02/06
Web of Science (SCI & SSCI)	All	105	37	15/02/06
ISI Proceedings	All	21	11	15/02/06
Biomed Central	All	8	0	17/02/06
Current Controlled Trials	All	8	1	17/02/06
National Research Register	All	66	22	17/02/06
Research Findings Register	All	4	2	09/02/06
ZETOC	All	2	2	17/02/06

Total References retrieved (after de-duplication): 212

Medline search strategy *(This search strategy is adapted to each database.)*

Prostate Cancer AND Watchful Waiting AND (Systematic Reviews or RCTs) filters

1. watchful wait$.tw.
2. (watch$ adj2 wait$).tw.
3. watchful observation.tw.
4. watchful surveillance.tw.
5. watchful monitoring.tw.

6. active surveillance.tw.
7. active monitoring.tw.
8. expectant manag$.tw.
9. expectant monitoring.tw.
10. expectant surveillance.tw.
11. deferred treatment$.tw.
12. deferred therap$.tw.
13. delayed treatment$.tw.
14. delayed therap$.tw.
15. conservative monitoring.tw.
16. or/1-15
17. exp Prostatic Neoplasms/
18. Prostatic Intraepithelial Neoplasia/
19. pin.tw.
20. (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.
21. or/17-20
22. 16 and 21

47. Health Economics Literature search details

(SIGN Health Economics filter added to above search)
[SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline	43	14/02/06
Premedline	1	14/02/06
Embase	54	14/02/06
Cochrane Library (except NHSEED)	7	15/02/06
NHSEED	7	15/02/06
Cinahl	7	17/02/06
Psycinfo	1	17/02/06
BNI	0	17/02/06
EconLit	1	17/02/06
Web of Science (SCI & SSCI)	3	15/02/06
ISI Proceedings	7	15/02/06
SIGLE	0	15/02/06
ZETOC	3	17/02/06
International Pharmaceutical Abstracts	2	15/02/06

National Research Register	7	17/02/06

48. Any further comments:

Sifting Criteria:

Animal studies excluded.

Other forms of monitoring included, e.g. active surveillance, to increase sensitivity of search and capture other literature that may be of relevance.

49. Update searches:

Search limited to 2005-2007 date range with SR & RCT filters applied.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	72	21	04/07/07
Premedline	2	0	04/07/07
Embase	49	26	09/07/07
Cochrane Library	14	5	09/07/07
Cinahl	7	4	04/07/07
Amed	0	0	04/07/07
BNI	0	0	04/07/07
Psychinfo	1	0	04/07/07
SIGLE	0	0	04/07/07
Web of Science (SCI & SSCI)	20	7	09/07/07

Health Economics Update searches

Database name	No of references found	Finish date of search
Medline	4	11/07/07
Premedline	0	11/07/07
Embase	4	11/07/07
Cochrane Library (except NHSEED)	1	11/07/07
NHSEED	0	11/07/07
Cinahl	4	11/07/07
Psycinfo	0	11/07/07
BNI	0	11/07/07
HMIC	0	11/0707
EconLit	0	11/07/07
Web of Science (SCI & SSCI)	7	11/07/07

SIGLE	0	11/07/07

Topic 11a: What is the most effective intervention for bowel toxicity following radical radiotherapy for prostate cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2005 -	619	48	08/05/2012
Premedline	May 7, 2012	17	2	08/05/2012
Embase	2005 -	698	82	10/05/2012
Cochrane Library	2005 -	698	61	09/05/2012
Web of Science (SCI & SSCI)	2005 -	1622	102	11/05/2012

Total References retrieved (after de-duplication): 195

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Prostatic Neoplasms/
2 Prostatic Intraepithelial Neoplasia/
3 (prostat$ adj3 (cancer$ or carcinoma$ or adeno$ or malignan$ or tum?r$ or neoplas$ or intraepithelial$)).tw.
4 PIN.tw.
5 1 or 2 or 3 or 4
6 exp Radiation Effects/
7 exp Radiation Injuries/
8 (radi$ adj (induce$ or relate$ or toxic$ or injur$ or effect$)).mp
9 (pelvi$ adj3 radiotherap$).mp
10 (pelvi$ adj3 radiation therapy).mp
11 Pelvic Neoplasms/rt [Radiotherapy]
12 or/6-11
13 Diarrhea/
14 diarrh?ea.mp
15 Steatorrhea/
16 steatorrh$.mp
17 ((gastrointestinal or intestinal) adj (toxicity or problem$ or symptom$ or dysfunction$ or complication$)).mp
18 (GI adj toxicity).mp
19 (rect$ adj pain).mp
20 (rect$ adj bleed$).mp
21 (gastrointestinal adj bleed$).mp
22 anorectal dysfunction.mp

23 (bowel adj (damage or toxicity or injury or discomfort)).mp
24 or/13-23
25 (radiation induced fibrosis or RIF).mp
26 (radiation adj (gastritis or proctitis or enteritis or colitis)).mp
27 proctopathy.mp
28 proctosigmoiditis.mp
29 exp Proctitis/
30 or/25-29
31 prostat$.mp
32 30 and 31
33 exp Diet/
34 exercise movement techniques/ or exercise therapy/
35 Sucralfate/
36 (sucralfate or carafate).mp.
37 exp Antidiarrheals/
38 Loperamide/
39 (loperamide or diamode or diar-aid or imodium or imotil).mp.
40 Diphenoxylate/
41 (colonaid or lomotil or lomanate or logen or lonox).mp.
42 exp Aminosalicylic Acids/
43 Sulfasalazine/
44 (sulfasalazine or azulfidine).mp.
45 (Asacol or Asacol HD or Pentasa or Salofalk or Dipentum or Colazal or Apriso or Lialda).mp.
46 Octreotide/
47 (octreotide or sandostatin).mp.
48 Formalin.mp. or Formaldehyde/
49 Misoprostol/
50 (misoprostol or cytotec).mp.
51 Butyrates/
52 butyrate.mp.
53 YAG laser.mp. or Lasers, Solid-State/
54 Hyperbaric oxygen therapy.mp. or Hyperbaric Oxygenation/
55 Codeine/
56 codeine.tw.
57 diet$.tw.
58 or/33-57

59 5 and (12 or 24)

60 12 and 24

61 12 and 30

62 5 and 58

63 12 and 58

64 12 and 24 and 58

65 30 and 58

66 or/59-65

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on prostate cancer.

3. Any further comments

Cinahl, BNI, AMED were not used for this search as not considered relevant to the topic. PsycINFO was checked and no unique references were found. Update topic so searched from 2005 onwards. Basic exclusions filter and Systematic Reviews and RCT filters were used as an intervention topic.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2012 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	206	12	14/05/2013
Premedline (13 May, 2013)	45	7	14/05/2013
Embase	235	21	14/05/2013
Cochrane Library	203	10	14/05/2013
Web of Science (SCI & SSCI)	889	17	14/05/2013

Total References retrieved (after de-duplication): 47

Topic 11b: What is the diagnostic yield of screening sigmoidoscopy in the detection of radiation induced bowel cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	480	45	26/04/2012
Premedline	Apr 20, 2012	13	2	26/04/2012
Embase	1974 -	797	56	26/04/2012
Cochrane Library	As per database	82	7	26/04/2012
Web of Science (SCI & SSCI)	1970 -	455	43	27/04/2012
Biomed Central	As per database	8	0	27/04/2012
PsycINFO	1806 -	12	1	26/04/2012

Total References retrieved (after de-duplication): 156

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Prostatic Neoplasms/

2 Prostatic Intraepithelial Neoplasia/

3 PIN.tw.

4 (prostat$ adj3 (cancer$ or carcinoma$ or adeno$ or malignan$ or tum?r$ or neoplas$ or intraepithelial$)).tw.

5 or/1-4

6 exp Sigmoidoscopy/

7 sigmoidoscop$.mp.

8 proctosigmoidoscop$.mp.

9 rectosigmoidoscop$.mp.

10 6 or 7 or 8 or 9

11 exp Colorectal Neoplasms/

12 ((colorect$ or colo rect$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.

13 ((colon or colonic) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.

14 ((rectal$ or rectum$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.

15 11 or 12 or 13 or 14

16 5 and 15

17 Neoplasms, Radiation-Induced/

18 radiotherap$.tw.

19 ((irradiation or radiation) adj (therap$ or treatment$)).tw.

20 ((pelvis or pelvic) adj3 (irradiation or radiation or radiotherap$)).tw.

21 (prostat$ adj3 (irradiation or radiotherap$ or radiation)).tw.

22 exp Radiotherapy/

23 17 or 18 or 19 or 20 or 21 or 22

24 16 and 23

25 5 and 10

26 24 or 25

27 Neoplasms, Second Primary/

28 (second$ adj primar$).ti.

29 27 or 28

30 5 and 23 and 29

31 26 or 30

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on prostate cancer.

3. Any further comments

Cinahl, BNI, AMED were not used for this search as not considered relevant to the topic. No date limit was used as not an exact update from the previous guideline. Basic exclusions filter only used.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2012 on-wards.

Database name	No of references found	No of references re-trieved	Finish date of search
Medline	83	4	14/05/2013
Premedline (13 May, 2013)	16	0	14/05/2013
Embase	296	15	14/05/2013
Cochrane Library	27	0	14/05/2013
PsycINFO	3	0	14/05/2013
Web of Science (SCI & SSCI)	74	3	14/05/2013
Biomed Central	3	0	14/05/2013

Total References retrieved (after de-duplication): 19

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer Clinical Guideline **Literature search summary**

Question title:

What are the interventions for sexual dysfunction (erectile dysfunction, fertility issues etc) for men with prostate cancer?

Question no: Topic 17

50. Literature search details

Database name	No of references found	No of references retrieved	Finish date of search
Medline	580	95	14/03/06
Premedline	11	4	14/03/06
Embase	636	66	14/03/06
EBM Reviews/Cochrane Library	153	22	14/03/06
Cinahl	15	3	14/03/06
BNI	13	7	14/03/06
Psychinfo	75	14	14/03/06
AMED	14	4	14/03/06
SIGLE	8	0	09/03/06
Web of Science (SCI & SSCI)	756	96	14/03/06
Biomed Central	14	3	14/03/06
National Research Register	17	2	09/03/06

Total References retrieved (after de-duplication): 215

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Prostatic Neoplasms/

2 Prostatic Intraepithelial Neoplasia/

3 (pin adj5 prostat$).tw

4 (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw

5 or/1-4

6 exp Sexual Dysfunction, Physiological/

7 Sexual Dysfunctions, Psychological/

8 exp Impotence/

9 exp Dyspareunia/

10 exp Coitus/
11 exp Penile Erection/
12 exp Orgasm/
13 exp Priapism/
14 exp Libido/
15 impoten$.mp.
16 dyspareun$.mp
17 priap$.mp
18 orgasm$.mp
19 libido.mp
20 (erecti$ adj (dysfunct$ or failure)).mp
21 (sex$ adj (dysfunct$ or satisf$ or problem$ or symptom$ or arous$ or activit$ or disorder$)).mp
22 (sex$ adj3 pain$).mp
23 sexual intercourse.mp
24 erect$.mp
25 or/6-24
26 exp Fertility/
27 fertil$.mp
28 26 or 27
29 25 or 28
30 5 and 29

51. Health Economics Literature search details
Not required

52. Any further comments:
Systematic reviews and RCTs filters applied to the search for the clinical review. In terms of sifting the results, no preventative references were included, only treatment of sexual dysfunction as a side effect after the primary treatment for prostate cancer.

53. Update Search
For the update search, the reviewer required only RCT's and so the search was re-executed using a RCT filter, date limit 2005-2007 and English language only.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	50	2	21/05/07
Premedline	1	0	21/05/07
Embase	120	2	21/05/07
Cochrane Library (OVID)	19 (Central & DSR)	1	24/05/07

Cinahl	8	0	21/05/07
BNI	3 (no filter)	0	21/05/07
Psychinfo	1	0	21/05/07
AMED	3 (no filter)	0	21/05/07
SIGLE	0	0	21/05/07
Web of Science	42	3	21/05/07
Biomed Central	15	0	21/05/07

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer Clinical Guideline **Literature search summary**

Question title:

What are the interventions for urinary incontinence following radical surgery or radical radiotherapy for prostate cancer?

Question no: Topic 18

54. Literature search details

Database name	No of references found	No of references retrieved	Finish date of search
Medline	472	126	23/03/06
Premedline	3	1	23/03/06
Embase	335	53	23/03/06
EBM Reviews/Cochrane Library	163	38	23/03/06
Cinahl	21	9	23/03/06
BNI	9	6	23/03/06
Psychinfo	14	1	23/03/06
AMED	10	8	23/03/06
SIGLE	0	0	23/03/06
Web of Science (SCI & SSCI)	441	121	23/03/06
Biomed Central	96	2	23/03/06
National Research Register	34	1 main reference	23/03/06
Research Findings Register	0	0	23/03/06

Total References retrieved (after de-duplication): 270

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Urinary Incontinence/

2 (incontinen$ or continen$).tw

3 1 or 2

4 exp Prostatectomy

5 prostatectom$.mp

6 (TUR or TURP).mp

7 (transurethral adj resection).mp

8 (radical adj surg$).mp
9 (prostat$ adj3 surg$).mp
10 or/4-9
11 exp Prostatic Neoplasms/
12 Prostatic Intraepithelial Neoplasia/
13 (pin adj5 prostat$).tw
14 (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw
15 or/11-14
16 exp Radiotherapy/
17 Brachytherapy/
18 brachytherap$.tw
19 IMBT.tw
20 PPB.tw
21 (interstitial adj (irradiation or radiation)).tw
22 (radiation adj (therap$ or treatment$)).tw
23 (three dimensional adj2 radiotherap$).tw
24 3D radiotherap$.tw
25 3DCRT.tw
26 conformal radiotherap$.tw
27 (conformal adj (irradiation or radiation)).tw
28 CFRT.tw
29 CRT.tw
30 (intensity modulat$ adj2 radiotherap$).tw
31 IMRT.tw
32 (neutron$ adj2 (therap$ or treatment$)).tw
33 external beam radiotherap$.tw
34 external beam RT.tw
35 EBRT.tw
36 high linear energy transfer radiation.tw
37 radiofrequency interstitial tumo$ ablation.tw
38 RITA.tw
39 (radionuclide adj2 (therap$ or treatment$)).tw
40 ultraso$ radiotherap$.tw
41 (particle beam adj2 (therap$ or treatment$)).tw
42 (somatostatin based radioactive tumo$ target$ adj2 (therap$ or treatment$)).tw
43 (proton$ adj2 (therap$ or treatment$)).tw

44 hadrontherap$.tw

45 (radical adj radiotherapy$).tw

46 or/16-45

47 3 and 10

48 3 and 15 and 46

49 47 or 48

55. Health Economics Literature search details

Database name	No of references found	Finish date of search
Medline	75	31/08/06
Premedline	2	31/08/06
Embase	36	31/08/06
Cochrane Library (except NHSEED)	54	31/08/06
NHSEED	16	31/08/06
Cinahl	5	31/08/06
AMED	1	31/08/06
BNI	0	31/08/06
Psycinfo	5	31/08/06
EconLit	0	31/08/06
Web of Science (SCI & SSCI)	28	31/08/06
SIGLE	0	31/08/06

Total References retrieved (after de-duplication): 182

56. Any further comments:
Systematic reviews and RCTs filters applied to basic search for the clinical review. In terms of sifting the results, no preventative references included, only treatment of urinary incontinence as a side effect after the primary treatment for prostate cancer. The health economics literature search was not undertaken at time of initial search as not deemed necessary, but revisited later. SIGN Health Economics filter & SCHARR Quality of Life filter applied to basic search for the health economics review.

57. Update Search
For the update search, the reviewer required only RCT's and so the search was re-executed using a RCT filter, date limit 2005-2007 and English language only.

Database name	No of references found	No of references re-trieved	Finish date of search
Medline	40	4	21/05/07
Premedline	32 (no filter)	5	21/05/07
Embase	159	12	21/05/07

Cochrane Library (OVID)	32 (Central & DSR)	7	24/05/07
Cinahl	8	3	21/05/07
BNI	5 (no filter)	2	21/05/07
Psychinfo	4 (no filter)	0	21/05/07
AMED	2 (no filter)	0	21/05/07
SIGLE	0	0	21/05/07
Web of Science (SCI & SSCI)	88	6	21/05/07
Biomed Central	8	0	21/05/07

An update search was also required for the health economics review and so the search was re-executed as before but with a date limit 2006- 2007 (and removed duplicates from last time search done).

Database name	No of references found	Finish date of search
Medline	7	22/05/07
Premedline	1	22/05/07
Embase	7	22/05/07
Cochrane Library (except NHSEED)	7	14/06/07
NHSEED	0	14/06/07
Cinahl	1	22/05/07
Psycinfo	0	22/05/07
AMED, BNI	0 in each	22/05/07
EconLit	0	22/05/07
Web of Science	4	22/05/07
SIGLE	0	22/05/07

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer **Clinical Guideline** **Literature search summary**

Question title: In men who have received treatment for prostate cancer, what is the most effective follow-up protocol

Question no: 16

58. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline		246	23	14/07/06
Premedline		37	2	18/07/06
Embase		154	21	18/07/06
Cochrane Library		128	0	18/07/06
Cinahl		6	4	18/07/06
BNI		3	1	18/07/06
Psychinfo		4	0	18/07/06
SIGLE		9	0	18/07/06
Web of Science (SCI & SSCI)		799	13	18/07/06
ISI Proceedings		112	2	18/07/06
Biomed Central		107	1	18/07/06
Current Controlled Trials		-	-	
National Research Register		-	-	
ZETOC		-	-	

Total References retrieved (after de-duplication): 56

Medline search strategy *(This search strategy is adapted to each database.)*

Prostate Cancer AND (Radiotherapy OR Prostatectomy) AND Treatment Outcome and Biochemical (Failure OR Relapse) AND Aftercare OR Followup

1 exp Radiotherapy/

2 radiotherap$.tw.

3 (radical adj radiotherap$).tw.

4 (radical or complete$ or total or en bloc).tw.

5 Brachytherapy/

6 brachytherap$.tw.
7 (interstitial adj (irradiation or radiation)).tw.
8 (radiation adj (therap$ or treatment$)).tw.
9 (three dimensional adj2 radiotherap$).tw.
10 3D radiotherap$.tw.
11 3DCRT.tw.
12 external beam radiotherap$.tw.
13 systemic radiotherap$.tw.
14 exp Treatment outcome/
15 curative.tw
16 or/1-15
16 exp Prostatic Neoplasms/
17 prostatic intraepithelial neoplasia/
18 pin.tw.
19 (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.
20 or/16-19
21 exp Prostatectomy/
22 (radical adj3 prostatectomy).mp
23 (remov$ adj3 prostate gland).mp.
24 RRP.tw.
25 (perineal adj prostatectomy).tw.
26 RPP.tw.
27 exp Treatment outcome/
28 curative.tw
29 or/21-28
31 (biochemical adj (relaps$ or fail$)).tw.
32 ((prostate specific antigen$ or PSA) adj (relaps$ or fail$)).tw.
33 ((prostate specific antigen$ or PSA) adj rise$).tw.
34 ((prostate specific antigen$ or PSA) adj recur$).tw.
35 Neoplasm Recurrence, Local/
36 or/31-36
37 Aftercare/
38 aftercare.tw.
39 after-care.tw.
40 followup.tw.
41 follow-up.tw.

42 ((post-treatment or posttreatment) adj1 surveillance).tw.

43 ((post-treatment or posttreatment) adj1 evaluation$).tw.

44 ((post-treatment or posttreatment) adj1 care).tw.

45 ((post-treatment or posttreatment) adj1 monitoring).tw.

46 or/37-45

59. Health Economics Literature search details

(SIGN Health Economics filter added to above search)

[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline		
Premedline		
Embase		
Cochrane Library (except NHSEED)		
NHSEED		
Cinahl		
Psycinfo		
BNI		
EconLit		
Web of Science (SCI & SSCI)		
ISI Proceedings		
SIGLE		
ZETOC		

60. Any further comments:

Sifting Criteria:

Chapter 5: Managing relapse after radical treatment

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer **Clinical Guideline** **Literature search summary**

Question title: What is the clinical importance of biochemical relapse after radical therapy? How should biochemical relapse be defined?

Question no: 7A

61. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline		827	176	26/05/06
Premedline		8	2	07/06/06
Embase		262	72	06/06/06
Cochrane Library		73	5	09/06/06
Cinahl		8	0	06/06/06
BNI		0	0	07/06/06
Psychinfo		0	0	07/06/06
SIGLE		0	0	09/06/06
Web of Science (SCI & SSCI)		77	36	09/06/06
ISI Proceedings		21	8	12/06/06
Biomed Central		121	1	09/06/06
Current Controlled Trials		17	0	12/06/06
National Research Register		5	0	12/06/06
ZETOC		43	7	12/06/06

Total References retrieved (after de-duplication): 266

Medline search strategy *(This search strategy is adapted to each database.)*

Radical treatment (Prostatectomy OR Radiotherapy OR Salvage Therapy OR Orchiectomy) AND (Biochemical relapse AND Prostate cancer)

1 (biochemical adj (relaps$ or fail$)).tw.

2 ((prostate specific antigen$ or PSA) adj rise$).tw.

3 ((prostate specific antigen$ or PSA) adj (relaps$ or fail$)).tw.
4 ((prostate specific antigen$ or PSA) adj recur$).tw.
5 Neoplasm Recurrence, Local/
6 or/1-5

7 exp Prostatic Neoplasms/
8 prostatic intraepithelial neoplasia/
9 pin.tw.
10 (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.
11 or/7-10

12 6 and 11

13 Prostatic Neoplasms/su [Surgery]
14 Prostatic Intraepithelial Neoplasia/su [Surgery]
15 pin.tw.
16 (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.
17 13 or 14
18 15 or 16

19 Prostatectomy/
20 prostatectom$.tw.
21 19 or 20
22 Surgery/
23 (surg$ or operat$ or remov$).tw.
24 22 or 23
25 18 and 24
26 17 or 21 or 25

27 Prostatectomy/
28 prostatectom$.tw.
29 resection.tw.
30 or/27-29
31 (radical or complete$ or total or en bloc).tw.
32 31 and 30
33 (LRP or TLRP or RALRP or RAP or RRP or RPP or EERP).tw.

34 heilbronn technique.tw.
35 33 or 34
36 32 or 35

37 exp Radiotherapy/
38 Radiotherapy, Adjuvant/
39 Brachytherapy/
40 brachytherap$.tw.
41 (interstitial adj (irradiation or radiation)).tw.
42 Radiotherapy, Conformal/
43 (radiation adj (therap$ or treatment$)).tw.
44 (three dimensional adj2 radiotherap$).tw.
45 3D radiotherap$.tw.
46 3DCRT.tw.
47 conformal radiotherap$.tw.
48 CFRT.tw.
49 (intensity modulat$ adj2 radiotherap$).tw.
50 IMRT.tw.
51 (neutron$ adj2 (therap$ or treatment$)).tw.
52 external beam radiotherap$.tw.
53 high linear energy transfer radiation.tw.
54 radiofrequency interstitial tumo$ ablation.tw.
55 RITA.tw.
56 (radionuclide adj2 (therap$ or treatment$)).tw.
57 ultraso$ radiotherap$.tw.
58 (particle beam adj2 (therap$ or treatment$)).tw.
59 (somatostatin based radioactive tumo$ target$ adj2 (therap$ or treatment$)).tw.
60 (proton adj2 (therap$ or treatment$)).tw.
61 hadrontherap$.tw.
62 (thermal adj2 (therap$ or treatment$)).tw.
63 (interstitial microwave$ thermal adj2 (therap$ or treatment$)).tw.
64 (microwave$ adj2 (therap$ or treatment$)).tw.
65 microwave$ hyperthermia.tw.
66 or/37-65

67 Orchiectomy/

68 (orchiectom$ or orchidectom$).tw.
69 castrat$.tw.
70 or/67-69

71 26 or 36 or 66 or 70
72 12 and 71

73 exp Salvage Therapy/
74 salvage.tw.
75 73 or 74
76 71 or 75
77 12 and 76

78 (American Society for therapeutic radiology and oncology).mp.
79 multivariate cox regression analysis.mp.
80 79 and prostate.mp
81 77 or 78 or 80

62. Health Economics Literature search details

(SIGN Health Economics filter added to above search)
[Indicate if SCHARR Quality of Life filter added to above search] yes

Database name	No of references found	Finish date of search
Medline	17	12/06/06
Premedline	0	12/06/06
Embase	8	12/06/06
Cochrane Library (except NHSEED)	6	12/06/06
NHSEED	7	12/06/06
Cinahl	0	12/06/06
Psycinfo	0	12/06/06
BNI	0	12/06/06
EconLit	0	12/06/06
Web of Science (SCI & SSCI)	0	12/06/06
ISI Proceedings	0	12/06/06
SIGLE	0	12/06/06
ZETOC	0	12/06/06

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer **Clinical Guideline** **Literature search summary**

Question title: In men with biochemical relapse following radical treatment for prostate cancer, what staging investigations are effective?

Question no: 7B

63. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline		245	59	19/07/06
Premedline		5	1	19/07/06
Embase		67	17	19/07/06
Cochrane Library		64	2	19/07/06
Cinahl		8	0	19/07/06
BNI		0	0	19/07/06
Psychinfo		0	0	19/07/06
SIGLE		0	0	20/07/06
Web of Science (SCI & SSCI)		366	38	20/07/06
ISI Proceedings		52	3	20/07/06
Biomed Central		48	0	20/07/06
Current Controlled Trials		-	-	
National Research Register		-	-	
ZETOC		-	-	

Total References retrieved (after de-duplication): 101

Medline search strategy *(This search strategy is adapted to each database.)*

Prostate Cancer AND (Radiotherapy OR Prostatectomy) AND Biochemical relapse AND (Biopsy OR MRI OR Bone scan OR Prostascint)

1 (biochemical adj (relaps$ or fail$)).tw.

2 ((prostate specific antigen$ or PSA) adj rise$).tw.

3 ((prostate specific antigen$ or PSA) adj (relaps$ or fail$)).tw.

4 ((prostate specific antigen$ or PSA) adj recur$).tw.

5 Neoplasm Recurrence, Local/

6 or/1-5

7 exp Prostatic Neoplasms/
8 prostatic intraepithelial neoplasia/
9 pin.tw.
10 (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.
11 or/7-10
11 exp Radiotherapy/
12 radiotherap$.tw.
13 (radical adj radiotherap$).tw.
14 (radical or complete$ or total or en bloc).tw.
15 Brachytherapy/
16 brachytherap$.tw.
17 (interstitial adj (irradiation or radiation)).tw.
18 (radiation adj (therap$ or treatment$)).tw.
19 (three dimensional adj2 radiotherap$).tw.
20 3D radiotherap$.tw.
21 3DCRT.tw.
22 external beam radiotherap$.tw.
23 systemic radiotherap$.tw.
24 or/11-23
25 exp Prostatectomy/
26 (radical adj3 prostatectomy).mp
27 (remov$ adj3 prostate gland).mp.
28 RRP.tw.
29 (perineal adj prostatectomy).tw.
30 RPP.tw.
31 or/25-30
32 Prostascint.tw
33 monoclonal antibody scan$
34 Indium-111.tw
35 computeri$ tomographic image$.tw
36 CT scan.tw
37 scintigra$.tw.

38 exp "Bone and Bones"/
39 isotope bone scan.mp.

40 bone$ scan$.tw.

41 bone$ imag$.tw.

42 or/38-41

43. exp magnetic resonance imaging/

45. magnetic resonance.tw.

46. MRI$1.tw.

47. NMR$1.tw.

50. MR imaging.tw.

51. MR scan$.tw.

54. (magnet$ adj3 (scan$ or imaging)).tw.

55. (diffusion adj2 (scan$ or imaging)).tw.

56. (planar adj (scan$ or imaging$)).tw.

57. (planar adj tomogra$).tw.

58. (echoplanar adj (scan$ or imaging)).tw.

61. SPECT$1.tw.

62. FMRI$.tw.

63. (functional adj2 (scan$ or imaging)).tw.

64. or/43-63

64. Health Economics Literature search details

(SIGN Health Economics filter added to above search)

[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline		
Premedline		
Embase		
Cochrane Library (except NHSEED)		
NHSEED		
Cinahl		
Psycinfo		
BNI		
EconLit		
Web of Science (SCI & SSCI)		
ISI Proceedings		
SIGLE		
ZETOC		

65. Any further comments:

Sifting Criteria:

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer **Clinical Guideline** **Literature search summary**

Question title: In men with biochemical relaspe following radical treatment for prostate cancer, what salvage therapies for local recurrence are effective?

Question no: Topic 7c

66. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	249	196	27/03/06
Premedline	All	3	2	27/03/06
Embase	All	136	84	27/03/06
Cochrane Library	All	63	16	29/03/06
Cinahl	All	4	4	27/03/06
BNI	All	0	0	27/03/06
Psychinfo	1967 – current	0	0	27/03/06
SIGLE	All	0	0	29/03/06
Web of Science (SCI & SSCI)	All	235	167	28/03/06
ISI Proceedings	All	35	26	28/03/06
Biomed Central	All	55	0	29/03/06
Current Controlled Trials	All	6	2	30/03/06
National Research Register	All	9	0	30/03/06
Research Findings Register	All	0	0	29/03/06
ZETOC	All	112	40	29/03/06

Total References retrieved (after de-duplication): 365

Medline search strategy *(This search strategy is adapted to each database.)*

Search String: Prostate Cancer AND Biochemical Relapse AND (Prostatectomy OR Radiotherapy OR Cryotherapy OR HIFU OR Surveillance OR Hormone Therapy) AND Salvage Therapy

1 (biochemical adj (relaps$ or fail$)).tw.

2 ((prostate specific antigen$ or PSA) adj (relaps$ or fail$)).tw.

3 ((prostate specific antigen$ or PSA) adj rise$).tw.

4 ((prostate specific antigen$ or PSA) adj recur$).tw.

5 Neoplasm Recurrence, Local/

6 or/1-5

7 exp Prostatic Neoplasms/
8 Prostatic Intraepithelial Neoplasia/
9 pin.tw.
10 (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.
11 or/7-10
12 6 and 11
13 Prostatic Neoplasms/su [Surgery]
14 Prostatic Intraepithelial Neoplasia/su [Surgery]
15 pin.tw.
16 (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.
17 13 or 14
18 15 or 16
19 Prostatectomy/
20 prostatectom$.tw.
21 19 or 20
22 Surgery/
23 (surg$ or operat$ or remov$).tw.
24 22 or 23
25 18 and 24
26 17 or 21 or 25
27 Prostatectomy/
28 prostatectom$.tw.
29 resection.tw.
30 or/27-29
31 (radical or complete$ or total or en bloc).tw.
32 31 and 30
33 (LRP or TLRP or RALRP or RAP or RRP or RPP or EERP).tw.
34 heilbronn technique.tw.
35 33 or 34
36 32 or 35
37 exp radiotherapy/
38 Radiotherapy, Adjuvant/
39 Brachytherapy/
40 brachytherap$.tw.
41 (interstitial adj (irradiation or radiation)).tw.
42 Radiotherapy, Conformal/

43 (radiation adj (therap$ or treatment$)).tw.
44 (three dimensional adj2 radiotherap$).tw.
45 3D radiotherap$.tw.
46 3DCRT.tw.
47 conformal radiotherap$.tw.
48 CFRT.tw.
49 (intensity modulat$ adj2 radiotherap$).tw.
50 IMRT.tw.
51 (neutron$ adj2 (therap$ or treatment$)).tw.
52 external beam radiotherap$.tw.
53 high linear energy transfer radiation.tw.
54 radiofrequency interstitial tumo$ ablation.tw.
55 RITA.tw.
56 (radionuclide adj2 (therap$ or treatment$)).tw.
57 ultraso$ radiotherap$.tw.
58 (particle beam adj2 (therap$ or treatment$)).tw.
59 (somatostatin based radioactive tumo$ target$ adj2 (therap$ or treatment$)).tw.
60 (proton adj2 (therap$ or treatment$)).tw.
61 hadrontherap$.tw.
62 (thermal adj2 (therap$ or treatment$)).tw.
63 (interstitial microwave$ thermal adj2 (therap$ or treatment$)).tw.
64 (microwave$ adj2 (therap$ or treatment$)).tw.
65 microwave$ hyperthermia.tw.
66 or/37-65
67 Cryotherapy/
68 Cryosurgery/
69 Hypothermia, Induced/
70 cryoablat$.tw.
71 (cryo$ adj ablat$).tw.
72 cryotreatment$.tw.
73 cryotherap$.tw.
74 cryotherm$.tw.
75 (cryo$ adj surgery).tw.
76 or/67-75
77 ((cryo$ or hypotherm$ or freez$) adj5 prostat$).tw.
78 Ultrasound, High-Intensity Focused, Transrectal/

79 (high intensity adj2 ultraso$).tw.
80 HIFU.tw.
81 or/78-80
82 watchful wait$.tw.
83 (watch$ adj2 wait$).tw.
84 watchful observation.tw.
85 watchful surveillance.tw.
86 watchful monitoring.tw.
87 active surveillance.tw.
88 active monitoring.tw.
89 expectant manag$.tw.
90 expectant monitoring.tw.
91 expectant surveillance.tw.
92 deferred treatment$.tw.
93 deferred therap$.tw.
94 delayed treatment$.tw.
95 delayed therap$.tw.
96 conservative monitoring.tw.
97 or/82-96
98 exp Antineoplastic Agents, Hormonal/
99 exp Androgen Antagonists/
100 antiandrogen$.tw.
101 ((androgen$ or hormone$) adj3 (ablat$ or block$ or withdraw$ or depriv$ or suppress$)).tw.
102 gonadotrophin releasing hormone analogue$.tw.
103 grha.tw.
104 exp Goserelin/
105 exp Cyproterone/
106 bicalutamide.tw.
107 exp Estrogens/
108 oestrogen$.tw.
109 exp leuprolide/
110 (leuprorelin or enatone or a-43818 or lupon or tap-144).tw.
111 exp Flutamide/
112 niftolid$.tw.
113 zoladex.tw.
114 eulexin.tw.

115 casodex.tw.
116 nilutamide.tw.
117 nilandrone.tw.
118 exp diethylstilbestrol/
119 exp gonadorelin/
120 (luteinizing hormone releasing hormone or LHRH).tw.
121 exp progestins/
122 megastrol.tw.
123 exp finasteride/
124 proscar.tw.
125 Orchiectomy/
126 (orchiectom$ or orchidectom$).tw.
127 castrat$.tw.
128 or/98-127
129 36 or 66 or 76 or 77 or 81 or 97 or 128
130 Salvage Therapy/
131 salvage.tw.
132 130 or 131
133 129 and 132
134 12 and 133

67. Health Economics Literature search details

(SIGN Health Economics filter added to above search)
[SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline	5	28/03/06
Premedline	0	28/03/06
Embase	6	28/03/06
Cochrane Library (except NHSEED)	3	29/03/06
NHSEED	1	29/03/06
Cinahl	1	28/03/06
Psycinfo	0	28/03/06
BNI	0	28/03/06
EconLit	0	29/03/06
Web of Science (SCI & SSCI)	8	28/03/06
ISI Proceedings	1	28/03/06

SIGLE	0	29/03/06
ZETOC	0	30/03/06

68. Any further comments:

Sifting Criteria:

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer (Update) Clinical Guideline

Chapter 6 – Locally Advanced Prostate Cancer **Literature search summary**

Topic 9a and 9b: Which patients with non-metastatic prostate cancer benefit from a combination of hormones and external beam radiotherapy? What is the optimal duration of hormone therapy when combined with external beam radiotherapy?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2006 -	276	80	19/03/2012
Premedline	Mar 16, 2012	11	3	19/03/2012
Embase	2006 -	866	90	19/03/2012
Cochrane Library	2006 -	190	55	19/03/2012
Web of Science (SCI & SSCI)	2006 -	654	101	20/03/2012
Biomed Central	2006 -	9	2	19/03/2012

Total References retrieved (after de-duplication): 215

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Prostatic Neoplasms/

2 Prostatic Intraepithelial Neoplasia/

3 (prostat$ adj3 (cancer$ or carcinoma$ or adeno$ or malignan$ or tum?r$ or neoplas$ or intraepithelial$)).tw.

4 PIN.tw.

5 1 or 2 or 3 or 4

6 exp Radiotherapy/

7 Radiotherapy, Adjuvant/

8 radiotherap$.tw.

9 (radiation adj (therap$ or treatment$)).tw.

10 external beam irradiation.tw.

11 external beam therap*.tw.
12 external beam treatment*.tw.
13 (EBRT or XRT).tw.
14 (CRT or 3DCRT or IMRT).tw.
15 conformal irradiation.tw.
16 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17 5 and 16
18 exp Antineoplastic Agents, Hormonal/
19 exp Androgen Antagonists/
20 antiandrogens.mp.
21 ((androgen$ or hormon$) adj3 (ablat$ or block$ or withdraw$ or depriv$ or supress$)).mp.
22 gonadotrophin releasing hormone analogue$.mp.
23 (luteinizing hormone releasing hormone or LHRH).mp.
24 grha.tw.
25 (zoladex or decapeptide).mp.
26 (eligard or leuprorelin or enatone or a-43818 or lupron or tap-144).mp.
27 exp Gonadotropin-Releasing Hormone/
28 exp Cyproterone/
29 (bicalutamide or casodex).mp.
30 exp Estrogens/
31 oestrogen.mp.
32 exp Flutamide/
33 (niftolid$ or eulexin).mp.
34 (nilutamide or nilandron$).mp.
35 exp Diethylstilbestrol/
36 exp Progestins/
37 exp Finasteride/
38 proscar.mp.
39 adjuvant hormon$ therap$.tw.
40 (neoadjuvant or neo-adjuvant hormon$ therap$).tw.
41 exp Orchiectomy/
42 (orchiectom$ or orchidectom$).tw.
43 or/18-42
44 17 and 43

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on prostate cancer.

3. Any further comments

Cinahl, BNI, AMED were not used for this search as not considered relevant to the topic. PsycINFO was checked and no unique references were found. Update topic so searched from 2006 onwards. Basic exclusions filter and Systematic Reviews and RCT filters were used as an intervention topic.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2012 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	115	22	16/05/2013
Premedline (15 May, 2013)	16	3	16/05/2013
Embase	356	39	16/05/2013
Cochrane Library	73	3	16/05/2013
Web of Science (SCI & SSCI)	290	36	16/05/2013
Biomed Central	6	2	16/05/2013

Total References retrieved (after de-duplication): 70

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer Clinical Guideline **Literature search summary**

Question title:

Bisphosphonates for prostate cancer for the control of pain and reducing skeletal events.

Question no: Topic 11A

69. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2005 onwards	41	29	06/02/2006
Premedline	2005 onwards	8	5	06/02/2006
Embase	2005 onwards	119	51	06/02/2006
Cochrane Library	2005 onwards	33	9	06/02/2006
Cinahl	2005 onwards	3	1	09/02/2006
BNI	2005 onwards	6	3	06/02/2006
Psychinfo	2005 onwards	4	0	06/02/2006
SIGLE	2005 onwards	0	0	06/02/2006
Web of Science (SCI & SSCI)	2005 onwards	69	24	06/02/2006
Biomed Central	2005 onwards	9	0	06/02/2006
Current Controlled Trials	2005 onwards	3	0	06/02/2006
National Research Register	2005 onwards	4	2	06/02/2006

Total References retrieved (after de-duplication): 72

Medline search strategy *(This search strategy is adapted to each database.)*

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. exp randomized controlled trials/
4. exp random allocation/
5. exp double blind method/
6. exp single-blind method/
7. or/1-6
8. animal/ not human/

9. 7 not 8

10. clinical trial.pt.

11. exp clinical trials/

12. (clin$ adj25 trial$).tw.

13. ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).tw.

14. exp placebos/

15. placebo$.tw.

16. random$.tw.

17. exp research design/

18. or/10-17

19. 18 not 8

20. 19 not 9

21. exp Comparative Study/

22. exp evaluation studies/

23. exp follow up studies/

24. exp prospective studies/

25. (control$ or prospectiv$ or volunteer$).tw.

26. or/21-25

27. 26 not 8

28. 26 not (9 or 20)

29. 9 or 20 or 28

30. exp prostate neoplasms/

31. exp prostatic intraepithelial neoplasia/

32. (pin adj5 prostat$).tw.

33. (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelia$ or adeno$)).mp.

34. or/30-33

35. exp bone neoplasms/sc

36. exp neoplasm metastasis/

37. exp "bone and bones"/

38. 36 and 37

39. ((bone$ or skelet$ or osseous or osteo$) adj5 (second$ or metast$ or spread$ or advanc$ or lesion$)).af.

40. or/35,38-39

41. exp prostate/

42. prostat$.af.
43. 41 or 42
44. 40 and 43
45. exp Diphosphonates/
46. exp organophosphorus compounds/
47. exp phosphoric acids/
48. (bisphosphonat$ or diphosphonat$).af.
49. etidron$.af.
50. didron$.af.
51. difosfen.af.
52. osteodidronel.af.
53. osteum.af.
54. "disodium dihydrogen(1-hydroxyethylidene)diphosphonate".af.
55. pamidronate.af.
56. APD.af.
57. aredia.af.
58. "disodium 3-amino-1-hydroxypropylidenebisphosphonate".af.
59. clodronate.af.
60. CL2MDP.af.
61. bonefos.af.
62. loron.af.
63. ascredar.af.
64. lodronat.af.
65. lytos.af.
66. ostac.af.
67. clastoban.af.
68. clasteon.af.
69. difosfonal.af.
70. ossiten.af.
71. mebonat.af.
72. "disodium (dichloromethylene) diphosphonate tetrahydrate".af.
73. tiludron$.af.
74. skelid.af.
75. "disodium dihydrogenfdiphosphonate hemihydrate".af.

76. risedron$.af.
77. actonel.af.
78. "sodium trihydrogen[1-hydroxy-2-(3-pyridyl)ethylidene]diphosphonate".af.
79. alendron$.af.
80. fosamax.af.
81. adronat.af.
82. alendros.af.
83. dronal.af.
84. "aminohydroxybutylidene diphosphonic acid".af.
85. neridron$.af.
86. AHDP.af.
87. "(6-amino-1-hydroxyhexylidene)diphosphonic acid".af.
88. zoledron$.af.
89. zometa.af.
90. ibandron$.af.
91. bondronat.af.
92. "(1-hydroxy-3-[methylpentylamino]propylidene)diphosphonic acid".af.
93. olpadron$.af.
94. OPD.af.
95. "(3-dimethylamino-1-hydroxypropylidene)bisphosphonate".af.
96. incadron.af.
97. YM175.af.
98. YM 175.af.
99. minodron$.af.
100. YM529.af.
101. YM 529.af.
115. or/45-101
116. 34 or 44
117. 29 and 115 and 116

70. Health Economics Literature search details

Database name	No of references found	Finish date of search
Medline	19	14/02/2006
Premedline	0	14/02/2006

Embase	49	14/02/2006
Cochrane Library (except NHSEED)	10	14/02/2006
NHSEED	2	14/02/2006
Cinahl	7	14/02/2006
Psycinfo	5	14/02/2006
BNI	0	14/02/2006
EconLit	0	14/02/2006
Web of Science	27	14/02/2006
SIGLE	0	14/02/2006

71. Any further comments:
This search was executed from 2005 onwards as it was an update of a Cochrane Review [1] which had last been searched March 2005. SIGN Health Economics filter & SCHARR Quality of Life filter applied to basic clinical search and run with no date limit as health economics was not covered in the Cochrane Review.
[1] *KK Yuen, M Shelley, WM Sze, T Wilt, MD Mason Bisphosphonates for advanced prostate cancer (2006)*

72. Update Search
For the update search, the reviewer required only RCT's and so the search was re-executed using a RCT filter, date limit 2005-2007 and English language only.

Database name	No of references found	No of references re-trieved	Finish date of search
Medline	34	9	21/05/07
Premedline	5	1	21/05/07
Embase	154	8	21/05/07
Cochrane Library	19	7	24/05/07
Cinahl	12	2	21/05/07
BNI	4	0	21/05/07
Psychinfo	6	0	21/05/07
SIGLE	0	0	21/05/07
Web of Science (SCI & SSCI)	39	5	21/05/07
Biomed Central	5	0	21/05/07
AMED	7	0	21/05/07

An update search was also required for the health economics review and so the search was re-executed as before but with a date limit 2005-2007 (and removed duplicates from last time search done).

Database name	No of references found	Finish date of search
Medline	5	24/05/07
Premedline	1	24/05/07

Embase	18	24/05/07
Cochrane Library (except NHSEED)	5	19/06/07
NHSEED	0	19/06/07
Cinahl	3	24/05/07
Psycinfo	1	24/05/07
BNI	0	24/05/07
EconLit	0	24/05/07
Web of Science	4	24/05/07
SIGLE	0	24/05/07

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer Clinical Guideline **Literature search summary**

Question title:

Clinical and cost-effectiveness of pelvic radiotherapy in patients receiving radical radiotherapy for prostate cancer?

Question no: Topic 9

73. Literature search details

Database name	No of references found	No of references re-trieved	Finish date of search
Medline	226	89	23/02/06
Premedline	0	0	23/02/06
Embase	150	73	23/02/06
EBM Reviews/Cochrane Library	68	38	23/02/06
Cinahl	3	1	23/02/06
BNI, Psychinfo, AMED	0 in each	0 in each	23/02/06
SIGLE	11	0	23/02/06
Web of Science (SCI & SSCI)	174	43	24/02/06
Biomed Central	25	1	24/02/06
National Research Register	22	4	24/02/06
Research Findings Register	0	0	23/02/06

Total References retrieved (after de-duplication): 156

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Prostatic Neoplasms/
2 Prostatic Intraepithelial Neoplasia/
3 (pin adj5 prostat$).tw.
4 (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.
5 or/1-4
6 exp radiotherapy/
7 Radiotherapy, Adjuvant/
8 Brachytherapy/
9 brachytherap$.tw.
10 IMBT.tw.

11 PPB.tw.
12 (interstitial adj (irradiation or radiation)).tw.
13 Radiotherapy, Conformal/
14 (radiation adj (therap$ or treatment$)).tw.
15 (three dimensional adj2 radiotherap$).tw.
16 3D radiotherap$.tw.
17 3DCRT.tw.
18 conformal radiotherap$.tw.
19 (conformal adj (irradiation or radiation)).tw.
20 CFRT.tw.
21 CRT.tw.
22 (intensity modulat$ adj2 radiotherap$).tw.
23 IMRT.tw.
24 (neutron$ adj2 (therap$ or treatment$)).tw.
25 external beam radiotherap$.tw.
26 external beam RT.tw.
27 EBRT.tw.
28 high linear energy transfer radiation.tw.
29 radiofrequency interstitial tumo$ ablation.tw.
30 RITA.tw.
31 (radionuclide adj2 (therap$ or treatment$)).tw.
32 ultraso$ radiotherap$.tw.
33 (particle beam adj2 (therap$ or treatment$)).tw.
34 (somatostatin based radioactive tumo$ target$ adj2 (therap$ or treatment$)).tw.
35 (proton$ adj2 (therap$ or treatment$)).tw.
36 hadrontherap$.tw.
37 or/6-36
38 WPRT.tw.
39 whole pelvic radiotherap$.tw.
40 38 or 39
41 exp pelvis/
42 (pelvis or pelvic).tw.
43 Pelvic Neoplasms/rt [Radiotherapy]
44 or/41-43
45 44 and 37
46 40 or 45

47 5 and 46

74. Health Economics Literature search details

Database name	No of references found	Finish date of search
Medline	17	22/02/06
Premedline	0	22/02/06
Embase	22	22/02/06
Cochrane Library (except NHSEED)	6	22/02/06
NHSEED	4	22/02/06
Cinahl	0	22/02/06
BNI, Psycinfo, AMED	0	22/02/06
EconLit	0	22/02/06
HMIC	1	22/02/06
Web of Science (SCI & SSCI)	12	22/02/06
ISI Proceedings	1	22/02/06
SIGLE	0	22/02/06

Total References retrieved (after de-duplication): 43

75. Any further comments:
Systematic reviews and RCTs filters were applied to the search for the clinical review. SIGN Health Economics & SCHARR Quality of Life filters were applied to the search for the health economics review.

76. Update Search
For the update search, the reviewer required only RCT's and so the search was re-executed using a RCT filter, date limit 2005-2007 and English language only.

Database name	No of references found	No of references re-trieved	Finish date of search
Medline	19	2	21/05/07
Premedline	7 (no filter)	1	21/05/07
Embase	33	2	21/05/07
Cochrane Library (OVID)	10 (Central & DSR)	0	24/05/07
Cinahl	0	0	21/05/07
BNI, Psychinfo, AMED	0 in each	0	21/05/07
SIGLE	0	0	21/05/07
Web of Science (SCI & SSCI)	9	0	21/05/07
Biomed Central	10	0	21/05/07

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer (Update) Clinical Guideline

Chapter 7 – Hormone Therapy **Literature search summary**

Topic 10: Is intermittent hormone therapy as effective as continuous hormone therapy in men receiving long-term hormonal therapy for prostate cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	678	130	21/05/2012
Premedline	May 18, 2012	23	6	21/05/2012
Embase	1974 -	628	189	21/05/2012
Cochrane Library	As per database	183	47	28/02/2012
Web of Science (SCI & SSCI)	1970 -	731	163	21/05/2012
Biomed Central	As per database	8	1	21/05/2012

Total References retrieved (after de-duplication): 271

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Prostatic Neoplasms/

2 Prostatic Intraepithelial Neoplasia/

3 (prostat$ adj3 (cancer$ or carcinoma$ or adeno$ or malignan$ or tum?r$ or neoplas$ or intraepithelial$)).tw.

4 PIN.tw.

5 1 or 2 or 3 or 4

6 (intermittent adj3 (androgen therap$ or androgen treatment or androgen ablation or androgen deprivation or androgen blockade or androgen suppress$ or anti-androgen)).tw.

7 (intermittent adj3 (hormon$ therap$ or hormon$ treatment or hormon$ ablation or hormon$ deprivation or hormon$ blockade or hormon$ suppress$ or hormonotherap$ or estrogentherap$)).tw.

8 (intermittent adj3 (ADT or HT or AD or PADT or LHRH)).tw.

9 (intermittent adj3 (endocrine therap$ or endocrine treatment)).tw.

10 ((continuous or complete) adj3 (androgen therap$ or androgen treatment or androgen ablation or androgen deprivation or androgen blockade or androgen suppress$ or anti-androgen)).tw.

11 ((continuous or complete) adj3 (hormon$ therap$ or hormon$ treatment or hormon$ ablation or hormon$ depriva-

tion or hormon$ blockade or hormon$ suppress$ or hormonotherap$ or estrogentherap$)).tw.

12 ((continuous or complete) adj3 (ADT or HT or AD or PADT or LHRH)).tw.

13 ((continuous or complete) adj3 (endocrine therap$ or endocrine treatment)).tw.

14 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13

15 exp Androgen Antagonists/

16 antineoplastic agents/ or antineoplastic agents, hormonal/

17 exp Gonadotropin-Releasing Hormone/

18 Drug Administration Schedule/

19 (intermittent adj (dose or dosage or therap$ or treatment or therap$ or schedule or regimen)).tw.

20 ((continuous or complete) adj (dose or dosage or therap$ or treatment or therap$ or schedule or regimen)).tw.

21 15 or 16 or 17

22 18 or 19 or 20

23 21 and 22

24 5 and 14

25 5 and 23

26 24 or 25

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on prostate cancer.

3. Any further comments

Cinahl, BNI, AMED were not used for this search as not considered relevant to the topic. PsycINFO was checked and no unique references were found. No date limit was used as not an exact update from the previous guideline. Basic exclusions filter only used.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2012 on-wards.

Database name	No of references found	No of references re-trieved	Finish date of search
Medline	88	16	14/05/2013
Premedline (13 May, 2013)	31	9	14/05/2013
Embase	143	45	14/05/2013
Cochrane Library	13	2	14/05/2013
Web of Science (SCI & SSCI)	134	34	14/05/2013
Biomed Central	4	0	14/05/2013

Total References retrieved (after de-duplication): 63

Topic 12a: What are the adverse cardiovascular effects of long-term androgen deprivation and how prevalent are they?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	384	95	18/07/2012
Premedline	July 17, 2012	26	13	18/07/2012
Embase	1974 -	736	151	19/07/2012
Cochrane Library	As per database	127	63	18/07/2012
Web of Science (SCI & SSCI)	1970 -	596	109	19/07/2012
Biomed Central	As per database	52	2	19/07/2012

Total References retrieved (after de-duplication): 216

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Prostatic Neoplasms/

2 Prostatic Intraepithelial Neoplasia/

3 (prostat$ adj3 (cancer$ or carcinoma$ or adeno$ or malignan$ or tum?r$ or neoplas$ or intraepithelial$)).tw.

4 PIN.tw.

5 1 or 2 or 3 or 4

6 exp Androgen Antagonists/

7 exp Antineoplastic Agents, Hormonal/

8 Orchiectomy/

9 exp Gonadotropin-Releasing Hormone/

10 ((androgen$ or hormon$ or endocrine) adj3 (therapy or treatment or ablat$ or block$ or withdraw$ or depriv$ or supress$ or effect$)).tw.

11 ADT.tw.

12 orchiectom$.tw.

13 6 or 7 or 8 or 9 or 10 or 11 or 12

14 5 and 13

15 exp Cardiovascular Diseases/

16 exp Thromboembolism/

17 exp Stroke/

18 ((cardiac or cardiovascular) adj3 (disease or mortality or morbidity or events or risk or complications or death)).tw.

19 15 or 16 or 17 or 18

20 14 and 19

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on prostate cancer.

3. Any further comments

No date limit was used as not an exact update from the previous guideline. Basic exclusions filter only used.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2012 on-wards.

Database name	No of references found	No of references re-trieved	Finish date of search
Medline	65	6	14/05/2013
Premedline (13 May, 2013)	31	12	14/05/2013
Embase	173	23	14/05/2013
Cochrane Library	24	0	14/05/2013
Web of Science (SCI & SSCI)	194	17	14/05/2013
Biomed Central	16	1	14/05/2013

Total References retrieved (after de-duplication): 45

Topic 12e: What is the most effective intervention for hot flushes as a result of long term androgen suppression for prostate cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	137	30	10/08/2012
Premedline	Aug 8, 2012	19	4	10/08/2012
Embase	1974 -	529	49	13/08/2012
Cochrane Library	As per database	117	15	10/08/2012
Web of Science (SCI & SSCI)	1970 -	314	71	10/08/2012
Biomed Central	As per database	5	1	10/08/2012
PsycINFO	1806 -	15	5	10/08/2012
AMED	1985 -	4	2	10/08/2012

Total References retrieved (after de-duplication): 93

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Prostatic Neoplasms/

2 Prostatic Intraepithelial Neoplasia/

3 (prostat$ adj3 (cancer$ or carcinoma$ or adeno$ or malignan$ or tum?r$ or neoplas$ or intraepithelial$)).tw.

4 PIN.tw.

5 or/1-4

6 (hot adj2 (flash$ or flush$)).mp.

7 (vasomotor adj4 (symptom$ or response$)).mp.

8 (sweat$ or nightsweat$ or perspir$).ti,ab.

9 exp Vasomotor System/

10 exp Hot Flashes/

11 progestogens.tw.

12 or/6-11

13 5 and 12

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on prostate cancer.

3. Any further comments

No date limit was used as not an exact update from the previous guideline. Basic exclusions filter and Systematic Reviews and RCT filters were used as an intervention topic.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2012 on-wards.

Database name	No of references found	No of references re-trieved	Finish date of search
Medline	20	1	14/05/2013
Premedline (May 13, 2013)	10	0	14/05/2013
Embase	91	2	14/05/2013
Cochrane Library	14	0	14/05/2013
Web of Science (SCI & SSCI)	52	4	14/05/2013
Biomed Central	2	1	14/05/2013
PsycINFO	4	0	14/05/2013
AMED	0	0	14/05/2013

Total References retrieved (after de-duplication): 4

Topic 12b: What are the most effective interventions (singly or in combination) for sexual dysfunction as a result of long term androgen suppression for prostate cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2006 -	212	74	23/07/2012
Premedline	July 20, 2012	8	1	23/07/2012
Embase	2006 -	505	71	23/07/2012
Cochrane Library	2006 -	164	41	23/07/2012
Web of Science (SCI & SSCI)	2006 -	450	68	23/07/2012
Biomed Central	2006 -	6	0	23/07/2012
PsycINFO	2006 -	148	25	23/07/2012
AMED	2006 -	6	0	23/07/2012

Total References retrieved (after de-duplication): 154

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Prostatic Neoplasms/

2 exp Prostatic Intraepithelial Neoplasia/

3 (pin adj5 prostat$).tw.

4 (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.

5 or/1-4

6 exp Sexual Dysfunction, Physiological/

7 Sexual Dysfunctions, Psychological/

8 exp Impotence/

9 exp Dyspareunia/

10 exp Coitus/

11 exp Penile Erection/

12 exp Orgasm/

13 exp Priapism/

14 exp Libido/

15 dyspareun$.mp.

16 priap$.mp.

17 orgasm$.mp.

18 libido.mp.

19 (erecti$ adj (dysfunct$ or failure)).mp.

20 (sex$ adj (dysfunct$ or satisf$ or problem$ or symptom$ or arous$ or activit$ or disorder$)).mp.

21 (sex$ adj3 pain$).mp.

22 sexual intercourse.mp.

23 erect$.mp.

24 impoten$.mp.

25 or/6-24

26 exp Fertility/

27 fertil$.mp.

28 26 or 27

29 25 or 28

30 5 and 29

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on prostate cancer.

3. Any further comments

Update topic so searched from 2006 onwards. Basic exclusions filter and Systematic Reviews and RCT filters were used as an intervention topic.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2012 on-wards.

Database name	No of references found	No of references re-trieved	Finish date of search
Medline	77	4	16/05/2013
Premedline (May 15, 2013)	19	4	16/05/2013
Embase	217	16	16/05/2013
Cochrane Library	55	1	16/05/2013
PsycINFO	11	0	16/05/2013
AMED	0	0	16/05/2013
Web of Science (SCI & SSCI)	183	10	16/05/2013
Biomed Central	2	1	16/05/2013

Total References retrieved (after de-duplication): 27

Topic 12c: What is the most effective intervention for osteoporosis as a result of long term androgen suppression for prostate cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	201 & 275 & 83	136 & 71 & 44	26/09/2012
Premedline	Aug 13, 2012	18	14	26/09/2012
	Sept 07, 2012	27	10	26/09/2012
	Sept 25, 2012	2	2	26/09/2012
Embase	1974 -	684 & 812 & 260	246 & 153 & 93	26/09/2012
Cochrane Library	As per database	304 & 117 & 216	138 and 29 and 8	26/09/2012
Web of Science (SCI & SSCI)	1970 -	1177 together & 125	185 together & 59	26/09/2012

Note – first search result is the bisphosphonates and second search result relates to the other drug interventions and third relates to exercise.

Total References retrieved (after de-duplication): 509 for bisphonates, denosumab, calcium and vitamin D; 116 for exercise

Medline search strategy *(This search strategy is adapted to each database)*

Bisphosphonates Search

1 exp Prostatic Neoplasms/

2 exp Prostatic Intraepithelial Neoplasia/

3 (pin adj5 prostat$).tw.

4 (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelia$ or adeno$)).mp.

5 or/1-4

6 exp bone neoplasms/sc

7 exp Neoplasm Metastasis/

8 exp "Bone and Bones"/

9 7 and 8

10 ((bone$ or skelet$ or osseous or osteo$) adj5 (second$ or metast$ or spread$ or advanc$ or lesion$)).af.

11 or/6,9-10

12 exp Prostate/

13 prostat$.af.

14 12 or 13

15 11 and 14

16 exp Diphosphonates/

17 exp Organophosphorus Compounds/

18 exp Phosphoric Acids/
19 (bisphosphonat$ or diphosphonat$).af.
20 etidron$.af.
21 didron$.af.
22 difosfen.af.
23 osteodidronel.af.
24 osteum.af.
25 "disodium dihydrogen(1-hydroxyethylidene)diphosphonate".af.
26 pamidronate.af.
27 APD.af.
28 aredia.af.
29 "disodium 3-amino-1-hydroxypropylidenebisphosphonate".af.
30 clodronate.af.
31 bonefos.af.
32 loron.af.
33 ascredar.af.
34 lodronat.af.
35 lytos.af.
36 ostac.af.
37 clastoban.af.
38 clasteon.af.
39 difosfonal.af.
40 ossiten.af.
41 mebonat.af.
42 "disodium (dichloromethylene) diphosphonate tetrahydrate".af.
43 tiludron$.af.
44 skelid.af.
45 "disodium dihydrogen{[(p-chlorophenyl)thio]methylene}diphosphonate hemihydrate".af.
46 risedron$.af.
47 actonel.af.
48 "sodium trihydrogen[1-hydroxy-2-(3-pyridyl)ethylidene]diphosphonate".af.
49 alendron$.af.
50 fosamax.af.
51 adronat.af.
52 alendros.af.
53 dronal.af.

54 "aminohydroxybutylidene diphosphonic acid".af.

55 neridron$.af.

56 AHDP.af.

57 "(6-amino-1-hydroxyhexylidene)diphosphonic acid".af.

58 zoledron$.af.

59 zometa.af.

60 ibandron$.af.

61 bondronat.af.

62 "(1-hydroxy-3-[methylpentylamino]propylidene)diphosphonic acid".af.

63 olpadron$.af.

64 OPD.af.

65 "(3-dimethylamino-1-hydroxypropylidene)bisphosphonate".af.

66 incadron.af.

67 YM175.af.

68 YM 175.af.

69 minodron$.af.

70 YM529.af.

71 YM 529.af.

72 or/16-71

73 5 or 15

74 72 and 73

75 limit 74 to yr=”2006 –Current”

Denosumab, Calcium and Vitamin D Search

1 exp Prostatic Neoplasms/

2 Prostatic Intraepithelial Neoplasia/

3 (prostat$ adj3 (cancer$ or carcinoma$ or adeno$ or malignan$ or tum?r$ or neoplas$ or intraepithelial$)).tw.

4 PIN.tw.

5 1 or 2 or 3 or 4

6 exp Calcium/

7 exp Calcium, Dietary/

8 calcium.tw.

9 exp Vitamin D/

10 (vitamin D or vitamin D2 or vitamin D3).tw.

11 (calcitriol or cholecalciferol or colecalciferol or ergocalciferol$ or alphacalcidol or alfacalcidol or hydroxycholecalciferol or dihydrotachysterol).tw.

12 exp Ergocalciferols/

13 exp Cholecalciferol/

14 Denosumab.tw.

15 (prolia or Xgeva).tw.

16 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

17 5 and 16

Exercise Search

1 Osteoporosis/

2 (osteoporo$ or osteopenia).mp.

3 Bone Density/

4 bone densit$.mp.

5 exp "Bone and Bones"/

6 (bone adj (loss$ or mass$)).mp.

7 bone mineral densit$.mp.

8 bone mineral content$.mp.

9 bone age.mp.

10 bone defect$.mp.

11 bone deminerali?ation.mp.

12 bone mineral$.mp.

13 bone strength.mp.

14 decalcifi$.mp.

15 deminerali?ed bone.mp.

16 or/1-15

17 Prostate/

18 exp Prostatic Neoplasms/

19 prostat$.mp.

20 or/17-19

21 16 and 20

22 exp Exercise/ or exp Exercise Therapy/

23 exp Sports/

24 Physical Fitness/

25 (exercis$ or sport$).mp.

26 physical fitness.mp.

27 physical activit$.mp.

28 or/22-27

29 21 and 28

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on prostate cancer.

3. Any further comments

Update topic for bisphosphonates intervention so searched from 2006 onwards, no date limit used on other interventions as not an exact update from the previous guideline. Basic exclusions filter and Systematic Reviews and RCT filters were used as appropriate an intervention topic. Cinahl, BNI, AMED and PsycINFO were checked and no unique references were found.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2012 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	76 & 88 & 18	17 & 11 & 2	16/05/2013
Premedline (15 May 2013)	19 & 35 & 5	9 & 11 & 2	16/05/2013
Embase	347 & 259 & 101	49 & 31 & 5	16/05/2013
Cochrane Library	29 & 13 & 37	0	16/05/2013
Web of Science (SCI & SSCI)	198 together & 31	28 together & 3	16/05/2013

Note – first search result is the bisphosphonates and second search result relates to the other drug interventions and third relates to exercise.

Total References retrieved (after de-duplication): 89 combined

Topic 12d: What is the most effective intervention for fatigue as a result of long term androgen suppression for prostate cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	253	40	07/08/2012
Premedline	Aug 6, 2012	64	1	07/08/2012
Embase	1974 -	1414	61	08/08/2012
Cochrane Library	As per database	238	37	07/08/2012
Web of Science (SCI & SSCI)	1970 -	1108	62	09/08/2012
Biomed Central	As per database	33	7	09/08/2012
PsycINFO	1806 -	77	12	07/08/2012
AMED	1985 -	23	6	07/08/2012

Total References retrieved (after de-duplication): 101

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Prostatic Neoplasms/

2 Prostatic Intraepithelial Neoplasia/

3 (prostat$ adj3 (cancer$ or carcinoma$ or adeno$ or malignan$ or tum?r$ or neoplas$ or intraepithelial$)).tw.

4 PIN.tw.

5 1 or 2 or 3 or 4

6 exp Fatigue/

7 fatigu$.ti,ab.

8 (exhaust$ or tired$ or weary or weariness).ti,ab.

9 (low adj energy).ti,ab.

10 or/6-9

11 5 and 10

12 exp Exercise/ or exp Exercise Therapy/

13 exercise.ti,ab.

14 ((strength or physical or resistance) adj3 (activity or intervention or train$)).ti,ab.

15 exp Diet/

16 exp Life Style/

17 exp Counseling/

18 social support/

19 ((psychosocial or psychological or lifestyle or dietary or social) adj3 (support or intervention or advice)).ti,ab.

20 (counselling or counseling).ti,ab.

21 or/12-20

22 5 and 21

23 11 or 22

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on prostate cancer.

3. Any further comments

No date limit was used as not an exact update from the previous guideline. Basic exclusions filter and Systematic Reviews and RCT filters were used as an intervention topic.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2012 on-wards.

Database name	No of references found	No of references re-trieved	Finish date of search
Medline	59	4	16/05/2013
Premedline (May 15, 2013)	12	3	16/05/2013
Embase	322	15	16/05/2013
Cochrane Library	50	3	16/05/2013
PsycINFO	11	3	16/05/2013
AMED	0	0	16/05/2013
Web of Science (SCI & SSCI)	212	16	16/05/2013
Biomed Central	18	6	16/05/2013

Total References retrieved (after de-duplication): 32

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer Clinical Guideline **Literature search summary**

Question title: 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?

Question no: Topic 12A

77. Literature search details

Database name	No of references found	No of references retrieved	Finish date of search
Medline	106	26	16/12/05
Premedine	3	1	16/12/05
Embase	109	21	16/12/05
Cochrane Library	90	0	19/12/05
BNI	0	0	16/12/05
Cinahl	8	0	16/12/05
Psychinfo	0	0	16/12/05
Web of Science	110	17	20/12/05
Biomed	15	1	20/12/05
SIGLE	2	0	20/12/05
National Research Register	0	0	20/12/05

Total References retrieved (after de-duplication): 47

78. **Medline search strategy** *(search strategies for each database are saved on OVID)*

Prostate Cancer AND (Spine AND MRI)

1. exp Prostatic Neoplasms/
2. Prostatic Intraepithelial Neoplasia/
3. pin.tw.
4. (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.

5. or/1-4
6. exp spine/
7. exp Spinal Cord/
8. (spine or spinal).tw.
9. (vertebra or vertebrae or vertebral).tw.
10. or/6-9
11. dorsal.tw.
12. cervical.tw.
13. lumbar.tw.
14. thoracic.tw.
15. 8 or 9
16. or/11-14
17. 15 and 16
18. Intervertebral Disk.tw.
19. sacrum.tw.
20. coccyx.tw.
21. or/18-20
22. 10 or 17 or 21
23. exp magnetic resonance imaging/
24. Magnetic Resonance Spectroscopy/
25. magnetic resonance.tw.
26. MRI$1.tw.
27. NMR$1.tw.
28. MRS$1.tw.
29. MRT.tw.
30. MR imaging.tw.
31. MR scan$.tw.
32. MR spectroscop$.tw.
33. MR elastograph$.tw.
34. (magnet$ adj3 (scan$ or imaging)).tw.
35. (diffusion adj2 (scan$ or imaging)).tw.
36. (planar adj (scan$ or imaging$)).tw.
37. (planar adj tomogra$).tw.
38. (echoplanar adj (scan$ or imaging)).tw.

39. (echoplanar adj tomogra$).tw.
40. zeugmatogra$.tw.
41. MRE.tw.
42. SPECT$1.tw.
43. FMRI$.tw.
44. (functional adj2 (scan$ or imaging)).tw.
45. or/23-44
46. 22 and 45
47. 5 and 46

79. Health Economics Literature search details

(SIGN Health Economics filter added to above search)

Database name	No of references found	Finish date of search
Medline	3	16/12/05
Premedline	0	16/12/05
Embase	1	16/12/05
NHSEED	0	19/12/05
Cochrane Library (except NHSEED)	16 (0 retrieved)	19/12/05
Cinahl	0	19/12/05
EconLit	0	20/12/05
HMIC	1	16/12/05
***W*eb of Science**	2	20/12/05

80. Any further comments *including difficulty of search if applicable***:**

Criteria of articles excluded from sift:

From titles only:

Animals

Obviously unrelated to prostate cancer

From abstracts:

Patients with existing spinal cord compression

Spinal cord compression where prostate cancer is mentioned only in passing

Other treatments where imaging is mentioned in passing

Spine coil receivers

Include spinal cord compression articles if unsure signs and symptoms already exist.

All language articles and dates were included in the sift

81. Update searches

Limited to date range 2005-2007

Database name	No of references found	No of references re-trieved	Finish date of search
Medline	21	5	23/07/07
Premedline	1	1	23/07/07
Embase	28	6	23/07/07
Cochrane Library	1	1	23/07/07
Cinahl	2	0	23/07/07
Psycinfo	0	0	23/07/07
Amed	1	0	23/07/07
BNI	0	0	23/07/07
Web of Science (SCI & SSCI)	19	3	23/07/07
SIGLE	0	0	23/07/07

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer Clinical Guideline **Literature search summary**

Question title:

1. Bisphosphonates for prevention of bone metastases in patients having hormone therapy for prostate cancer.

2. Can Bisphosphonates be used to reduce the risk of bone complications from androgen deprivation?

Question no: Topic 11B and 11C

82. Literature search details

Database name	No of references found	No of references re-trieved	Finish date of search
Medline	640	71	15/05/06
Premedline	6	6	15/05/06
Embase	451	64	16/05/06
Cochrane Library	130	11	15/05/06
Cinahl	17	6	15/05/06
BNI	1	0	15/05/06
Psychinfo	5	0	15/05/06
SIGLE	0	0	16/05/06
Web of Science (SCI & SSCI)	407	46	17/05/06
Biomed Central	12	0	15/05/06
Current Controlled Trials	0	0	15/05/06
National Research Register	45	5	15/05/06
AMED	17	1	15/05/06

Total References retrieved (after de-duplication): 159

Medline search strategy *(This search strategy is adapted to each database.)*

1. prostat$.af.
2. exp Diphosphonates/
3. exp organophosphorus compounds/
4. exp phosphoric acids/
5. (bisphosphonat$ or diphosphonat$).af.
6. etidron$.af.
7. didron$.af.

8. difosfen.af.
9. osteodidronel.af.
10. osteum.af.
11. "disodium dihydrogen(1-hydroxyethylidene)diphosphonate".af.
12. pamidronate.af.
13. APD.af.
14. aredia.af.
15. "disodium 3-amino-1-hydroxypropylidenebisphosphonate".af.
16. clodronate.af.
17. CL2MDP.af.
18. bonefos.af.
19. loron.af.
20. ascredar.af.
21. lodronat.af.
22. lytos.af.
23. ostac.af.
24. clastoban.af.
25. clasteon.af.
26. difosfonal.af.
27. ossiten.af.
28. mebonat.af.
29. "disodium (dichloromethylene) diphosphonate tetrahydrate".af.
30. tiludron$.af.
31. skelid.af.
32. "disodium dihydrogenfdiphosphonate hemihydrate".af.
33. risedron$.af.
34. actonel.af.
35. "sodium trihydrogen[1-hydroxy-2-(3-pyridyl)ethylidene]diphosphonate".af.
36. alendron$.af.
37. fosamax.af.
38. adronat.af.
39. alendros.af.
40. dronal.af.
41. "aminohydroxybutylidene diphosphonic acid".af.

42. neridron$.af.
43. AHDP.af.
44. "(6-amino-1-hydroxyhexylidene)diphosphonic acid".af.
45. zoledron$.af.
46. zometa.af.
47. ibandron$.af.
48. bondronat.af.
49. "(1-hydroxy-3-[methylpentylamino]propylidene)diphosphonic acid".af.
50. olpadron$.af.
51. OPD.af.
52. "(3-dimethylamino-1-hydroxypropylidene)bisphosphonate".af.
53. incadron.af.
54. YM175.af.
55. YM 175.af.
56. minodron$.af.
57. YM529.af.
58. YM 529.af.
59. or/2-58
60. 1 and 59

83. Health Economics Literature search details

Database name	No of references found	Finish date of search
Medline	23	15/05/06
Premedline	0	15/05/06
Embase	68	15/05/06
Cochrane Library (except NHSEED)	117	16/05/06
NHSEED	3	16/05/06
Cinahl	4	15/05/06
Psycinfo	1	15/05/06
AMED, BNI	0	15/05/06
EconLit	0	15/05/06
Web of Science	13	17/05/06
SIGLE	0	16/05/06

84. Any further comments:
Topic 11B&C will have had some results come up for 11A and also Topic 20, so a broad simple search was used to cover this topic. SIGN Health Economics filter & SCHARR Quality of Life filter were applied to basic clinical search for

the health economics review.

85. Update Search

For the update search, the reviewer required only RCT's and so the search was re-executed using a RCT filter, date limit 2005-2007 and English language only.

Database name	No of references found	No of references re-trieved	Finish date of search
Medline	34	9	21/05/07
Premedline	5	1	21/05/07
Embase	154	8	21/05/07
Cochrane Library	19	7	24/05/07
Cinahl	12	2	21/05/07
BNI	4	0	21/05/07
Psychinfo	6	0	21/05/07
SIGLE	0	0	21/05/07
Web of Science (SCI & SSCI)	39	5	21/05/07
Biomed Central	5	0	21/05/07
AMED	7	0	21/05/07

An update search was also required for the health economics review and so the search was re-executed as before but with a date limit 2005-2007 (and removed duplicates from last time search done).

Database name	No of references found	Finish date of search
Medline	5	24/05/07
Premedline	1	24/05/07
Embase	18	24/05/07
Cochrane Library (except NHSEED)	5	19/06/07
NHSEED	0	19/06/07
Cinahl	3	24/05/07
Psycinfo	1	24/05/07
BNI	0	24/05/07
EconLit	0	24/05/07
Web of Science	4	24/05/07
SIGLE	0	24/05/07

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer Clinical Guideline **Literature search summary**

Question title: Clinical and cost-effectiveness of strontium-89 in patients with hormone refractory prostate cancer and bone metastases (as compared to standard care)?

Question no: Topic 12B

86. Literature search details

Database name	No of references found	No of references re-trieved	Finish date of search
Medline	160	124	13/12/05
Premedline	4	4	13/12/05
Embase	239	158	14/12/05
Cochrane Library	52	27	14/12/05
Cinahl	8	7	15/12/05
BNI	0	0	15/12/05
Psychinfo	2	2	15/12/05
SIGLE	0	0	15/12/05
Web of Science	124	124 (sifted in RM)	15/12/05
Biomed Central	15	2	15/12/05
Current Controlled Trials	32	5	15/12/05
National Research Register	10	5	15/12/05

Total References retrieved (after de-duplication): 269

Medline search strategy *(This search strategy is adapted to each database.)*

Prostate Cancer AND Bone Metastases AND Strontium

1. exp Prostatic Neoplasms/
2. Prostatic Intraepithelial Neoplasia/
3. pin.tw.
4. (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.
5. or/1-4
6. Strontium Radioisotopes/
7. Strontium/
8. strontium.tw.

9. 89Sr.tw.
10. 89stron$.tw.
11. sr89.tw.
12. metastron$.tw.
13. or/6-12
14. exp Bone Neoplasms/sc [Secondary]
15. exp Neoplasm metastasis/
16. exp Bone/ and bones/
17. 15 and 16
18. (bone$ adj10 metasta$).tw.
19. (bony adj metasta$).tw.
20. (skelet$ adj3 metasta$).tw.
21. ((spine or spinal) adj2 metasta$).tw.
22. (osseous adj3 metasta$).tw.
23. (osteo$ adj3 metasta$).tw.
24. or/18-23
25. 14 or 17 or 24
26. 5 and 25
27. 13 and 26

87. Health Economics Literature search details

(SIGN Health Economics filter added to above search)
(SCHARR Quality of Life filter added to above search)

Database name	No of references found	Finish date of search
Medline	10	13/12/05
Premedline	0	13/12/05
Embase	18	14/12/05
Cochrane Library (except NHSEED)	16	14/12/05
NHSEED	4	14/12/05
Cinahl	1	15/12/05
Psycinfo	1	15/12/05
BNI	0	15/12/05
EconLit	0	15/12/05
Web of Science	18	15/12/05

88. Any further comments:

Sifting Criteria

Include:

References on bone pain

References that do not specify stage of cancer

References comparing strontium to other treatments

Exclude:

Animal studies

Economic Search on Cochrane Library: 9 retrieved and sent to Bangor only due to duplication of records

SIGLE, Web of Science, Biomed, Current Controlled Trials and NRR databases were searched without the bone metastases set to improve sensitivity.

89. Update searches

Limited to date range 2005-2007

Database name	No of references found	No of references retrieved	Finish date of search
Medline	16	11	18/07/07
Premedline	1	1	18/07/07
Embase	89	14	18/07/07
Cochrane Library	2	2	18/07/07
Cinahl	2	0	18/07/07
Psycinfo	2	0	18/07/07
Amed	4	0	18/07/07
BNI	0	0	18/07/07
Web of Science (SCI & SSCI)	18	16	18/07/07
SIGLE	0	0	18/07/07

Health Economics Update searches

Database name	No of references found	Finish date of search
Medline	1	18/07/07
Premedline	0	18/07/07
Embase	8	18/07/07
Cochrane Library (except NHSEED)	0	18/07/07
NHSEED	0	18/07/07
Cinahl	0	18/07/07
Psycinfo	0	18/07/07

BNI	0	18/07/07
HMIC	0	18/07/07
EconLit	0	18/07/07
Web of Science (SCI & SSCI)	1	18/07/07

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer **Clinical Guideline** **Literature search summary**

Question title: What is the most effective Management of obstructive uropathy in patients with hormone refractory prostate cancer

Question no: 28

90. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline		356	9	07/11/06
Premedline		1	1	07/11/06
Embase		106	8	07/11/06
Cochrane Library		8	0	07/11/06
Cinahl		11	0	07/11/06
BNI		12	0	07/11/06
Psychinfo		0	0	07/11/06
SIGLE		0	0	07/11/06
Web of Science (SCI & SSCI)		144	2	07/11/06
ISI Proceedings		2	1	07/11/06
Biomed Central		67	0	07/11/06
Current Controlled Trials		-	-	
National Research Register		-	-	
ZETOC		-	-	

Total References retrieved (after de-duplication): 18

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp Prostatic Neoplasms/
2. prostatic intraepithelial neoplasia/
3. pin.tw.
4. (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.
5. or/1-4
6. exp Neoplasms, Hormone-Dependent/

7. hormone$ refractor$.tw.
8. HRPCa.tw.
9. or/6-8
10. exp Ureteral Obstruction/
11. exp Urologic Diseases/
12. (obstruct$ adj3 uropath$).tw.
13. exp Urinary Tract/
14. urinar$ tract$ obstruct$.tw.
15. exp Urethra/
16. exp Urination Disorders/
17. exp Prostatic Hyperplasia/
18. or/10-17
19. exp Kidney Failure/
20. renal$ failure$.tw.
21. exp Renal Dialysis/
22. renal$ impair$.tw.
23. exp Urinary Diversion/ or exp Urinary Catheterization/ or exp Nephrostomy, Percutaneous/
24. nephrostom$.tw.
25. exp "prostheses and implants"/
26. exp Stents/
27. stent$.tw.
28. dialysis$.tw.
29. or/19-28
30. 5 and 9
31. 30 and 18
32. 31 and 29
33. from 32 keep 2,4-5
34. 10 and 20
35. 34 and 5
36. from 35 keep 3,6-9,13
37. 33 or 36

91. Health Economics Literature search details

(SIGN Health Economics filter added to above search)
[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline		
Premedline		
Embase		
Cochrane Library (except NHSEED)		
NHSEED		
Cinahl		
Psycinfo		
BNI		
EconLit		
Web of Science (SCI & SSCI)		
ISI Proceedings		
SIGLE		
ZETOC		

92. Any further comments:

Sifting Criteria:

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer **Clinical Guideline** **Literature search summary**

Question title: What is the most effective delivery of palliative care for men with prostate cancer?

Question no: 25

93. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline		438	29	09/10/06
Premedline		13	0	09/10/06
Embase		366	11	09/10/06
Cochrane Library		58	0	09/10/06
Cinahl		16	1	10/10/06
BNI		2	1	09/10/06
Psychinfo		12	1	09/10/06
SIGLE		0	0	10/10/06
Web of Science (SCI & SSCI)		120	7	10/10/06
ISI Proceedings		15	2	10/10/06
Biomed Central		45	0	09/10/06
Current Controlled Trials		-	-	
National Research Register		-	-	
ZETOC		-	-	

Total References retrieved (after de-duplication): 42

Medline search strategy *(This search strategy is adapted to each database.)*

Palliative Care AND Prostate Cancer (RCT and SR filters applied)

1 exp Prostatic Neoplasms/

2 prostatic intraepithelial neoplasia/

3 pin.tw.

4 (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.

5 or/1-4

6 exp Palliative Care/

7 palliative therap$.tw.

8 palliative treatment$.tw.

9 palliative medicine$.tw.

10 exp Terminal Care/
11 end of life.tw.
12 exp Hospice Care/
13 palliative care pathway$.tw.
14 exp Home Care Services/
15 (care adj3 dying).tw.
16 palliative care support.tw.
17 palliation$.tw.
18 end stage$.tw.
19 exp Critical Pathways/ or Liverpool Pathway.mp.
20 or/6-19
21 5 and 20

94. Health Economics Literature search details

(SIGN Health Economics filter added to above search)
[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline		
Premedline		
Embase		
Cochrane Library (except NHSEED)		
NHSEED		
Cinahl		
Psycinfo		
BNI		
EconLit		
Web of Science (SCI & SSCI)		
ISI Proceedings		
SIGLE		
ZETOC		

95. Any further comments:

Sifting Criteria:

NATIONAL COLLABORATING CENTRE FOR CANCER

Prostate Cancer (Update) Clinical Guideline

Health Economics

1. Literature search details

Database name	No of references found	Finish date of search
Medline (2010 onwards, SIGN HE filter)	165	16/11/2011
Premedline (Nov 15, 2011)	40	16/11/2011
Embase (2010 onwards, SIGN HE filter)	508	16/11/2011
Cochrane: HTA	185	16/11/2011
Cochrane: NHSEED	109	16/11/2011

Total References retrieved (after de-duplication): 827

Medline search strategy *(This search strategy is adapted to each database)*

1. exp Prostatic Neoplasms/
2. prostatic intraepithelial neoplasia/
3. PIN.tw.
4. (prostat$ adj3 (cancer$ or carcinoma$ or adeno$ or malignan$ or tum?r$ or neoplas$ or intraepithelial$)).tw.
5. or/1-4

2. Any further comments

SIGN Health Economics filter used on the guideline population search for Medline/Premedline and Embase, no filter used the HTA and EED databases. A full search was undertaken with no date limit to ensure full coverage of topics for the economic plan and for dealing with different health economic analyses from the last guideline.

3. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 16/11/2011 onwards for the first update, and then 27/03/2013 onwards for the second update.

Database name	No of references found	Finish date of search
Medline (SIGN HE filter)	221	27/03/2013
Premedline (Mar 26, 2013)	111	27/03/2013
Embase (SIGN HE filter)	382	27/03/2013
Cochrane: HTA & EED (2010 onwards)	78	27/03/2013

Total References retrieved (after de-duplication): 581

Database name	No of references found	Finish date of search
Medline (SIGN HE filter)	17 (1)	17/05/2013
Premedline (May 16, 2013)	112 (11)	17/05/2013
Embase (SIGN HE filter)	42 (3)	17/05/2013
Cochrane: HTA (2012 onwards)	12 (3)	17/05/2013
Cochrane EED (2012 onwards)	19 (3)	17/05/2013

Total References retrieved (after de-duplication & sifting): 18

Appendix C - Consensus survey for an active surveillance protocol

Summary

The guideline development group felt that the variation in UK active surveillance protocols indicated a need for standardized protocol. However the group felt that due to the lack of published evidence about the effectiveness of active surveillance protocols any such recommendations could not be implemented without first seeking consensus within the prostate cancer community. For this reason the group decided to use a modified Delphi formal process (Strauss and Ziegler, 1975) to seek consensus about the ideal active surveillance protocol for low risk localised prostate cancer. The guideline group invited 210 health professionals and patients to participate in the consensus process. 152 respondents took part in round 1, 120 in round 2 and 102 in round 3.

Following three rounds consensus (defined as agreement between at least 2/3rds of respondents) was reached on several components of the active surveillance protocol, see Table 133.

Table 133. Active surveillance protocol for low risk localised prostate cancer: consensus survey results

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

Key: ×, consensus not reached; ✓, consensus reached ; †, consensus on parts of this item; -, item not included in survey round.

Process for consensus on an active surveillance protocol

Introduction

There are 2 types of 'observational' approaches to localised prostate cancer, in which men do not undergo any form of immediate active treatment, but are monitored instead. The objectives of these 2 approaches, active surveillance and 'watchful waiting' are quite different:

Active Surveillance (AS)

> This is part of a 'curative' strategy and is aimed at men with localised prostate cancer who are suitable for radical treatments, keeping them within a "window of curability" whereby only those whose tumours are showing signs of progressing, or those with a preference for inter-

vention are considered for radical treatment. Active surveillance may thus avoid or delay the need for radiation or surgery.

The following definition is adapted from that of the Prostate Cancer Foundation:

'During active surveillance, prostate cancer is carefully monitored for signs of progression. A PSA blood test and digital rectal exam (DRE) are usually administered periodically, along with a repeat biopsy of the prostate, usually within one year and at intervals thereafter if indicted by test results. These tests are usually supplemented by imaging of the prostate with magnetic resonance (MR) scanning. If symptoms develop, or if tests indicate the cancer is growing, curative treatment might be warranted.'

The term 'active monitoring' is used to describe an approach employed by some clinicians, which follows the principles of AS but omits the requirement for re-biopsy and/or MR scanning. This strategy remains under investigation in research trials and data should be available in the coming years.

Watchful Waiting (WW)

This is part of a 'controlling' strategy, and is aimed at men with localised prostate cancer who are either not suitable for, or do not ever wish to receive, curative treatment, and instead involves the deferred use of hormone therapy. Accordingly WW avoids the use of surgery or radiation, but implies that curative treatment will not be available; men on WW who require treatment would receive long-term hormone therapy to control their cancer. A significant number of men on WW follow up need no treatment at all during the rest of their lives.

Men are followed up as per local policy (usually every 6 months) and are offered treatment only if they develop symptomatic progression or express a preference for intervention.

In summary, "Active surveillance is a disease management strategy that avoids curative treatment until it is warranted, based on defined indicators of disease progression. In contrast, watchful waiting is a disease management strategy that forgoes curative treatment and initiates intervention only when symptoms arise" (Ganz et al, 2011) or the disease begins to progress more rapidly.

Evidence about the most effective active surveillance protocol

Our literature searches identified no research studies designed to compare different active surveillance protocols. A recent systematic review (Dahabreh et al, 2012) summarised protocols for follow up in 16 cohorts of men on active surveillance for low risk or clinically localised (T1 or T2) prostate cancer. Most of these protocols used PSA kinetics, DRE and re-biopsy.

Survey of UK active surveillance protocols

A survey of active surveillance protocols currently in use by the 31 Cancer Networks in England, Wales and Northern Ireland was undertaken by NCC-C in 2012. Twenty-three protocols for the follow-up of patients on active surveillance were received from the 19 Cancer Networks which responded to the survey. Over half (57%) of the protocols recommended PSA testing at 3-monthly intervals initially for a period of between 12 and 24 months or until stable. Five (22%) recommended PSA testing at 4-monthly intervals initially for between 12 and 24 months. One (4%) protocol recommended PSA testing ≤ every 3 months for an initial period of 24 months; while one recommended testing between every 3-6 months, and another every 4-6 months.

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

is recommended at the same frequency as PSA testing (3- or 4-monthly initially reducing to 6-monthly), and one (4%) recommended DRE testing 6-monthly.

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

Two protocols also made a recommendation regarding measurement of PSA doubling time; one recommended measuring this at 6-monthly intervals (at the same frequency as PSA testing following the initial 3-monthly period). The other recommended measuring PSA doubling time after 1 year of follow-up. One protocol also recommended undertaking MRI annually (alongside continuous 4-6 monthly PSA testing).

Consensus process

The guideline development group felt that the variation in UK active surveillance protocols indicated a need for standardized protocol. However the group felt that due to the lack of published evidence about the effectiveness of active surveillance protocols any such recommendations could not be implemented without first seeking consensus within the prostate cancer community. For this reason the group decided to use a modified Delphi formal process (Strauss and Ziegler, 1975; NICE, 2013) to seek consensus about the ideal active surveillance protocol. The process for this consensus process is detailed below.

Participants

The guideline group will invite around 200 people to participate in the Delphi process. These participants will include health professionals and patients or their carers. The guideline development group themselves can also participate – provided they form 15% or less of the consensus group. Participants must agree to comply with NICE methods and confidentiality requirements and will be invited from the following organizations:

- Royal College of Pathologists
- Royal College of Radiologists – Oncology and Radiology
- Royal College of General Practitioners
- British Association of Urological Surgeons (BAUS)
- British Urology Group
- Department of Health
- Prostate Cancer Charity (other charities will also be included)
- British Society of Uro-radiology
- British Association of Urology Nurses (BAUN)

Delphi procedure

Following discussion with the guideline development group the NCC-C technical team (and director) overseen by Noel Clarke, Professor of Urological Oncology in Manchester, will develop the first round of the Delphi questionnaire as a series of questions about the elements of an active surveillance protocol (see appendix 1). These statements will be informed by the results of the NCC-C survey of UK active surveillance protocols. Consensus group members will rate each statement according their agreement with it or will give a quantitative judgment, depending on the type of question.

All members of the consensus group will be sent this questionnaire using the Survey Monkey web service. Responses will be anonymous. Using features of survey monkey each member of the consensus group will be sent a unique link to the Delphi survey. Their responses will be anonymous but will contain a unique code which will allow the technical team to follow their responses across survey rounds and to feed back results to them.

After each round the responses will be analysed and summarised by the NCC-C technical staff. These results will be fed back to the consensus group members by e-mail. Each consensus group member will see the average response of the whole group for each item in the previous round alongside their own answers to each item.

Consensus is defined as at least 70% agreement on a given item. When consensus on an item is reached it will be removed from the next round of the survey. At least three rounds of the survey are anticipated with a gap of two weeks between each round – but the final number of rounds will be limited by the guideline development time. The participants will be able to re-rate any remaining statements in the subsequent rounds with the aim of reaching consensus.

Where there is disagreement, statements can be reworded between rounds – with the aim of improving agreement. Rewording of statements will be agreed by the technical team, the NCC-C director and Professor Clarke following discussion of the survey results and qualitative analysis of any free-text comments.

Recommendations

In the two weeks following the final round the results of the survey will be summarized by the NCCC technical team in a report and circulated to all consensus group members. The guideline group will consider this report as evidence when drafting their recommendations about active surveillance protocols.

It may not be possible to reach consensus on all of the components of an active surveillance protocol in the time available. In this case the guideline group can word their recommendations to reflect the areas of uncertainty or can restrict their recommendations to areas where there is consensus.

There is a small risk that consensus will not be reached on any component of the active surveillance protocol. In this case the guideline group can choose to base any recommendations on their clinical experience or may decide not to make any recommendations for this topic.

References

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Results of consensus survey

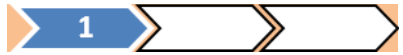
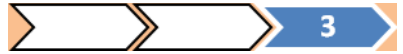
1. Survey respondents

1 2 3 **Table 1.1.In what capacity have you experienced active surveillance for prostate cancer?**

In what capacity have you experienced active surveillance for prostate cancer? Please tick any that apply.

Answer Options	Round 1		Round 2		Round 3	
	Response Percent	Response Count	Response Percent	Response Count	Response Percent	Response Count
Man diagnosed with prostate cancer	21.1%	32	25.5%	27	23.5%	24
Partner or carer of a man with prostate cancer	0.7%	1	0.0%	0	0.0%	0
Support worker	1.3%	2	1.7%	2	2.0%	2
Urologist	32.2%	49	31.7%	38	27.5%	28
Pathologist	16.4%	25	16.7%	20	16.7%	17
Radiologist	4.6%	7	5.0%	6	5.9%	6
Oncologist	7.2%	11	6.7%	8	7.8%	8
Specialist Nurse	15.1%	23	14.2%	17	16.7%	17
Nurse consultant	1.3%	2	0.8%	1	1.0%	1
General Practitioner	0.7%	1	0.8%	1	1.0%	1
No experience of AS for prostate cancer	0.7%	1	0.0%	0	0.0%	0
Other	4.4%	7	-	-	-	-
answered question		**152**		**120**		**102**
skipped question		**0**		**0**		**0**

Key

	Question asked in survey rounds 1, 2 and 3
	Question asked in survey round 1 only
	Question asked in survey round 2 only
	Question asked in survey round 3 only

2. Prostate re-biopsy before enrolment on active surveillance

Table 2.1 Should men undergo a prostate re-biopsy before enrolment on AS?

Men considering active surveillance for low risk localised prostate cancer should undergo a second prostate biopsy before enrolment. (Assume that the man's initial prostate biopsy included at least 10 cores).

	Round 1		Round 2		Round 3	
Answer Options	**Response Percent**	**Response Count**	**Response Percent**	**Response Count**	**Response Percent**	**Response Count**
Agree	31.5%	47	32.5%	38	-	-
Neutral (neither agree nor disagree)	22.1%	33	-	-	-	-
Disagree	**46.3%**	69	**67.5%**	80	-	-
	answered question	**149**		**117**		**-**
	skipped question	**3**		**3**		**-**

The Neutral answer option was removed in round 2. This question was removed in after round 2 because consensus was reached in round 2

1 2

Table 2.2 Technique of prostate re-biopsy before enrolment on active surveillance

What technique should be used for re-biopsy prior to enrolment on active surveillance for low risk localised prostate cancer? (Assume that the man's initial prostate biopsy included at least 10 cores).

	Round1		Round 2		Round 3	
Answer Options	**Response Percent**	**Response Count**	**Response Percent**	**Response Count**	**Response Percent**	**Response Count**
No re-biopsy should be done before enrolment	**53.4%**	78	**60.9%**	70	-	-
10 to 14 cores transrectal ultrasound (TRUS) guided biopsy	14.4%	21	9.6%	11	-	-
More than 14 cores TRUS biopsy	4.1%	6	2.6%	3	-	-
Transperineal template biopsy	28.1%	41	27.0%	31	-	-
	answered question	**146**		**115**		**-**
	skipped question	**6**		**5**		**-**

This question was removed in round 3 because consensus was reached in round 2 on the role of re-biopsy before enrolment

2

Table 2.3 Comments about re-biopsy before enrolment

Biopsy is not without risk. The placing of needles at biopsy is imprecise, and so there will be inevitable differences between successive series of biopsies. There comes a point when you accept the assessment as adequate for the purpose, and for almost all circumstances that should be the index biopsy.
Particular attention should be given to the anterior portion of the prostate which might harbour large tumours not sampled in standard biopsy protocols
Can detect higher grade cancers in the central gland with saturation biopsies - perhaps only do this for men with high PSA densities
No clinical evidence to support this unless men are very keen to consider other treatment options
Initially I had 12 cores (TRUS) which found nothing, only the template biopsy found my cancer.
I don't think we have sufficient data to answer this question. It should be considered. The same goes for question 3
The evidence to date is based upon a single set of biopsies
Ideally template but resources mean this is not yet in place
I don't think it is necessary
question 2 becomes nul and void with my response
Provided there is not a lengthy time span between detection and enrolment
The PRIAS study shows upgrade is most likely reason to leave AS
MPR MRI would be better
I have thought about this since Round 1 and changed my mind , because of my increasing concerns about biopsy morbidity.
Active surveillance should be available from the first biopsy or MRI Scan that positively identifies cancer
If the clinical and MRI picture are in keeping with localised disease they do not need to have a repeat biopsy prior to active surveillance
Depends on any factors that don't quite add up, eg palpable disease and v low core biopsy sample
not unless MRI shows area that may not have been biopsied
If following radio therapy (from a Gleeson count of 9) and psa remains below 1 - is it necessary?
actually within 6 months of enrolement as per the guys protocol
Second set within six months if same predicts likelihood of staying on surveillance
A second biopsy is only necessary when there are worrying features on histology(e.g. higher volume or possible early gland fusion.)
For me , biopsy was very painful and have encountered many weeks of discomfort
enroll but as part of the enrollment book for mpMRI 4-6 months from decision to perform AS

important for patients peace of mind
12 cores is more acceptable in international programmes and is what most units do as a minimum
This should be template biopsy and ideally preceeded by a multiparametric MRI
Biopsy is an invasive procedure which carries a small risk of spread (we know of confirmed cases). It should be a last resort
However in younger patients I agree ie <65
I think MRI is a better test than repeat biopsy to address the issue of sampling error on initial biopsy
There is no guarantee that the second biopsy would be any better/accurate. Where do you draw the line? One is enough for this protocol, which means to me, to start making changes to lifestyle..
If PSA reading is not rising materially, then it would appear a further biopsy is not required prior to enrolment
Why, if the original biopsy was adequate?

3. Mp-MRI before enrolment on AS

1 2

Table 3.1. Should men undergo mp-MRI before enrolment on AS?

Men considering active surveillance for low risk localised prostate cancer should undergo multi-parametric magnetic resonance imaging (see definition below) before enrolment. (Assume that each man's initial prostate biopsy included at least 10 cores).

	Round 1		Round 2		Round 3	
Answer Options	**Response Percent**	**Response Count**	**Response Percent**	**Response Count**	**Response Percent**	**Response Count**
Agree	**65.1%**	**97**	**83.8%**	**98**	**-**	**-**
Neutral (neither agree nor dis-agree)	23.5%	35	-	-	-	-
Disagree	11.4%	17	16.2%	19	-	-
	answered question	**149**		**117**		**-**
	skipped question	**3**		**3**		**-**

The Neutral answer option was removed in round 2. This question was removed in round 3 because consensus was reached in round 2

4. Prostate re-biopsy during active surveillance

1

Table 4.1. When should prostate re-biopsy be done during AS?

In what circumstances should prostate biopsy be repeated after enrolment on active surveillance for low risk localised prostate cancer? Please choose all that apply.

Answer Options	Response Percent	Response Count
Never	3.4%	5
If there are clinical or radiological changes	53.4%	79
Routinely - even if there are no clinical or radiological changes. (Please specify below when routine biopsy or biopsies should be done)	60.8%	90
	answered question	**148**
	skipped question	**4**

This question was split into 3 questions for round 2 to better reflect the underlying concepts.

1

Table 4.2. Which tests indicate a prostate re-biopsy should be done during AS?

Which tests are useful in deciding whether a prostate re-biopsy is necessary during active surveillance for low risk localised prostate cancer? Please choose all that apply.

Answer Options	Response Percent	Response Count
Prostate-specific antigen (PSA)	**96.2%**	**76**
Digital rectal examination (DRE)	**69.6%**	**55**
Multi-parametric magnetic resonance imaging (MRI)	**74.7%**	**59**
Other test(s) (please specify)		7
	answered question	**79**
	skipped question	**73**

This question was skipped if respondents disagreed with re-biopsy after clinical/radiological changes. This question was removed after round 1, because consensus was reached.

2

Table 4.3. Re-biopsy after clinical/radiological changes during AS (Round 2 only)

Prostate re-biopsy should be done if there are clinical or radiological changes during active surveillance for low risk localised prostate cancer.

Answer Options	Response Percent	Response Count
Agree	**90.4%**	**104**
Disagree	9.6%	11
	answered question	**115**
	skipped question	**5**

This question was removed after round 2, because consensus was reached.

2

Table 4.4. Routine re-biopsy during AS (Round 2 only)

Prostate re-biopsy should be done routinely at specified time points during active surveillance for low risk localised prostate cancer (even if there are no clinical or radiological changes).

Answer Options	Response Percent	Response Count
Agree	68.1%	79
Disagree	31.9%	37
	answered question	**116**
	skipped question	**4**

This question was removed after round 2, because consensus was reached.

2

Table 4.5. Timing of routine re-biopsy during AS (Round 2 only)

At what time points during the first ten years of active surveillance for low risk localised prostate cancer should routine prostate re-biopsies be done? For example if you believe biopsies should be done every 2 years then tick 2,4,6,8 and 10 years.

Answer Options	Response Percent	Response Count
Before enrolment	12.2%	10
0.5 years after enrolment	1.2%	1
1.0 year after enrolment	51.2%	42
1.5 years after enrolment	9.8%	8
2.0 years after enrolment	54.9%	45
2.5 years after enrolment	1.2%	1
3.0 years after enrolment	32.9%	27
3.5 years after enrolment	1.2%	1
4.0 years after enrolment	42.7%	35
4.5 years after enrolment	2.4%	2
5.0 year after enrolment	37.8%	31
5.5 years after enrolment	0.0%	0
6.0 years after enrolment	41.5%	34
6.5 years after enrolment	0.0%	0
7.0 years after enrolment	23.2%	19
7.5 years after enrolment	4.9%	4
8.0 years after enrolment	34.1%	28
8.5 years after enrolment	0.0%	0
9.0 years after enrolment	17.1%	14

9.5 years after enrolment	0.0%	0
10.0 years after enrolment	52.4%	43
	answered question	**82**
	skipped question	**38**

This question was reworded for round 3. This question was skipped if the respondent disagreed with routine re-biopsy during AS.

3

Table 4.6. Timing of re-biopsy during active surveillance (Round 3 only)

When should routine prostate re-biopsy be done during the first five years of active surveillance for low risk localised prostate cancer?

Answer Options	Response Percent	Response Count
Never	17.8%	18
Annually for 5 years	5.0%	5
At 1,3 and 5 years	54.5%	55
Other frequency (see table below)	23.7%	23
	answered question	**101**
	skipped question	**1**

3 **Table 4.7 Other biopsy frequencies suggested in round 3**

Every 2 years for six years	2 years and 4 years
Not More than every two years, but to be dependant on trend of PSA tests	At 2 years and 5 years
Template biopsy at initiation of as and 3 yrly	2,4,6 years
1, 4 and 7 years	At 1,2 and then by consensus between clinician and patient
2 years	Depends on type of first biopsy - if template biopsy year 2-3, 5 and 10
After 1 year and then individual taylormade according to evidence of disease progression	At 1 year. no further biopsy if stable
1,5, 5 years	2 and 4 years
At 1 year	Every two yrs
At 18 months and pssoibly 3 years, but mpMRI is likley to become surrogate	2 and 5 years
1 year. After that only if PSA rises or MRI abnormal.	Between 6 months and 1 year
Cannot define this with the data available	If access to Multiparametric MRI then this could replace re biopsies
2,5,10 years	

5. Multi-parametric MRI during active surveillance

1 **Table 5.1. When should mp-MRI be done during AS?**

When should multi-parametric MRI be done during active surveillance for low risk localised prostate cancer? Please choose all that apply.

Answer Options	Response Percent	Response Count
Never	7.5%	11
If there are clinical changes (for example in PSA or DRE)	56.2%	82
Routinely - even if there are no clinical changes (please specify below when routine MRI should be done)	42.5%	62
	answered question	**146**
	skipped question	**6**

The answer options were not mutually exclusive. This question was split into 3 questions for round 2 to better reflect the underlying concepts.

2 **Table 5.2. Mp-MRI after clinical/radiological changes during AS?**

Multi-parametric MRI (mp-MRI) should be done if there are clinical changes (for example in PSA or DRE) during active surveillance for low risk localised prostate cancer.

Answer Options	Response Percent	Response Count
Agree	**82.9%**	**97**
Disagree	17.1%	20
	answered question	**117**
	skipped question	**3**

This question was removed after round 2, because consensus was reached.

2

Table 5.3. Routine mp-MRI during AS (Round 2 only)

Multi-parametric MRI (mp-MRI) should be done routinely at specific time points during active surveillance for low risk localised prostate cancer (even if there are no clinical changes).

Answer Options	Response Percent	Response Count
Agree	52.1%	61
Disagree	47.9%	56
	answered question	**117**
	skipped question	**3**

2

Table 5.4. Time points for mp-MRI during AS (Round 2 only)

At what time points during the first ten years of active surveillance for low risk localised prostate cancer should routine multiparametric MRI be done? For example if you believe mp-MRI should be done every 2 years then tick 2,4,6,8 and 10 years.

Answer Options	Response Percent	Response Count
Before enrolment	25.8%	16
0.5 years after enrolment	1.6%	1
1.0 year after enrolment	53.2%	33
1.5 years after enrolment	9.7%	6
2.0 years after enrolment	58.1%	36
2.5 years after enrolment	1.6%	1
3.0 years after enrolment	45.2%	28
3.5 years after enrolment	6.5%	4
4.0 years after enrolment	51.6%	32
4.5 years after enrolment	3.2%	2
5.0 year after enrolment	33.9%	21
5.5 years after enrolment	4.8%	3
6.0 years after enrolment	54.8%	34
6.5 years after enrolment	1.6%	1
7.0 years after enrolment	32.3%	20
7.5 years after enrolment	6.5%	4
8.0 years after enrolment	40.3%	25
8.5 years after enrolment	1.6%	1
9.0 years after enrolment	30.6%	19

At what time points during the first ten years of active surveillance for low risk localised prostate cancer should routine multiparametric MRI be done? For example if you believe mp-MRI should be done every 2 years then tick 2,4,6,8 and 10 years.		
Answer Options	**Response Percent**	**Response Count**
9.5 years after enrolment	3.2%	2
10.0 years after enrolment	51.6%	32
	answered question	**62**
	skipped question	**58**

This question was skipped if the respondent disagreed with routine mp-MRI during AS.

Table 5.5. Routine mp-MRI during AS

Multi-parametric MRI (mp-MRI) should be done routinely at specific time points during active surveillance for low risk localised prostate cancer (even if there are no clinical changes).		
Answer Options	**Response Percent**	**Response Count**
Agree	49.0%	50
Disagree	15.7%	16
Neither agree or disagree, more evidence is needed to establish the role of routine mp-MRI during active surveillance	35.3%	36
Comments about your answer (optional – see table below)		9
	answered question	**102**
	skipped question	**0**

3

Table 5.6. Comments about the above question (Round 3 only)

I have been told that this can substitute for template biopsy
Should be done at the start
At year 1 and before re-biopsy at year 1.. After that only if PSA rises
The increase in MRI for surveillance will improve the reliability of this monitoring tool. this should be done in conjunction with repeat biopsies and done on alternate years.
At time of re-biopsy
If no change in PSA, DRE or amount and grade of cancer on repeat biopsy, then MR I feel is unecessary.
mp MRI should be done prior to AS to identify patients with focal abnormality suitable for targeted biopsy (transperineal)
PSA doubling within a year should be an indication for an MRI or any other "large" noticeable change. I do not think a routine scan is necessary. The less medical interference the better.
"Routinely" needs to be defined, as well as "clinical changes"

5. PSA measurement during active surveillance

1 **Table 6.1. PSA doubling time**

PSA doubling time (the time taken for PSA level to double in value) should be calculated in men on active surveillance for low risk localised prostate cancer.

Answer Options	Response Percent	Response Count
Agree	**77.2%**	**112**
Neutral (neither agree nor disagree)	15.9%	23
Disagree	6.9%	10
	answered question	**145**
	skipped question	**7**

This question was removed after round 1 because consensus was reached.

1 **Table 6.2. PSA velocity**

PSA velocity (the speed of change of PSA over time) should be calculated in men on active surveillance for low risk prostate cancer.

Answer Options	Response Percent	Response Count
Agree	**70.1%**	**103**
Neutral (neither agree nor disagree)	22.4%	33
Disagree	7.5%	11
	answered question	**147**
	skipped question	**5**

This question was removed after round 1 because consensus was reached.

1

Table 6.3. Frequency of PSA measurement during active surveillance (Round 1 only)

How often should prostate specific antigen (PSA) be measured in men on active surveillance for low risk localised prostate cancer?

Answer Options	Response Percent	Response Count
PSA should never be measured	0.0%	0
Every month	1.4%	2
Every 2 months	1.4%	2
Every 3 months	48.6%	71
Every 4 months	17.8%	26
Every 6 months	30.8%	45
	answered question	**146**
	skipped question	**6**

This question was rephrased for round 2

2

Table 6.4. Frequency of PSA measurement during active surveillance

How often should prostate specific antigen (PSA) be measured in men on active surveillance for low risk localised prostate cancer?

Answer Options	Response Percent	Response Count
Every 3 months	59.5%	66
Every 6 months	40.5%	45
Other (please specify)		18
	answered question	**111**
	skipped question	**9**

This question was rephrased for round 3

3

Table 6.5. Frequency of PSA measurement during active surveillance

How often should prostate specific antigen (PSA) be measured in men on active surveillance for low risk localised prostate cancer?

Answer Options	every 3 months	every 4 months	every 6 months	Response Count
During the first year of active surveillance	66 (65.4%)	14 (13.9%)	21 (20.8%))	101
During the second year of active surveillance	25 (24.5%))	29 (28.4%)	48 (47.1%)	102
During the fifth year of active surveillance	7 (7.1%)	12 (12.1%)	**80 (81.0%)**	99
			answered question	**102**
			skipped question	**0**

7. Involvement of primary care in PSA monitoring during active surveillance

1 2

Table 7.1. PSA monitoring in primary care during active surveillance

PSA monitoring can be carried out in primary care for men on active surveillance for low risk localised prostate cancer.

	Round 1		Round 2		Round 3	
Answer Options	**Response Per-cent**	**Response Count**	**Response Percent**	**Response Count**	**Response Percent**	**Response Count**
Agree	45.2%	66	63.5%	73	-	-
Neutral (neither agree nor disagree)	19.9%	29	-	-	-	-
Disagree	34.9%	51	36.5%	42	-	-
answered question		**146**		**115**		**-**
skipped question		**6**		**5**		**-**

This question was rephrased after round 2. Respondents had the option to add specific comments during round 2

2

Table 7.2. Comments about primary care PSA monitoring in round 2

Shared - alternate PSAs with GP and urologist/specialist nurse
Assuming selected on the basis of TP biopsy
Testing can be carried out in primary care, but urology departments should maintain a central register of all patients under surveillance with ongoing PSA results as a fail safe procedure. Missing results should be chased up, and patients removed from active surveillance properly notified.
should be carried out either in primary care or new approach - give patient ownership and opportunity for alternative settings
Too easy for a PSA change to be missed in Primary care.

GP should also be able to confidently examine prostate and be able to spot sig.ns of disease progression
There are so many new developments in research I should like to see my Consultant every 4 months even if it is litterally for a couple of minutes to report no change in PSA level
this is an active management - if in primary care patients should not be suitable for surveillance but watchful waiting.
Only people who are happy to examine the prostate on each visit should monitor these men
Provided there is a co-operative care model
I consider that monitoring should be carried out by a consultant
Patients appreciate support form attending a specialist clinic
i have seen many disasters due to poor education of GPs
After first 2 years
PSA can be carried out in primary care however MRI scanning may be less easy to arrange. also PSA is only one indicator of disease status (MRI, DRE etc)
But needs an agreed protocol
It's too subtle for primary care, and men often need to re-discuss rational for AS
Can be carried out in primary care provided there is register of patients, formal monitoring for patients lost to follow up, clear guidelines for each patient and easy access to advice
If you are saying just taking the blood test, then obviously that could be done in primary care, but if there is discussion about changes in the PSA then that needs to be handled by specialists. I think that the issues surrounding active surveillance are so complex that even specialists have to be careful how they discuss matters. The PIVOT trial would suggest that active surveillance is good but I am concerned it should be "active" and not "passive" surveillance.
Often doesnt work in practice, we use remote monitoring with PSA tracking database
I think they should be monitored by a Urologist for a period of time prior to referral to primary care.
If there are solid governance protocols eg remote moniotring then GP follow up is possible
I think it's possible only if there's a GP with a special interest in the problem, who liaises with urologists who also do this.
active surveillance should not be carried out in primary care
Having checks done by experienced cancer doctors more benifical than Doctors who are overworked !
only once we have well established evidence and protocol in secondary care. most gp has no idea how complex the log formula for calculating psa-

doubling time is or how to do it is
Need dre also
Yes, In the long term for a pt with stable disease
this may save persons travelling long distances
Gps are sometimes poor at arranging and acting on results, and do not like this protocol
Recall systems and clear guidelines need to be in place
Results of discharge to primary care after RP show very great variation in understanding by GPs
Depends on the knowledge base of person monitoring and if set protocols are in place
If the PSA is within bounds - such as not doubling within a six monthly period then there is no need for consultant input.
but patients need MRI in secondary care

3

Table 7.3. PSA monitoring in primary care during active surveillance

PSA monitoring can be carried out in primary care (for example by G.P.s) for men on active surveillance for low risk localised prostate cancer IF urology departments maintain a register of such patients with a PSA tracking database and have agreed protocols and recall systems.

Answer Options	Response Percent	Response Count
Agree	**84.2%**	**85**
Disagree	15.8%	16
Comments about your answer (optional –see below)		22
	answered question	**101**
	skipped question	**1**

3

Table 7.4. Comments about primary care PSA monitoring in round 3

I would feel happier to be under active care of an acknowledged consultant
I have not seen such a system work in practice.
but annual appointment with urologist
Only if very strict control
Absolutely not - if this were a reccommendation then it would be ignored
GP 's need a good level of training to be able to safely monitor these patients. All patients should be followed up by urologist in first year.
I have anxiety about whether GPs will pick up subtle changes in prostate texture
AS is not all about the PSA - need to DRE and use clinical judgement too
I feel that GP.s are not so familiar with the prostate situation - I would have more confidence with the experts !
After 3 years maybe but up to that patients like to see a specialist who can answer their questions
See previous cooments about "active" vs "passive" surveillance
if repeat biopsies and repeat MRI are to be utilised then PSA surveillance in Primary care will make this whole programme fragmented and i'm not sure this is in thebest interest of patients
this is an active, ongoing treatment, if not on active surveillance they should be on watchful waiting for discharge to primary care with a PSA threshold for re-referral
We either discharge to the GP or keep the patient us keeping clinical responsibility for tracking patient means the patient will be lost in a no mans land.
I think PSA monitoring is not very useful and so it doesnt matter who does it
Tracking systems are easy to talk about but the practicalities are considerable. All patients should be confirmed low risk disease following TP biopsy before considering discharge to Primary care follow up
What is a PSA tracking database? Does this mean the Consultant actually monitoring?
An excellent idea, tracking, protocols and recall system.
If I've got to spend time tracking PSA's I might as well see the patients as well. How would my time be reimbursed for maintaining and monitoring the register?

I want the monitoring to be done by my consultant
As long as see also done and trus biopsies
GPs need to be better informed of what constitutes significant changes to PSA levels so referral to urology be initiated

8. Digital rectal examination during active surveillance

1 2

Table 8.1 How often should DRE be done during active surveillance? (Rounds 1 & 2)

How often should digital rectal examination be done in men on active surveillance for low risk localised prostate cancer?

	Round 1		Round 2		Round 3	
Answer Options	**Response Percent**	**Response Count**	**Response Percent**	**Response Count**	**Response Percent**	**Response Count**
Never	13.1%	19	12.7%	15		
Every 2 months	0.0%	0	-	-	-	-
Every 3 months	12.4%	18	-	-	-	-
Every 4 months	2.8%	4	35.6%	42	-	-
Every 6 months	33.8%	49	-	-	-	-
Every year	37.9%	55	51.7%	61	-	-
answered question		**145**		**118**		**-**
skipped question		**7**		**2**		**-**

The number of options was reduced for round 2 and this question was rephrased for round 3.

3 **Table 8.2 How often should DRE be done during active surveillance?**

How often should digital rectal examination (DRE) be performed in men on active surveillance for low risk localised prostate cancer?				
Answer Options	**never**	**every 6 months**	**annually**	**Response Count**
During the first year of active surveillance	15 (15.3%)	41 (41.8%)	42 (42.9%)	98
During the second year of active surveillance	15 (15.6%)	28 (29.2%)	53 (55.2%)	96
During the fifth year of active surveillance	16 (16.3%)	9 (9.2%)	**73 (74.5%)**	98
			answered question	**99**
			skipped question	**3**

9. Reducing the intensity of active surveillance

1 2

Table 9.1 When could the intensity of AS be reduced?

After what time should the follow-up protocol for active surveillance of men with low risk localised prostate cancer be reduced (for example by reducing the frequency of tests)?

	Round 1		Round 2		Round 3	
Answer Options	**Response Percent**	**Response Count**	**Response Percent**	**Response Count**	**Response Percent**	**Response Count**
Never	11.6%	17	12.0%	14	-	-
After 1 year of active surveillance	6.1%	9	7.7%	9	-	-
After 2 years of active surveillance	27.9%	41	26.5%	31	-	-
After 5 years of active surveillance	19.7%	29	12.8%	15	-	-
After 10 years of active surveillance	4.8%	7	6.8%	8	-	-
At any time with the clinician's and patient's agreement	29.9%	44	34.2%	40	-	-
answered question		**147**		**117**		**-**
skipped question		**5**		**3**		**-**

This question was rephrased for round 3. Respondents could add comments during round 2 – see below:

2

Table 9.2 Comments on reducing the intensity of AS during round 2

Assuming that all parameters confirm low risk disease inc MRI & TP Biopsy after 5 years patient could be discharged to primary care with parameters for re referral. If patient Intermediate risk then FU should continue shared between Primary & secondary care for 10 years
After 5 years it would be fair to have a serious conversation about continuing, with 10 years as a reasonable long stop decision point, but surveillance should be cancelled earlier with clinician and patient agreement.
Depends on biological age and when things change from active surveillance (implying treatment intervention) to monitoring
When the patient reaches an age or develops other co-morbidities where radical treatment would no longer be considered
Patient,s choice is very important. However they need to be explicitly warned about risk of unrecognised disease progression if they decide to prolong diagnostic intervall
I think it wrong to set a rigid timetable, but there should be a minimum period for which I am not qualified to give an opinion
Would then go to every 6 months for the next 3 years and then annual PSA only
This is a difficult one because there is always a chance that the cancer could be more active and the PSA rise
This should be tailored to the age of the patient at the time of detection. There should be active surveillance until the patient reaches an age or develops circumstances where they will not longer benefit from radical treatment or until the the patient or the clinican wishes to stop.
If restaging biopsies are negative reduce to 6 monthly
Only if the patient will not benefit from active treatment (life expectancy less then 10 years)
Until it's possible to predict who will progress, it should go on until 70 years or so unless both GP and patient agree
if you have a template biopsy it may well be that depending on age of patient that evidence will show in future that no follow up is needed only for some group . centres like cambridge and guys who perform lots of template biopsies will be best placed to answer this question in the near future. s
Depends on patients sge- men over 75 less aggressive protocol of watchful waiting
decreases at both 1 and 2 years possible
again as agreed with specialists experience
We don't know the answer so need to keep an eye on these patients
I'm not qualified to answer that
Dependant on increasing co-morbidity/age etc.
PSA 6 monthly thereafter
After seven years I think is optimum - as I believe that it is a general time span of change for most of humanity.
typically when patients get sufficiently old or frail that radical treatment would no longer be appropriate

This is dependent of the clinical scenario and maybe appropriate in some cases
I don't know the answer to this.

3

Table 9.3 When could the intensity of AS be reduced?

In men with low risk localised prostate cancer who have not developed any adverse risk factors and who remain candidates for curative treatment, at what time should the follow-up protocol for active surveillance be reduced? (We acknowledge that the protocol might be reduced at any time with the clinician's and patient's agreement).

Answer Options	Response Percent	Response Count
Never	27.7%	28
After 2 years of active surveillance	17.8%	18
After 5 years of active surveillance	47.5%	48
Other (please specify – see below)	6.9	7
	answered question	**101**
	skipped question	**1**

3

Table 9.4 Comments on other time points for reducing the intensity of AS during round 3

depends on age and life expectancy of patient
depends on the pt's age/ comorbilities - might not be suitable for further treatment options and his PSA
Follow up should be life-long
until no longer a candidate for curative treatment
10 years
Seven years would be preferable.
At 75 yrs old
when life. expectancy is less than 10 yearsmove to watchful wait protocol

Survey Questions Round 1

Why are we doing this survey?

Active surveillance is part of a curative strategy and is aimed at men with localised prostate cancer who are suitable for radical treatments, keeping them within a 'window of curability' so that only those whose tumours are showing signs of progressing, or those with a preference for intervention move into radical treatments. Active surveillance may thus avoid or delay the need for radiation or surgery.

However, there is a lack of evidence about which active surveillance protocol is most effective in keeping men within the window of curability. The group updating the nICE guideline for prostate cancer is therefore seeking the consensus opinion of the prostate cancer community to help define the optimal active surveillance protocol in England and Wales. This survey aims to measure that consensus.

In this survey we assume that the proposed active surveillance protocol is for a man with low-risk localised prostate cnacer. Low risk localised prostate cnacer is defined here as:

- Clinical stage T1c
- Gleason score of 3+3
- Prostate-specific antigen (PSA) level of 10 ng/ml or less
- Diagnosed using prostate biopsy of at least 10 cores
- With cancer in less than 50% of the ottal number of biopsy cores
- With less than 10 mm of any core involved

Your personal or professional experience of active surveillance for prostate cancer

1. In what capacity have you experienced active surveillance for prostate cancer? Please tick any that apply.

- Man diagnosed with prostate cancer
- Partner or carer of a man with prostate cancer
- Support worker (for example in a cancer charity or support group)
- Urologist
- Pathologist
- Radiologist
- Oncologist
- Specialist Nurse
- Nurse consultant
- General Practitioner
- I have no personal or professional experience of active surveillance for prostate cancer
- Other (please specify)

Tests BEFORE enrolment onto active surveillance

2. Men considering active surveillance for low risk localised prostate cancer should undergo a second prostate biopsy before enrolment. (Assume that the man's initial prostate biopsy included at least 10 cores).

- Agree

- Neutral (neither agree nor disagree)
- Disagree

3. What technique should be used for re-biopsy prior to enrolment on active surveillance for low risk localised prostate cancer? (Assume that the man's initial prostate biopsy included at least 10 cores).

- No re-biopsy should be done before enrolment
- 10 to 14 cores transrectal ultrasound (TRUS) guided biopsy
- More than 14 cores TRUS biopsy
- Transperineal template biopsy

4. Men considering active surveillance for low risk localised prostate cancer should undergo multi-parametric magnetic resonance imaging (see definition below) before enrolment. (Assume that each man's initial prostate biopsy included at least 10 cores).

- Agree
- Neutral (neither agree nor disagree)
- Disagree
- Multi-parametricMRI incorporates both morphological T2-weighted sequences and functional t echniques (for example diffusion-weighted MRI or dynamic contrast-enhanced MRI).

Repeat biopsy DURING active surveillance

5. In what circumstances should prostate biopsy be repeated after enrolment on active surveillance for low risk localised prostate cancer? Please choose all that apply.

- Never
- If there are clinical or radiological changes
- Routi-
  nely - even if there are no clinical or radiological changes. (Please specify below when routine biopsy or biopsies should be done)

- Clinical or radiological changes that prompt biopsy during active surveillance

6. Which tests are useful in deciding whether a prostate re-biopsy is necessary during active surveillance for low risk localised prostate cancer? Please choose all that apply.

- Prostate-specific antigen (PSA)
- Digital rectal examination (DRE)
- Multi-parametric magnetic resonance imaging (MRI)
- Other test(s) (please specify)
- Repeat multi-parametric MRI DURING active surveillance

7. When should multi-parametric MRI be done during active surveillance for low risk localised prostate cancer? Please choose all that apply.

- Never
- If there are clinical changes (for example in PSA or DRE)
- Routi-
  nely - even if there are no clinical changes (please specify below when routine MRI should be done)

- PSA monitoring during active surveillance

8. How often should prostate specific antigen (PSA) be measured in men on active surveillance for low risk localised prostate cancer?

- PSA should never be measured
- Every month
- Every 2 months
- Every 3 months
- Every 4 months
- Every 6 months

9. PSA doubling time (the time taken for PSA level to double in value) should be calculated in men on active surveillance for low risk localised prostate cancer.

- Agree
- Neutral (neither agree nor disagree)
- Disagree

10. PSA velocity (the speed of change of PSA over time) should be calculated in men on active surveillance for low risk prostate cancer.

- Agree
- Neutral (neither agree nor disagree)
- Disagree

11. PSA monitoring can be carried out in primary care for men on active surveillance for low risk localised prostate cancer.

- Agree
- Neutral (neither agree nor disagree)
- Disagree
- Digital rectal examination during active surveillance

12. How often should digital rectal examination be done in men on active surveillance for low risk localised prostate cancer?

- Never
- Every 2 months
- Every 3 months
- Every 4 months
- Every 6 months
- Every year
- Reducing the intensity of active surveillance

13. After what time should the follow-up protocol for active surveillance of men with low risk localised prostate cancer be reduced (for example by reducing the frequency of tests)?

- Never
- After 1 year of active surveillance
- After 2 years of active surveillance
- After 5 years of active surveillance
- After 10 years of active surveillance
- At any time with the clinician's and patient's agreement

Comments (optional)

14. If you have any comments about your answers above or about the optimal protocol for active surveillance in men with low risk localised prostate cancer, please add them here.

Survey Questions Round 2

Introduction

This is the second round of the consensus survey to help define an active surveillance protocol for low risk localised prostate cancer. We have removed any items from the survey where consensus was reached in the first round (agreement of 70% or more). We have also reworded some of the questions in the light of responses from the first round.

The survey is done on behalf of the group updating the NICE guideline for prostate cancer

In this survey we assume that the proposed active surveillance protocol is for a man with low-risk localised prostate cancer Low risk localised prostate cancer is defined here as:

- Clinical stage T1c
- Gleason score of 3+3
- Prostate-specific antigen (PSA) level of 10 ng/ml or less
- Diagnosed using prostate biopsy of at least 10 cores
- With cancer in less than 50% of the total number of biopsy cores
- With less than 10 mm of any core involved.

We are trying to define an optimal active surveillance protocol, so please don't feel constrained by the protocol currently used in your own organisation or whether the tests are available locally - instead try to imagine what you believe is the ideal active surveillance protocol.

Tests BEFORE enrolment onto active surveillance

The questions on this page relate to men diagnosed with low risk localised prostate cancer on their initial prostate biopsy and who are considering active surveillance. Are additional tests required before enrolment?

2. Men considering active surveillance for low risk localised prostate cancer should undergo a second prostate biopsy before enrolment. (Assume that the man's initial prostate biopsy included at least 10 cores).

- Agree
- Disagree
- Comments about your answer (optional)

3. What technique should be used for re-biopsy prior to enrolment on active surveillance for low risk localised prostate cancer? (Assume that the man's initial prostate biopsy included at least 10 cores).

- No re-biopsy should be done before enrolment
- 10 to 14 cores transrectal ultrasound (TRUS) guided biopsy
- More than 14 cores TRUS biopsy

- Transperineal template biopsy

4. Men considering active surveillance for low risk localised prostate cancer should undergo multi-parametric magnetic resonance imaging (see definition below) before enrolment. (Assume that each man's initial prostate biopsy included at least 10 cores).

- Agree
- Disagree

Multi-parametric MRI incorporates both morphological T2-weighted sequences and functional techniques (for example diffusion-weighted MRI or dynamic contrast-enhanced MRI).

Repeat biopsy DURING active surveillance

The following questions in this survey relate to men with low risk localised prostate cancer who are enrolled on active surveillance. What tests should be done during active surveillance?

5. Prostate re-biopsy should be done if there are clinical or radiological changes during active surveillance for low risk localised prostate cancer.

- Agree
- Disagree

6. Prostate re-biopsy should be done routinely at specified time points during active surveillance for low risk localised prostate cancer (even if there are no clinical or radiological changes).

- Agree
- Disagree

Time points for routine repeat prostate biopsy DURING active surveillance.

7. At what time points during the first ten years of active surveillance for low risklocalised prostate cancer should routine prostate re-biopsies be done? For example ifyou believe biopsies should be done every 2 years then tick 2,4,6,8 and 10 years.

- Before enrolment
- 0.5 years after enrolment
- 1 year after enrolment
- 1.5 years after enrolment
- 2 years after enrolment
- 2.5 years after enrolment
- 3 years after enrolment
- 3.5 years after enrolment
- 4 years after enrolment
- 4.5 years after enrolment
- 5 years after enrolment
- 5.5 years after enrolment
- 6 years after enrolment
- 6.5 years after enrolment
- 7 years after enrolment
- 7.5 years after enrolment
- 8 years after enrolment

- 8.5 years after enrolment
- 9 years after enrolment
- 9.5 years after enrolment
- 10 years after enrolment

Repeat multi-parametric MRI DURING active surveillance

8. Multi-parametric MRI (mp-MRI) should be done if there are clinical changes (for example in PSA or DRE) during active surveillance for low risk localised prostate cancer.

- Agree
- Disagree

9. Multi-parametric MRI (mp-MRI) should be done routinely at specific time points during active surveillance for low risk localised prostate cancer (even if there are no clinical changes).

- Agree
- Disagree

Time points for routine mp-MRI DURING active surveillance.

10. At what time points during the first ten years of active surveillance for low risk localised prostate cancer should routine multiparametric MRI be done? For example if you believe mp-MRI should be done every 2 years then tick 2,4,6,8 and 10 years.

- Before enrolment
- 0.5 years after enrolment
- 1 year after enrolment
- 1.5 years after enrolment
- 2 years after enrolment
- 2.5 years after enrolment
- 3 years after enrolment
- 3.5 years after enrolment
- 4 years after enrolment
- 4.5 years after enrolment
- 5 years after enrolment
- 5.5 years after enrolment
- 6 years after enrolment
- 6.5 years after enrolment
- 7 years after enrolment
- 7.5 years after enrolment
- 8 years after enrolment
- 8.5 years after enrolment
- 9 years after enrolment
- 9.5 years after enrolment
- 10 years after enrolment

PSA monitoring during active surveillance

11. How often should prostate specific antigen (PSA) be measured in men on active surveillance for low risk localised prostate cancer?

- Every 3 months
- Every 6 months
- Other (please specify)

12. PSA monitoring can be carried out in primary care (for example by G.P.s) for men on active surveillance for low risk localised prostate cancer.

- Agree
- Disagree
- Comments about your answer (optional)

Digital rectal examination during active surveillance

13. How often should digital rectal examination be done in men on active surveillance for low risk localised prostate cancer?

- Never
- Every 6 months
- Every year

Reducing the intensity of active surveillance

14. After what time should the follow-up protocol for active surveillance of men with low risk localised prostate cancer be reduced (for example by reducing the frequency of tests)?

- Never
- After 1 year of active surveillance
- After 2 years of active surveillance
- After 5 years of active surveillance
- After 10 years of active surveillance
- At any time with the clinician's and patient's agreement
- Comments about your answer (optional)

Comments (optional)

15. If you have any comments about your answers above or about the optimal protocol for active surveillance in men with low risk localised prostate cancer, please add them here.

Survey Questions Round 3

Introduction

This is the third round of the consensus survey to help define an active surveillance protocol for low risk localised prostate cancer. We have removed any items from the survey where consensus was reached in the second round (agreement of 2/3 or more). We have also reworded some of the questions in the light of responses from the second round. The survey is done on behalf of the group updating the NICE guideline for prostate cancer

In this survey we assume that the proposed active surveillance protocol is for a man with low risk localised prostate cancer. Low risk localised prostate cancer is defined here as

- Clinical stage T1c
- Gleason score of 3+3
- Prostate-specific antigen (PSA) level of 10 ng/ml or less
- Diagnosed using prostate biopsy of at least 10 cores
- With cancer in less than 50% of the total number of biopsy cores
- With less than 10 mm of any core involved.

We acknowledge that men whose prostate cancer does not meet this definition might choose active surveillance. You will have the opportunity to put your views about definitions of low risk prostate cancer and the appropriateness of active surveillance when the draft guideline is released for stakeholder consultation in 2013.

We are trying to define an optimal active surveillance protocol, so please don't feel constrained by the protocol currently used in your own organisation or whether the tests are available locally - instead try to imagine what you believe is the ideal active surveillance protocol

Repeat biopsy DURING active surveillance

2. When should routine prostate re-biopsy be done during the first five years of active surveillance for low risk localised prostate cancer?

- Never
- Annually for 5 years
- At 1, 3 and 5 years
- Other (please specify)

Repeat multi-parametric MRI DURING active surveillance

3. Multi-parametric MRI (mp-MRI) should be done routinely at specific time points during active surveillance for low risk localised prostate cancer (even if there are no clinical changes).

- Agree
- Disagree
- Neither agree or disagree, more evidence is needed to establish the role of routine mp-MRI during active surveillance
- Comments about your answer (optional)

Frequency of routine tests during active surveillance

4. How often should prostate specific antigen (PSA) be measured in men on active surveillance for low risk localised prostate cancer?

	every 3 months	every 4 months	every 6 months
During the first year of active surveillance			
During the second year of active surveillance			
During the fifth year of active surveillance			

5. How often should digital rectal examination (DRE) be performed in men on active surveillance for low risk localised prostate cancer?

	never	every 6 months	annually
During the first year of active surveillance			
During the second year of active surveillance			
During the fifth year of active surveillance			

Primary care involvement in active surveillance for prostate cancer.

6. PSA monitoring can be carried out in primary care (for example by G.P.s) for men on active surveillance for low risk localised prostate cancer IF urology departments maintain a register of such patients with a PSA tracking database and have agreed protocols and recall systems.

- Agree
- Disagree
- Comments about your answer (optional)

Reducing the intensity of active surveillance

7. In men with low risk localised prostate cancer who have not developed any adverse risk factors and who remain candidates for curative treatment, at what time should the follow-up protocol for active surveillance be reduced? (We acknowledge that the protocol might be reduced at any time with the clinician's and patient's agreement).

- Never
- After 2 years of active surveillance
- After 5 years of active surveillance
- Other (please specify)
- Comments (optional)

8. If you have any comments about your answers above or about the optimal protocol for active surveillance in men with low risk localised prostate cancer, please add them here.

Appendix D – Rationale for the top five 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 **[2008].**

Potential Criterion	**Explanation**	
Importance to patients of the population	What would be the impact of any new of altered guidance on the population(for example, acceptability to patients, quality of life, morbidity or disease prevalence, severity of disease, or mortality)?	Able to target those who need treatment more effectively May avoid unnecessary treatment
Relevance to NICE guidance	How would the answer to this question change future NICE guidance (that is, generate new knowledge and/or evidence)? How important is the question to the overall guideline? High: the research is essential to inform future updates of key recommendations in the guideline Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates Low: the research is of interest and will existing evidence gaps	Be able to more accurately define risk categories and thereby appropriate treatments – leading to a more individualised care pathway. High
Relevance to the NHS	What would be the impact on the NHS and (where relevant) the public sector of any new of altered guidance (for example, financial advantage, effect on staff, impact on strategic planning, or service delivery)?	Decreased mortality and morbidity from prostate cancer. Reduce spend/more predictable by more targeted treatments. Give better idea of numbers of men needing which treatments allowing more precision when commissioning services.
National priorities	Is the question relevant to a national priority area (such as a National Service Framework or White Paper)? The relevant document should be specified	Yes. Improving Outcomes – a Strategy for Cancer Welsh equivalent ”Together for Health, Cancer Delivery Plan for the NHS to 2016”
Current evidence base	What are the problems with the current evidence base?)that is, why is further research required?) Are there any relevant ongoing trials that may resolve the uncertainty?	Poor quality evidence and heterogeneity between studies. Means can’t draw any conclusions from the evidence base. PROTECT may provide information to assist with this research question.
Equality	Does the research recommendation have any relevance to equality? For example, does it focus on groups needing special	No

	consideration, or focus on a technology that is not available for use by people with certain disabilities? What is known about the impact of the intervention on the health gradient?	
Feasibility	Can the proposed research be carried out within a realistic timescale? Would the sample size required to resolve the question be feasible? Would the expense needed to resolve the question be warranted? Are there any ethical or technical issues?	Yes, bearing in mind the natural history of prostate cancer. Yes Yes No
Other comments	Any other important issues that should be mentioned, such as potential funders, outcomes of previous attempts to address this issue or methodological problems	Prostate Cancer UK is a potential funder. Future research would require realistic funding. Previous trials in this area were hampered because of small sample size and a lack of clinically well annotated biopsy repositories, lack of validation cohorts

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

Potential Criterion	**Explanation**	
Importance to patients of the population	What would be the impact of any new of altered guidance on the population(for example, acceptability to patients, quality of life, morbidity or disease prevalence, severity of disease, or mortality)?	Define optimal combination of ADT and radiotherapy in this group of patients. Potential quality of life benefits by reducing breadth of side effects. Potential improvements in time to relapse.
Relevance to NICE guidance	How would the answer to this question change future NICE guidance (that is, generate new knowledge and/or evidence)? How important is the question to the overall guideline? High: the research is essential to inform future updates of key recommendations in the guideline Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates Low: the research is of interest and will existing evidence gaps	Clarify the role of androgen deprivation therapy in patients receiving high dose radiotherapy – currently don't have any evidence on high-dose. Potentially increase the impact and strength of current recommendations on radiotherapy. Medium
Relevance to the NHS	What would be the impact on the NHS and (where relevant) the public sector of any new of altered guidance (for example, financial advantage, effect on staff, impact on strategic planning, or service delivery)?	Alter radiotherapy planning arrangements – help define future radiotherapy utilisation. If radiotherapy comes out as more effective, would need more radiotherapy but less hormones.
National priorities	Is the question relevant to a national priority area (such as a National Service Framework or White Paper)? The relevant document should be specified	Improving Outcomes – a Strategy for Cancer Welsh equivalent "Together for Health, Cancer Delivery Plan for the NHS to 2016"IMRT A guide for commissioners by NCAT on behalf of NRAG Radiotherapy: developing a world class service for England, NRAG 2007
Current evidence base	What are the problems with the current evidence base?)that is, why is further research required?) Are there any relevant ongoing trials that may resolve the uncertainty?	Used lower dose of radiotherapy than current practice, and non_IMRT techniques. Brachytherapy evidence based on small trials. No
Equality	Does the research recommendation have any relevance to equality? For example, does it focus on groups needing special consideration, or focus on a technology that is not available for use by people with	No

	certain disabilities? What is known about the impact of the intervention on the health gradient?	
Feasibility	Can the proposed research be carried out within a realistic timescale? Would the sample size required to resolve the question be feasible? Would the expense needed to resolve the question be warranted? Are there any ethical or technical issues?	Yes Yes Yes No
Other comments	Any other important issues that should be mentioned, such as potential funders, outcomes of previous attempts to address this issue or methodological problems	Radiotherapy innovation fund announced by Government in 2012 – available from April 2013.

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

Potential Criterion	**Explanation**	
Importance to patients of the population	What would be the impact of any new of altered guidance on the population(for example, acceptability to patients, quality of life, morbidity or disease prevalence, severity of disease, or mortality)?	Currently role of local salvage is unknown; on basis of this work patients could make informed choice regarding value of local salvage balancing chance of further disease control with toxicity
Relevance to NICE guidance	How would the answer to this question change future NICE guidance (that is, generate new knowledge and/or evidence)? How important is the question to the overall guideline? • High: the research is essential to inform future updates of key recommendations in the guideline • Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates • Low: the research is of interest and will existing evidence gaps	Establish role of local salvage which at present is unknown; future NICE guidance could give clear options for value of local salvage High/medium
Relevance to the NHS	What would be the impact on the NHS and (where relevant) the public sector of any new of altered guidance (for example, financial advantage, effect on staff, impact on strategic planning, or service delivery)?	Currently few patients receive local salvage and this takes many forms; surgery, radiotherapy, HiFU, cryotherapy are all used. This would standardise approach to this problem but there are implications for more resources in one or more of these areas
National priorities	Is the question relevant to a national priority area (such as a National Service Framework or White Paper)? The relevant document should be specified	Improving Outcomes – a Strategy for Cancer Welsh equivalent ”Together for Health, Cancer Delivery Plan for the NHS to 2016”
Current evidence base	What are the problems with the current evidence base?)that is, why is further research required?) Are there any relevant ongoing trials that may resolve the uncertainty?	There are only very poor quality cohort data in selected patients for the efficacy and toxicity of local treatment in relapse No trials known
Equality	Does the research recommendation have any relevance to equality? For example, does it focus on groups needing special consideration, or focus on a technology that is not available for use by people with certain disabilities? What is known about the impact of the inter-	No

	vention on the health gradient?	
Feasibility	Can the proposed research be carried out within a realistic timescale? Would the sample size required to resolve the question be feasible? Would the expense needed to resolve the question be warranted? Are there any ethical or technical issues?	Yes Yes Yes
Other comments	Any other important issues that should be mentioned, such as potential funders, outcomes of previous attempts to address this issue or methodological problems	No

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

Potential Criterion	**Explanation**	
Importance to patients of the population	What would be the impact of any new of altered guidance on the population(for example, acceptability to patients, quality of life, morbidity or disease prevalence, severity of disease, or mortality)?	Reduction in severity of osteoporosis and risk of morbidity from skeletal related events. Improved quality of life.
Relevance to NICE guidance	How would the answer to this question change future NICE guidance (that is, generate new knowledge and/or evidence)? How important is the question to the overall guideline? • High: the research is essential to inform future updates of key recommendations in the guideline • Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates • Low: the research is of interest and will existing evidence gaps	Significant numbers of men on ADT have osteoporosis. The impact of assessment and treatment to prevent skeletal related events in men on ADT is a key issue in prostate cancer treatment. The optimal type of treatment remains poorly defined in this group of men
Relevance to the NHS	What would be the impact on the NHS and (where relevant) the public sector of any new of altered guidance (for example, financial advantage, effect on staff, impact on strategic planning, or service delivery)?	Would allow targeted treatment of ADT induced osteoporosis
National priorities	Is the question relevant to a national priority area (such as a National Service Framework or White Paper)? The relevant document should be specified	N/A
Current evidence base	What are the problems with the current evidence base? (that is, why is further research required?) Are there any relevant ongoing trials that may resolve the uncertainty?	The data on osteoporosis in this particular group of patients are weak.
Equality	Does the research recommendation have any relevance to equality? For example, does it focus on groups needing special consideration, or focus on a technology that is not available for use by people with certain disabilities? What is known about the impact of the intervention on the health gradient?	N/A
Feasibility	Can the proposed research be carried out within a realistic timescale?	Yes Large numbers of men are commenced on ADT for > 6

	Would the sample size required to resolve the question be feasible? Would the expense needed to resolve the question be warranted? Are there any ethical or technical issues?	months and therefore eligible for inclusion in prospective studies. Skeletal related events such as hip fracture and associated mortality indicate the need for focussed and effective treatment. DXA scan equipment and other novel scanning equipment based on CT scans and MRI widely available.
Other comments	Any other important issues that should be mentioned, such as potential funders, outcomes of previous attempts to address this issue or methodological problems	

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

Potential Criterion	**Explanation**	
Importance to patients of the population	What would be the impact of any new of altered guidance on the population(for example, acceptability to patients, quality of life, morbidity or disease prevalence, severity of disease, or mortality)?	It would be helpful for men to know whether the effect continues with exercise regimens of longer than 12 weeks and help them and their clinicians determine the best exercise programme throughout their ADT.
Relevance to NICE guidance	How would the answer to this question change future NICE guidance (that is, generate new knowledge and/or evidence)? How important is the question to the overall guideline? • High: the research is essential to inform future updates of key recommendations in the guideline • Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates • Low: the research is of interest and will existing evidence gaps	It would help to inform more specific recommendations to men and health professionals on the duration of exercise programmes whilst on ADT. High – this is an area of growing importance as more men are being diagnosed with prostate cancer, many of whom will be prescribed long term ADT. It would help make future updates more specific.
Relevance to the NHS	What would be the impact on the NHS and (where relevant) the public sector of any new of altered guidance (for example, financial advantage, effect on staff, impact on strategic planning, or service delivery)?	It would provide more specific guidance to health professionals who are prescribing exercise interventions to men on long term ADT. This may make any exercise programmes more cost-effective as they could potentially provide greater clinical/patient benefit if found to be effective over a longer period of time. There may be an impact on public health or social services if longer duration exercise programmes are found to have additional benefits on men's health/lifestyles. Planning would be needed to ensure longer term programmes could be provided.
National priorities	Is the question relevant to a national priority area (such as a National Service Framework or White Paper)? The relevant document should be specified	• Improving Supportive and Palliative Care for Adults with Cancer, NICE 2004 • Improving Outcomes: A Strategy for Cancer, DH

		2011 • Together for Health, Welsh Government 2012 • National Standards for Rehabilitation of Adult Cancer Patients, Welsh Assembly Government 2010
Current evidence base	What are the problems with the current evidence base?)that is, why is further research required?) Are there any relevant ongoing trials that may resolve the uncertainty?	Interventions that the evidence is based on were only for a maximum of 12 weeks. It is therefore not possible to recommend whether a regular, supervised combined resistance and aerobic exercise programme should be extended for a longer term. NB men on long term ADT will be on the therapy for many months/years and so may benefit from potential continued impact of longer-term structured exercise. Not aware of any relevant ongoing trials.
Equality	Does the research recommendation have any relevance to equality? For example, does it focus on groups needing special consideration, or focus on a technology that is not available for use by people with certain disabilities? What is known about the impact of the intervention on the health gradient?	The intervention may not be accessible for men with particular disabilities who are unable to partake in the recommended forms of exercise. However research could be carried out to determine whether adapted exercise programmes would be as beneficial for this group of men.
Feasibility	Can the proposed research be carried out within a realistic timescale? Would the sample size required to resolve the question be feasible? Would the expense needed to resolve the question be warranted? Are there any ethical or technical issues?	Yes Yes Yes – improvements to QoL may be cost effective and reduce the reliance of other interventions No
Other comments	Any other important issues that should be mentioned, such as potential funders, outcomes of previous attempts to address this issue or methodological problems	Potential funders: Prostate Cancer UK, Macmillan Cancer Support, Movember Foundation