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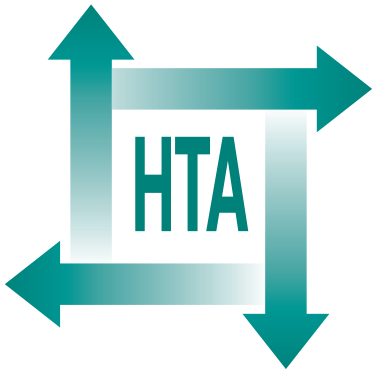

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Abstract

Clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer: a systematic review

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Objectives: To evaluate the clinical and cost-effectiveness of new and emerging technologies for early, localised prostate cancer.
Data sources: Electronic databases, reference lists of relevant articles and various health services research-related resources.
Review methods: A list of new and emerging technologies was identified and agreed. A systematic review was undertaken and selected studies were reviewed against a set of criteria. An economic model was developed and used to compare the specified newer treatments with the traditional approaches.
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 life (QoL) for brachytherapy patients was lower 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.
Conclusions: The results of the clinical effectiveness review should be viewed in the context of the quality of the available evidence. Very few randomised controlled trials (RCTs) were identified, with the majority of included studies being descriptive case series, open to patient selection bias and measuring surrogate end-points with short-term follow-up. It is difficult therefore to draw conclusions on the relative benefits or otherwise of the newer technologies owing to the lack of substantive evidence of any quality and the lack of comparisons between the newer technologies and with standard treatments. Given the lack of high-quality clinical evidence with long-term follow-up and the uncertainty surrounding the assumptions in the economic analysis, the following areas are recommended for further research: RCTs with sufficient follow-up to measure benefits in terms of overall survival to include QoL measurement to establish trade-offs between potential adverse events and benefits of treatment; the identification of prognostic risk factors among men diagnosed with early prostate cancer; QoL studies to compare the utility of health states among patients on active monitoring, patients receiving treatment and the comparable healthy population; the relationship between surrogate end-points and survival; and the adoption of standard definitions for adverse events.

Contents

List of abbreviations

3D-CRT	three-dimensional conformal radiotherapy
ADT	androgen deprivation therapy
AHFMR	Alberta Heritage Foundation for Medical Research
AHT	adjuvant hormonal therapy
BAUS	British Association of Urological Surgeons
bDFS	biochemical disease-free survival
bNED	biochemical no evidence of disease
BPH	benign prostatic hyperplasia
CI	confidence interval
CT	computed tomography
DFS	disease-free survival
DRE	digital rectal examination
DVH	dose–volume histogram
EBRT	external beam radiation therapy
FFS	failure-free survival
HCHS	hospital and community health services
HDRIr-192	high-dose-rate iridium-192
HIFU	high-intensity focused ultrasound
HRG	health resource group
HRQoL	health-related quality of life
I-125	iodine-125
ICER	incremental cost-effectiveness ratio
IIEF	International Index of Erectile Function
IMRT	intensity-modulated conformal radiotherapy
IMTT	interstitial microwave thermal therapy
iPSA	initial prostate-specific antigen
LH-RH	luteinising hormone-releasing hormone
LUTS	lower urinary tract symptoms
MLC	multileaf collimator
MRI	magnetic resonance imaging
Nd-YAG	neodymium–yttrium aluminium garnet
NHT	neoadjuvant hormonal therapy
NICE	National Institute for Clinical Excellence
NVB	neurovascular bundle
Pd-103	palladium-103
PCSWG	Prostate Cancer Speciality Working Group
PFS	progression-free survival
PSA	prostate-specific antigen
QALY	quality-adjusted life-year
QoL	quality of life

continued

List of abbreviations *continued*

RCT	randomised controlled trial
RFS	relapse-free survival
RITA	radiofrequency interstitial tumour ablation
RP	radical prostatectomy
RPI	retail price index
RR	relative risk
RTOG	Radiation Therapy and Oncology Group
SCIM-RT	short-course intensity-modulated radiotherapy
SG	standard gamble
SRT	standard radiotherapy
TAB	total androgen blockade
TNM	size of the primary *t*umour, extent of lymph-*n*ode involvement, presence or absence of *m*etastases
TRUS	transrectal ultrasound sonography
TTO	time trade-off
TURP	transurethral resection of the prostate

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Cancer of the prostate is the second most common cancer in men in England and Wales with an incidence rate of approximately 71 per 100,000. In 1999 there were 8500 deaths from prostate cancer, accounting for approximately 12% of cancer-related deaths and 3% of all deaths in men. Following the availability of prostate-specific antigen (PSA) testing, which allows symptom-free detection of the disease, there has been a sharp rise in the reported incidence of prostate cancer.

Current management of early prostate cancer includes watchful waiting, radical prostatectomy or radiotherapy. All treatments for prostate cancer may cause unwanted side-effects, including impotence and incontinence. A number of relatively new treatments are being studied in an attempt to develop therapies for early localised cancer that are effective and minimally invasive and result in fewer side-effects. New and emerging treatments include developments in radiotherapy [including brachytherapy, three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated conformal radiotherapy], new techniques in cryosurgery and hormonal therapies. Other therapies, including gene therapy, are in the very early stages of development.

Objectives

This report is a review of the clinical and cost-effectiveness of new and emerging technologies for early, localised prostate cancer. A systematic review was undertaken to identify new and emerging technologies and to evaluate clinical and cost-effectiveness through assessment of the best available evidence. The review aimed to assess clinical effectiveness in terms of survival, disease-free survival, quality of life (QoL), including complications and adverse events) and acceptability.

Methods and results

The first stage of the literature search identified 15 interventions for inclusion in the review:

- *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
- high linear energy transfer radiation
- radionuclide therapy
- vaccine therapy.

Those treatments in italics are selected for discussion.

Further systematic searching was undertaken to identify all literature relating to these interventions. In total, 104 studies evaluating 12 interventions were included in the review of clinical effectiveness. The majority of evidence was of poor quality in the form of case series. No evidence was identified relating to high linear energy transfer radiation, radionuclide therapy or vaccine therapy.

The highest quality evidence identified [13 randomised controlled trials (RCTs)] evaluated the effectiveness of NHT. No evidence of benefit was seen in terms of biochemical disease-free survival. One RCT and three case series evaluated AHT. There was no evidence of benefit in terms of survival, but there was some conflicting evidence that higher risk patients may benefit. The largest number of studies, most of which were descriptive case series, reported results for brachytherapy. There was some evidence to suggest that brachytherapy 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. Evidence in terms of complications was mixed. Lower quality evidence reported fewer complications than for standard treatments. Higher quality evidence suggested that disease-specific QoL for brachytherapy patients was lower

than for patients receiving standard treatments. The review of 3D-CRT identified four RCTs evaluating treatment-related morbidity. 3D-CRT achieved significantly fewer gastrointestinal complications than standard radiotherapy. Evidence in the form of case series suggested that higher radiation doses achieved better disease control, although patient characteristics were often reported as independent indicators of control. The review of IMRT was based on several case series, the largest of which suggested that IMRT may reduce late gastrointestinal toxicity compared with 3D-CRT. The review of cryotherapy was based on case-series evidence which reported high rates of impotence. Owing to the paucity and poor quality of evidence identified for the remaining interventions (hormonal monotherapy, HIFU, IMTT, RITA, laser photocoagulation and gene therapy), conclusions regarding their clinical effectiveness cannot be drawn.

The results of the clinical effectiveness review should be viewed in the context of the quality of the available evidence. Very few RCTs were identified, with the majority of included studies being descriptive case series, open to patient selection bias and measuring surrogate end-points with short-term follow-up. It is difficult therefore to draw conclusions on the relative benefits or otherwise of the newer technologies owing to the lack of substantive evidence of any quality and the lack of comparisons between the newer technologies and with standard treatments.

No relevant cost-effectiveness studies were identified. An economic model was therefore developed to explore the potential cost-effectiveness of newer treatments. Owing to the lack of disease-free survival data both for the treatments included in the review and for traditional treatments, cost-effectiveness estimates were based on the impact of adverse events on quality-adjusted life-years (QALYs). Owing to the paucity of evidence relating to adverse events for the majority of interventions, the assessment of cost-effectiveness was restricted to brachytherapy, 3D-CRT and cryotherapy compared with standard treatments. Of the new treatments included in the analysis, only cryotherapy appeared potentially not to be cost-effective compared with traditional treatments, owing to the associated high incidence of impotence. The economic analysis is based, however, on the assumption that newer and traditional treatments are equally effective in terms of survival and results are sensitive to the estimates of adverse events and utility values.

Recommendations for research

Given the lack of high-quality clinical evidence with long-term follow-up and the uncertainty surrounding the assumptions in the economic analysis, the following areas are recommended for further research:

- RCTs with sufficient follow-up to measure benefits in terms of overall survival to include QoL measurement to establish trade-offs between potential adverse events and benefits of treatment.
- The identification of prognostic risk factors among men diagnosed with early prostate cancer.
- QoL studies to compare the utility of health states among patients on active monitoring, patients receiving treatment and the comparable healthy population.
- The relationship between surrogate end-points and survival.
- The adoption of standard definitions for adverse events.

Chapter 1

Aim of the review

The aim of the review is to evaluate the clinical and cost-effectiveness of new and emerging technologies for early, localised [tumour, node, metastases (TNM) stages 1 and 2] prostate cancer. The specific aims of the review are:

- to identify new and emerging technologies (including but not restricted to brachytherapy and cryotherapy)
- to evaluate clinical effectiveness in terms of survival, disease-free survival, quality of life (QoL, including the adverse consequences such as incontinence and impotence) and acceptability to patients
- to evaluate cost-effectiveness in comparison with current standard treatment
- to estimate the possible overall cost in England and Wales.

Chapter 2
Background

Description of underlying health problem

Cancer of the prostate is the second most common cancer in men in England and Wales. The most recent data available report 18,300 new cases in 1997, a crude incidence rate of 71 per 100,000.[1] Sharp rises in reported incidence rates were seen in the early 1990s following the availability of prostate-specific antigen (PSA) testing, which is able to diagnose prostate cancer in symptom-free men. In 1999 there were 8500 deaths from prostate cancer: these accounted for approximately 12% of cancer deaths and 3% of all deaths in men. Trends in mortality rates show that mortality in the late 1990s was slightly below the peak in 1993–5. About 64% of men diagnosed with prostate cancer in the 3-year period 1990–2 were alive at the beginning of 1993, whereas 38% of men diagnosed in the 10 years 1983–92 were alive at the beginning of 1993. Relative survival from prostate cancer for cases diagnosed in England and Wales during 1991–3 was approximately 80% at 1 year and just under 50% at 5 years, overall increases of 12–16% points since the early 1970s.

A review of prostate cancer by Chamberlain and colleagues in 1996 includes a section on the burden of disease on health services.[2] Prostate cancer was reported most frequently as the reason for consultation with general practitioners (GPs) amongst men with cancer. The cost to the NHS for 1994 was estimated. In primary care the cost of consultations with GPs was over £2 million, while costs of prescribing for prostate cancer were £24 million (total NHS costs of prescribing were £3730 million in 1994). Hospital inpatient costs were estimated to be £19 million at 1994 prices. The review was not able to estimate outpatient costs, but it is thought that these are considerable given the large number of men with prostate cancer who are managed with active surveillance. The same is true for home nursing costs, which are expected to be significant given the thousands of men who die from prostate cancer each year.

Current service provision

Screening and diagnosis

At present, it is not NHS policy to screen for prostate cancer. Recent systematic reviews have argued against screening until more information is available on the natural history of the disease and the optimum treatment of organ-confined disease.[2–4] Benefits of screening are unproven, whereas much is known about the risks of screening and resultant treatments.[5]

There are clear guidelines for managing patients who present, usually to their GP, with lower urinary tract symptoms (LUTS).[5] The Prostate Cancer Speciality Working Group (PCSWG) recommends that patients presenting with LUTS have a digital rectal examination (DRE) by someone who performs these on a regular basis.[5] For this examination the doctor uses a finger to feel for prostate enlargement and surface irregularities, via the rectum. The drawbacks of this test are that it is unable to detect tumours in the anterior and medial lobes of the prostate, and it appears to be of limited value in detecting early-stage cancer. Because not all tumours are palpable a GP can be alerted to the presence of such a tumour by an elevated PSA. It is accepted, therefore, that a GP would want to make use of such a diagnostic tool for patients with significant symptoms. The development of PSA testing is relatively recent. PSA is a glycoprotein secreted only by prostate epithelium. The amount of PSA absorbed into the blood, and hence the serum level, increases when the baseline membrane is damaged. Thus, high levels are found in men with prostate cancer. High levels are also sometimes found in men with acute prostatitis and moderately raised levels are found in men with benign prostatic hyperplasia (BPH).[2]

Although the majority of prostate cancers appear to be very slow growing and not life-threatening, a minority of cases progress rapidly, invading surrounding tissues and metastasising, usually to bone.[2] Once diagnosed, therefore, it is important

to establish accurately how far the disease has progressed (disease stage) to help to determine treatment decisions and ultimately prognosis. In Europe the TNM staging system is most commonly used. T refers to the size of the primary tumour, N describes the extent of lymph-node involvement and M refers to the presence or absence of metastases. In stage T1 the tumour is located within the prostate gland only and is too small to be felt on DRE. In stage T2 the tumour is still located only within the prostate but can be felt on DRE. A stage T3 tumour will have spread from the prostate into the immediate surrounding tissue. The seminal vesicles may be included. In stage T4 the tumour is still within the pelvic region but may have spread to other areas; that is, metastatic disease may be present. Both T3 and T4 are often referred to as locally advanced disease. (For the purposes of this review, early, localised prostate cancer is defined as being either stage T1 or T2, with no lymph-node involvement or metastases.)

For radiological staging purposes magnetic resonance imaging (MRI) is thought to give the most accurate and complete assessment of local disease and spread.[5] When this is not available other methods of radiological staging are required: transrectal ultrasound (TRUS) is often used as an aid to biopsy, computed tomography (CT) is used to detect spread to the lymph nodes and radionuclide bone scans may detect metastases.

Before treatment commences confirmation of a diagnosis of prostate cancer is required via histological examination of prostate tissue from biopsy samples. This examination provides information on the grade of the tumour, which is an important prognostic indicator. That is, along with other clinical information it helps to predict the aggressiveness of the tumour and consequently aids decisions about treatment. The most commonly used scheme for reporting histological grade is the Gleason score. Within this scheme there are five possible tissue patterns, with 1 being well differentiated (good prognosis) and 5 being poorly differentiated (poor prognosis). The two most frequent patterns are added together to give a score. Gleason scores 2–4 are considered low grade, 5–7 medium grade and 8–10 high grade.

Current treatments for early localised prostate cancer

The viable options for treatment of early, localised disease (T1–T2) are total prostatectomy, radical radiotherapy and surveillance.[5] Radical prostatectomy (RP) involves major surgery that attempts to remove the tumour. Until recently complications included impotence (nearly all patients) and incontinence (up to 20%), but with the recent introduction of a nerve-sparing surgical technique, complications have been reduced.[5] Five-year metastasis-free survival ranges from 56 to 100% depending on the grade of the tumour.[6] External beam is the traditional method of delivering radiotherapy to the prostate. Risks include bowel and bladder damage and impotence. Impotence rates of 30% and incontinence rates of 1% are commonly quoted.[7] After treatment patients are normally followed up in the same way as those who are managed with surveillance. Disease-specific survival following radical radiotherapy ranges from 74 to 96% at 5 years and from 62 to 86% at 10 years.[8] Patients who are managed by surveillance receive no treatment but instead are monitored for signs of disease progression. Active monitoring or active surveillance is similar in principle to 'watchful waiting' in that patients receive no treatment. Monitoring, however, is 'active', involving regular check-ups that include PSA testing, DRE, symptom history and, where indicated, TRUS to detect local progression of the cancer, as well as bone X-rays and other imaging or biochemical tests to monitor the development of metastases.

The PCSWG has stated that "The available literature does not enable us to state whether radical radiotherapy or total prostatectomy are superior in curative efficacy, or whether either offers benefits compared with surveillance for patients with early prostate cancer, with the possible exception of those with poorly differentiated tumours".[5] Consequently, the group recommends that choice of treatment be based on the "balance of morbidity (whether psychological or physical), and on the patient's own perceptions and reactions to the alternatives". However, patients with a life expectancy of more than 10 years are generally more likely to be offered radical treatments compared with men whose life expectancy is less than 10 years.

At present there are very few good-quality data on current service provision in the UK. Recently, however, the British Association of Urological Surgeons (BAUS) conducted an audit of newly presenting urological cancers for the period January to December 2000.[9] The audit report includes some analysis of types of treatment for prostate cancer. It shows that in 2000, 32% of all known newly presented prostate cancers were treated with the intention of curing the disease.

The remainder were treated palliatively (52%) or with surveillance (16%). Further analysis of the database revealed that in men with localised prostate cancer, curative resection was attempted in 80% of men under 70, but only 40% of men over 70 years (Clarke NW, Christie Hospital NHS Trust: personal communication).

Given the lack of high-quality evidence for treatments options for early localised disease, the NHS Prostate Cancer Programme[10] includes plans to implement a clinical trial to evaluate the effectiveness of treatments for clinically localised prostate cancer. The ProtecT study is currently underway and will evaluate the effectiveness, cost-effectiveness and acceptability to men with localised prostate cancer of active monitoring, RP and radical radiotherapy.

Description of new and emerging technologies

There are several relatively new therapies that aim to treat early localised cancer effectively in terms of survival, which are minimally invasive and which aim to reduce complications. Progress with technique and the level of research into these treatment options is varied. New techniques in radiotherapy include brachytherapy, three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated conformal radiotherapy (IMRT). Studies into the effectiveness of brachytherapy and 3D-CRT studies have been conducted. Currently, cryosurgery has become somewhat more acceptable than previously because of new techniques aimed at minimising complications. Many studies have investigated the effectiveness of neoadjuvant and adjuvant hormone therapies in combination with radiotherapy and radical prostatectomy (RP) (although hormone 'downstaging' is no longer used as a prelude to RP (Clarke NW, Christie Hospital NHS Trust: personal communication). There has been some research into hormonal monotherapy, but this does not appear to be a valid treatment option for early, localised disease. Gene therapy is in its infancy and very little clinical effectiveness research has been done in this field with regard to early, localised disease.

Investigation of the clinical effectiveness of any prostate cancer treatment should include long-term, overall survival. The main objective of the ProtecT trial in evaluating clinical effectiveness is the assessment of survival at 5, 10 and 15 years following treatment. However, as in many other studies it will also measure short- and medium-term outcomes, such as disease progression. Often, owing to the short duration of many studies and the consequent lack of long-term follow-up, disease progression is the only reported outcome. Disease progression is thought to give some indication of the likelihood of longer term survival. There are, however, differing definitions of disease progression. Biochemical no evidence of disease (bNED) rates are often reported at varying times post-treatment. This measure relates to levels of serum PSA and/or rising levels of PSA. A rising PSA level can pre-date other signs of progression. There is controversy, however, about the use and interpretation of serial changes in PSA values for assessing outcomes and determining prognosis.[11] Because new and emerging treatment studies have shorter follow-up periods than studies into the more traditional treatments, disease progression, either biochemical or clinical, is the most commonly measured outcome. For many of these treatments it will be years before overall survival can be reported.

This report reviews new and emerging technologies for the treatment of early prostate cancer: a component of the NHS Prostate Cancer Programme.[10] It reviews 'new' treatment options as detailed above and seeks to identify and review other emerging technologies. In the absence of long-term outcomes the review reports surrogate end-points. It also reports QoL and treatment-related complications.

Chapter 3

Effectiveness

Methods for reviewing effectiveness

A systematic review of existing evidence of the clinical and cost-effectiveness of new and emerging technologies for early, localised prostate cancer was undertaken. No relevant evidence of cost-effectiveness was identified. An economic model was therefore developed. The methods of systematic review are reported in this section. The methods used to develop the economic model are reported in Chapter 4.

The methods of systematic review, in terms of search strategy and inclusion and exclusion criteria are usually defined a priori, by a focused clinical question. While the question for this review was defined in terms of population (early, localised prostate cancer) and outcomes (survival, QoL and cost-effectiveness), the question was not focused in terms of intervention (new and emerging technologies). In addition, given that this review is of a number of new and emerging technologies, the evidence base for each technology was of varying volume and quality. As a result, the review incorporated an iterative element at the search strategy and inclusion and exclusion stages, to establish what constituted a 'new and emerging' technology, and to identify the 'best available' evidence for each technology.

Defining 'new and emerging' technologies

At the earlier stages of the review scoping searches were undertaken to identify and agree a list of relevant new and emerging technologies. A new and emerging technology was defined as any intervention that did not constitute 'usual practice' in the treatment of early prostate cancer (conventional surgery, conventional radiotherapy, watchful waiting or active surveillance) and that generated reasonable evidence of evaluation or discussion in the scientific and clinical literature. A draft list of relevant interventions was discussed and agreed with clinical experts. The agreed list formed part of the inclusion criteria as detailed below.

Search strategy

The search aimed to identify all literature relating to new and emerging technologies for treating early prostate cancer, including brachytherapy and cryotherapy. The main searches were conducted in January and February 2002.

Sources searched

Fifteen electronic bibliographic databases were searched, covering biomedical, science, social science, health economic and grey literature. A list of databases is provided in Appendix 1.

In addition, the reference lists of relevant articles were handsearched and various health services research-related resources were consulted via the Internet. These included health technology assessment organisations, guideline-producing agencies, generic research and trials registers, and specialist sites. A list of these additional sources is given in Appendix 2.

Search terms

A combination of free-text and thesaurus terms was used. 'Population' search terms (e.g. prostate, prostatic diseases, neoplasm, carcinoma, adenocarcinoma) were combined with 'intervention' terms (e.g. brachytherapy, radiotherapy, radiation, microwave therapy, cryotherapy, dexamethasone, Photofrin). Two searches were performed in MEDLINE, EMBASE and the Cochrane Library to account for 'new' terms that were found through the initial searches on these databases (other databases were searched after all of the relevant terms had been decided upon). These were supplemented by a specific basic search on PSA as an outcome measure, using terms such as prostate-specific antigen, AND outcome measure AND prostate, and prostatic diseases (MEDLINE and English language only). Copies of the search strategies used in the major databases are included in Appendix 3. Search strategies in electronic format are available from the authors.

Search restrictions

The searches performed in MEDLINE, EMBASE, Biological Abstracts and the Science and Social Science Citation Indexes were limited to 1992 to the present (the EBM reviews – ACP Journal Club database runs only from 1991) to aid the restriction of the technologies assessed to those that are new and emerging only. No language or

study/publication-type restrictions were applied to the main searches, except to the Science and Social Science Citation Indexes, which were limited to English language only. An economic evaluation filter was used in the main searches performed in MEDLINE and EMBASE to assist with the identification of articles for the cost-effectiveness aspect of the review (refer to Appendix 4).

Inclusion and exclusion criteria

Inclusion and exclusion criteria were applied in two stages.

Stage 1

Titles, abstracts and full papers were reviewed according to the following inclusion criteria:

1. Study population of early, localised (T1 and T2) prostate cancer. (Papers where T1 and T2 constituted less than 50% of the study population or where subgroup analysis was not undertaken were excluded.)

2. Evaluation of one or more of the following interventions:
   - neoadjuvant hormonal therapy (NHT)
   - adjuvant hormonal therapy (AHT)
   - hormonal monotherapy
   - brachytherapy
   - three-dimensional conformal radiotherapy (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
   - high linear energy transfer radiation
   - radionuclide therapy
   - vaccine therapy.

3. Reporting of one or more of the following outcomes:
   - survival
   - disease-free survival (DFS)
   - QoL (including complications and adverse consequences such as incontinence and impotence) and acceptability.

Given that this review is of new and emerging treatments, many studies lacked long-term follow-up. Studies tended to use levels of serum PSA as an intermediate end-point, which is thought to indicate disease progression. All such studies were included as long as the remaining inclusion criteria were met.

All studies included at stage 1 were graded according to the following hierarchy of evidence:

- systematic review
- level 1 [randomised controlled trial (RCT)]
- level 2 (well-designed controlled trial without randomisation)
- level 3 (well-designed cohort or case–control analytical study)
- level 4 (comparison between times or places with or without the intervention)
- level 5 (opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees).

Stage 2

To restrict the review to the best available evidence, inclusion criteria based on the quality of studies were applied. The volume and quality of studies included at stage 1 varied greatly from technology to technology. One of the following inclusion principles was therefore applied to the evidence base for each technology.

- Where sufficient high-quality evidence (level 1) existed, lower quality evidence was excluded.
- Where very little evidence had been identified all studies were included.
- Where the majority of evidence was of poor quality (level 5 case series) a cut-off level based on sample size and follow-up was agreed and applied.

Studies included at this stage form the basis for the review. Details of the specific inclusion criteria for each technology are reported in *Table 1* and in the Results section.

Quality assessment strategy

Owing to the broad inclusion criteria and the varying nature of the quality and type of included study no formal quality assessment of included studies was undertaken other than the grading of evidence described above.

Data extraction and synthesis

Data were extracted into a previously prepared proforma by a single reviewer (AM or EC according to technology). Owing to the methodological and clinical heterogeneity of included studies it was not appropriate to pool results across studies. Instead, a detailed qualitative assessment is presented.

TABLE 1 *All technologies: quantity and quality of included studies*

Technology	Total incl. studies	Level[a]						Inclusion criteria
		Sys. revs	1	2	3	4	5	
NHT	17	4	13	–	–	–	–	Sys. revs Evidence level 1
AHT	7	1	1	–	2	–	3	Sys. revs All levels 1–5
Hormonal monotherapy	1	–	–	–	–	–	1	Sys. revs All levels 1–5
Brachytherapy	24	4	2	–	4	1	13	Sys. revs All levels 1–4 Level 5 ($n \geq 100$, follow-up ≥ 5years)
3D-CRT	25	–	4	–	1	–	20	Sys. revs All levels 1–4 Level 5 ($n \geq 100$, follow-up ≥ 3years)
IMRT	4	–	–	–	–	–	4	Sys. revs All levels 1–5
Cryotherapy	12	–	–	–	–	–	12	Sys. revs All levels 1–4 Level 5 ($n \geq 30$, follow-up ≥ 1 year)
HIFU	8	–	–	–	–	–	8	Sys. revs All levels 1–5
IMTT	1	–	–	–	–	–	1	Sys. revs All levels 1–5
RITA	2	–	–	–	–	–	2	Sys. revs All levels 1–5
Laser photocoagulation	1	–	–	–	–	–	1	Sys. revs All levels 1–5
Gene therapy	2	–	–	–	–	–	2	Sys. revs All levels 1–5
High linear energy transfer radiation	–	–	–	–	–	–	–	No evidence identified
Radionuclide energy	–	–	–	–	–	–	–	No evidence identified
Vaccine therapy	–	–	–	–	–	–	–	No evidence identified
Totals	104	9	20	–	7	1	67	

[a] Sys. revs: systematic reviews; level 1: RCT; level 2: well-designed controlled trial without randomisation; level 3: well-designed cohort or case–control analytical study; level 4: comparison between times or places with or without the intervention; level 5: opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

Results

Quantity and quality of research available

The literature search retrieved a total of 17,274 references across all databases. When all duplicates had been removed 9806 unique references remained and were considered for inclusion in the review. Following the application of the initial inclusion criteria (based on population, intervention and outcomes) 9340 papers were excluded. The remaining 466 papers were assessed according to the study quality inclusion criteria agreed for each intervention. A total of 104 papers formed the basis of this review with several papers included in more than section of the review (i.e. for more than one intervention). Results of the selection of studies for inclusion are shown in *Figure 1*.

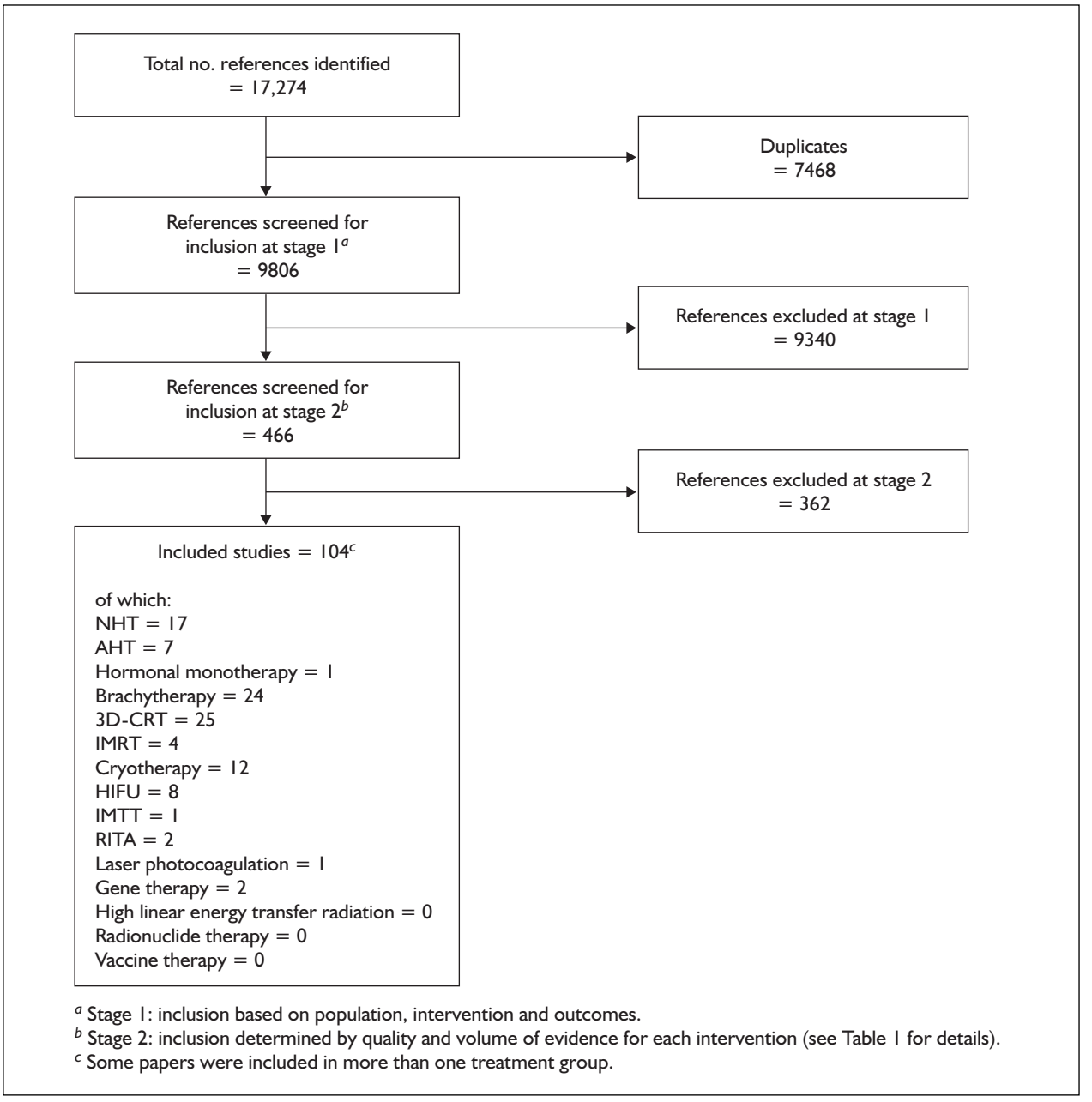


FIGURE 1 *Inclusion/exclusion flow diagram*

The review of NHT is based on the highest quality evidence (including 13 RCTs). The review of brachytherapy identified the largest number of references, most of which were case series (evidence level 5). Several technologies, including all of the thermal treatments, have undergone very little evaluation. All relevant papers identified were included in these reviews. No evidence was identified for several technologies (high linear energy transfer radiation, radionuclide therapy, vaccine therapy and hormonal monotherapy). See *Table 1* for a summary of the inclusion criteria and the quantity and quality of evidence for each technology.

The results for each technology are reported below. For each intervention a brief description is given. This is followed by details of the quantity and quality of included and excluded studies. Study results are presented by outcome, and a conclusion regarding the clinical effectiveness evidence for the intervention as a whole is based on those results. The data extraction tables for all included studies, by intervention, are given in Appendix 5.

NHT

The role of NHT in the management of early localised prostate cancer is to reduce the volume

TABLE 2 *NHT summary table*

Total incl. studies	Level						Inclusion criteria
	Sys. revs	1	2	3	4	5	
17	4	13	–	–	–	–	Sys. revs Evidence level 1
Conclusion: No evidence of benefit in terms of bDFS.							

of the prostate tumour before definitive therapy. This helps to reduce the side-effects of radiotherapy. NHT also improves the efficacy of radiotherapy by what is thought to be a synergistic interaction on cell killing.

Hormonal therapy is usually given 3 months before radiotherapy. Although serum PSA is used as a surrogate end-point after treatment for prostate cancer, it may be a particularly difficult end-point to interpret after hormonal therapy because PSA is decreased by such therapy. Short-term clinical results therefore need to be interpreted with care.

In total, 62 papers were found that studied the effects of NHT. Thirteen of the 17 reviews of NHT were excluded because they were not systematic. Nineteen randomised clinical trial papers (evidence level 1) were found although in total they contained results from 13 primary studies. The remaining 26 papers fell into evidence levels 2 (n = 5), 3 (n = 7) and 5 (n = 14). Because there was a relatively high number of papers in the evidence level 1 category a decision was taken to exclude all other papers in evidence level categories 2–5. This review is based therefore on four systematic reviews and 13 RCTs. Details of included studies are given in Appendix 5 (*Tables 34* and *35*). Conclusions based on included studies are summarised in *Table 2*.

One identified study was excluded because it did not meet the population inclusion criteria in that it studied locally advanced disease. The Radiation Therapy and Oncology Group (RTOG) 86-10 Phase III trial reports recent results of androgen deprivation before and during radiotherapy.[12] It is important in that it found highly significant improvements in local control, reduction in disease progression and overall survival for patients with Gleason score 2–6 who received a short course of androgen ablation.
Seven of the 13 primary studies were multicentre trials and the remainder came from single institutions. Comparisons were made between those patients given NHT and definitive treatment and those who had definitive treatment only. NHT was used before RP in all but one study,[13] which focused on NHT before external beam radiation therapy (EBRT). It should be noted that hormone downstaging is no longer used in advance of surgery and that the latter study therefore provides the only comparison relevant to current practice. The median sample size from all of the clinical trial studies was 145 and it ranged from 56 to 547. Four studies included T1 to T2 patients only.[14–17] The remainder also included T3 patients. Five of the 12 trials presented pathological results obtained immediately postoperatively.[14,18–21] Longer term follow-up was not available from these studies. The remaining studies followed patients from 5 months to 5 years post-operatively. Follow-up for the NHT + EBRT patients was 24 months.

In the only study to follow all patients for 5 years,[17] Soloway and co-workers found there was no difference in biochemical disease-free survival (bDFS) between the two groups: 64.8% for the NHT + RP group and 67.6% in the RP bDFS only group (p = 0.663). In the three other studies that measured bDFS,[16,22,23] findings were similar in that there was no difference in survival rates between treatment groups at 38, 36 and 48 months follow-up.

Two studies found no difference in the rate of organ-confined disease postoperatively between the two treatment groups,[14,15] while a third paper[20] found that there was a 57.8% increase in the incidence of organ-confined disease in the NHT group compared with the RP-only group. All four studies that compared rates of positive surgical margins (unfavourable outcome) between NHT + RP and RP-only groups[18–20] found statistically significant differences postoperatively in favour of the NHT patients: 23 versus 41% (p = 0.013), 13 versus 38.5% (p = 0.0006), 19 versus 46% (p = 0.01) and 7.8 versus 33.8%

($p < 0.0001$). Gleave and co-workers compared 3 months and 8 months preoperative therapy.[24] In the 3-month group 23% had positive margins compared with only 12% in the 8-month group ($p = 0.0001$). This study also found that mean preoperative PSA was 57% lower in the 8-month group ($p = 0.0141$). All studies that measured PSA levels preoperatively found that for patients receiving NHT, PSA levels were significantly reduced. One other surgical study[15] measured PSA and found no difference between the two treatment groups at 35 months. The EBRT study[13] found that although there was a difference between the intervention and control groups at 12 months in terms of positive biopsies, the difference had disappeared at 24 months, and there was no difference in PSA levels between the two groups.

In interpreting these results the relevance of the comparisons should be borne in mind. Only one of the 13 included studies looks at the use of NHT before radiotherapy.[13] Many of the studies that have been reviewed are not yet able to report on longer term survival and progression. Favourable interim results in terms of positive surgical margins are usually found, although organ-confined disease postoperatively appears to be similar in both intervention and control groups. Of those studies that have longer patient follow-up data, no differences in bDFS are found. This includes the evaluation of NHT before radiotherapy.[13] These results would tend to indicate that surrogate end-points such as PSA levels and positive surgical margins measured after hormonal therapy are less easy to interpret. It is important, therefore, to await the longer term results of these trials to determine whether lower rates of PSA progression and positive surgical margins have any impact on clinical disease-free survival. Three systematic reviews from 1998, 1999 and 2001,[25–27] which include some of the primary studies included here, also conclude that longer term clinical evidence will be required to determine whether pathological stage and surgical margins are good surrogates for final treatment outcomes.

AHT

AHT is given in conjunction with definitive treatment for early localised prostate cancer. Its role, like NHT, is to reduce prostate tumour volume, and it can be given to patients before, during and after treatment.

Although not fitting the eligibility criteria for this review, two important clinical trials were found, which showed that patients with locally advanced disease who received AHT had better overall survival rates at 5 years than patients receiving radiotherapy alone.[28,29] A third large study found that for patients receiving AHT along with radiation therapy, DFS was statistically better than for patients having radiotherapy alone. Once again this study was not included in this review because it studied men with locally advanced, non-metastatic disease.[30]

Four reviews of AHT were found, one of which was a systematic review and has therefore been included here.[31] One clinical trial was found (evidence level 1) comparing hormonal therapy before, during and after EBRT versus EBRT alone ($n = 120$).[13] There were two retrospective matched case–control studies (evidence level 3). One compared 3D-CRT plus AHT with treatment by 3D-CRT alone ($n = 484$).[32] The other compared EBRT plus AHT with treatment by EBRT alone ($n = 112$).[33] The three remaining studies were evidence level 5. Two studied EBRT plus AHT and EBRT alone; in one study $n = 1586$[34] and in the other $n = 54$.[35] The former is a retrospective study of patients treated at one institution. The latter is a non-randomised prospective study, also from one institution. The third study measured QoL in men before and after receiving 3D-CRT plus AHT ($n = 144$).[36] Details of included studies are given in Appendix 5 (*Tables 36* and *37*). Conclusions based on included studies are summarised in *Table 3*.

TABLE 3 *AHT summary table*

	Level						
Total incl. studies	**Sys. revs**	**1**	**2**	**3**	**4**	**5**	**Inclusion criteria**
7	1	1	–	2	–	3	Sys. revs All levels 1–5
Conclusions: Some evidence of lower QoL with regard to sexual function. Some evidence of benefit in terms of biochemical and pathological outcomes. No evidence of benefit in terms of survival although, conflicting evidence that higher risk patients may benefit.							

The clinical trial and the two matched case–control studies included patients with disease stages T1–T3. Evidence level 5 studies did not present details of clinical stage, but one[34] categorised patients into risk group based on Gleason grade, stage and PSA. The median follow-up of patients in all studies was 32 months, with a range of 3–98 months.

Results from the clinical trial show that at 12 months 62% of patients who had EBRT alone (group 1) had residual disease (positive biopsy) compared with 30% of patients who had AHT before, during and after EBRT (group 2). Group 3 patients had the same treatment as group 2 plus total antiandrogen blockade (TAB), and among these patients 4% had residual disease. Differences were statistically significant ($p = 0.0005$). At 24 months similar differences remained ($p = 0.0001$). At 12 months a similar advantage among the different groups was seen in PSA levels, but by 24 months PSA differences between the groups were not statistically significant.

Both matched case–control studies showed a significant difference between intervention and control groups in terms of bNED rates at 5 years, in favour of AHT patients: 55 versus 31% in one study ($p = 0.02$) and 71 versus 43% ($p = 0.0088$) in the other. There were no statistically significant differences in overall survival or cause-specific survival between treatment groups at 5 years.

In the large retrospective case review study of 1586 patients, no statistically significant difference in PSA failure rates (three consecutive rising PSA values at least 3 months apart) was found between treatment groups (EBRT plus AHT and EBRT alone) in the low prognostic risk group. In the intermediate- and high-risk groups differences between treatment groups were statistically significant. Patients in the EBRT + AHT groups had a 5-fold [relative risk (RR) 0.2, 95% confidence interval (CI) 0.1 to 0.3] and a 2.5-fold (RR 0.4, 95% CI 0.2 to 0.8) reduction in risk of failure, in the intermediate- and high-risk groups, respectively.

Of the two remaining evidence level 5 papers, one looked at QoL and the other at bone breakdown. In the former study, patients receiving AHT were more likely to be impotent and have ejaculatory problems than those receiving EBRT only, although the AHT group expressed more satisfaction with their sex life than the EBRT only group. In the latter study, bone breakdown was more likely in patients receiving AHT.

The review paper was a meta-analysis study of patients in five prostate cancer trials.[31] It included patients in clinical stages T1–T4 who received radiotherapy alone or radiotherapy with a variety of different hormone therapies. Patients were split into risk groups based on PSA, stage and grade, with group 1 being the lowest risk and group 4 the highest. Patients in groups 2, 3 and 4 had a disease-specific survival benefit at 8 years if specific hormone therapies were received. (Group 1 patients were excluded from the analysis because of the small number of patients receiving AHT.) The authors recommend that prospective randomised trials be used to confirm these results.

There appears to be reasonable evidence of a lower QoL in patients receiving AHT with regard to sexual function. In terms of clinical outcomes the higher quality papers (evidence levels 1 and 3) suggest that AHT patients have better biochemical, and to some extent pathological, outcomes than those patients who have definitive treatment alone. As for NHT patients, there appears to be no evidence of a survival advantage for AHT patients. The meta-analysis results, however, appear to show that AHT has a survival benefit for higher risk patients if the appropriate hormone therapy is chosen. Consequently, with conflicting results and the small numbers of good-quality studies into this therapy, the conclusion has to be that better evidence on a survival advantage for AHT is required from large randomised clinical trials.

Hormonal monotherapy

Hormonal therapy alone has in the main been prescribed for patients with locally advanced or metastatic disease. That is, the intention is to improve quality and length of life rather than to cure the disease. Some authors have argued in their reviews (not systematic) that hormonal monotherapy is worthwhile for patients with early localised prostate cancer as an alternative to watchful waiting[37] or because of the impact on QoL.[38,39] These views are based on reviews of studies of monotherapy for locally advanced and metastatic disease. One study was identified that prescribed triple androgen blockade for men with localised prostate cancer after they had refused localised therapy.[40] The sample size was 110 and the study was a review of consecutive patients treated at one institution. Median follow-up was relatively short at 36 months. Results showed that after 3 months 95% of the patients' serum PSA had dropped to ≤ 0.1 ng/ml. At a median follow-up of 36 months PSA levels had remained stable. The authors of the study acknowledge that further

TABLE 4 *Hormonal monotherapy summary table*

Total incl. studies	Level						Inclusion criteria
	Sys. revs	1	2	3	4	5	
1	–	–	–	–	–	1	Sys. revs All levels 1–5
Conclusion: Insufficient evidence to draw conclusions regarding the effectiveness of this intervention.							

TABLE 5 *Brachytherapy summary table*

Total incl. studies	Level						Inclusion criteria
	Sys. revs	1	2	3	4	5	
24	4	2	–	4	1	13	Sys. revs All levels 1–4 Level 5 ($n \geq 100$, follow-up ≥ 5 years)
Conclusions: Some evidence to suggest that brachytherapy is better than standard treatments in terms of bDFS for lower risk patients, although worse for intermediate- and high-risk patients. Evidence in terms of complications is mixed. Level 5 evidence reports similar or lower rates of complications when compared with standard treatments. Level 3 evidence suggests that disease-specific QoL is lower for brachytherapy than for standard treatments. General HRQoL is similar when compared with standard treatments.							

longer term outcomes are required before a comparison can be made with more radical treatments. Details of this study are given in Appendix 5 (*Table 38*). Conclusions based on included studies are summarised in *Table 4*.

Brachytherapy

Brachytherapy is the targeted delivery of radiation through implants directly to the prostate gland. This is through permanent implants of iodine-125 (I-125) or palladium-103 (Pd-103) seeds, or temporary implantation with iridium-192 wires through hollow needles. Modern prostate brachytherapy is performed under TRUS guidance and may be used as monotherapy, as a boost to another primary therapy such as EBRT, or as a primary therapy with another treatment such as EBRT used as a boost, with or without adjuvant/neoadjuvant androgen deprivation therapy (ADT).

Altogether, 158 papers were identified evaluating a range of brachytherapy interventions. The majority of studies ($n > 100$) were case series (level 5). It was decided to exclude all level 5 studies with fewer than 100 patients and with follow-up of less than 5 years. The remaining 24 included studies fell into the categories systematic review ($n = 4$), level 1 ($n = 2$), level 3 ($n = 4$), level 4 ($n = 1$) and level 5 ($n = 13$). Details of included studies are given in Appendix 5 (*Tables 39* and *40*). Conclusions based on included studies are summarised in *Table 5*.

The Alberta Heritage Foundation for Medical Research (AHFMR)[41] recently published a systematic review on brachytherapy for prostate cancer including studies published up to early 1999. Three other systematic reviews were also identified. Crook and colleagues[42] examined the evidence for brachytherapy in clinically localised prostate cancer, Vicini and colleagues[43] reviewed brachytherapy to determine whether an optimal method of implantation could be identified and Vicini[44] reviewed evidence relating to radiotherapy, including brachytherapy, in an attempt to determine an optimal radiotherapeutic method. Together, the four studies reviewed the evidence on brachytherapy in the treatment of prostate cancer up to 2001. For the current review results from existing reviews have been updated with evidence published since that date and with evidence meeting the inclusion criteria of the current review but not included in previous reviews.

Studies included in the current review evaluated a range of brachytherapy interventions within the main treatment modalities of brachymonotherapy

and brachytherapy in combination with EBRT with or without androgen deprivation. Of the 24 primary studies, four reported comparisons between brachytherapy and current treatments[45–48] and six reported comparisons between different brachytherapy interventions.[49–54] However, only two studies randomised patients to treatments[53,54] and in several studies patients were reported as being allocated to treatments according to risk group.[46,51,52] In addition, case series without controls often reported overall results for a number of brachytherapy interventions and again in some studies treatment was allocated according to risk group.

The inclusion criterion relating to the definition of early localised prostate cancer as stage T1–T2 was observed. Some studies included a proportion of patients with stage T3 tumours. Other patient characteristics (initial PSA level, Gleason score) varied greatly both within and between studies. The median number of subjects was 229 and ranged from 34 (evidence level 1)[53] to 2222 (evidence level 5).[45] The inclusion criterion relating to follow-up was observed. Any level 5 study reporting results at 5 years' follow-up or more was included. However, there was a wide range of length of follow-up within some studies. Full details are given in Appendix 5 (*Table 40*).

The four systematic reviews reported effectiveness in terms of actuarial, clinical and biochemical disease control/DFS. Two of the four systematic reviews reported complications.[41,42] The 20 included primary studies assessed the effectiveness in terms of actuarial, clinical and biochemical disease control/DFS (n = 15), complications and QoL (n = 9), with some studies reporting both (n = 4).

Of the four studies comparing brachytherapy with current treatments, two studies reported bDFS.[45,46] In a retrospective case series of over 2000 subjects, Brachmann and colleagues[45] compared brachymonotherapy with EBRT. There was no overall significant difference between the two treatments in terms of failure-free survival (FFS) at 5 years (71 vs 69%, respectively). For intermediate-risk patients with initial PSA (iPSA) 10–20 ng/ml or high-risk patients in terms of Gleason score, a significant difference in favour of EBRT was reported. In a retrospective case series of 540 patients Stokes[46] compared brachymonotherapy with EBRT and with RP. No significant differences in actuarial bDFS were reported for low- and intermediate-risk patients. For high-risk patients a significant difference in favour of RP was reported, with no significant difference between brachytherapy and EBRT.

Of the six studies comparing different brachytherapy interventions, three reported bDFS.[49,51,52] A fourth study[50] measured clinical DFS but limits to the validity of the study are reported by the authors. Cha and co-workers[49] undertook a retrospective matched pair comparison of brachytherapy isotopes (Pd-103 vs I-125). There was no significant difference overall at 5 years in terms of PSA relapse-free survival (RFS) (85.9 vs 87.1%, respectively), nor when analysed by high or low Gleason score. A further comparison of Pd-103 and I-125[51] suggested marginally better outcomes in favour of Pd-103. A retrospective case series reported by Sharkey and colleagues[52] compared biochemical control following brachymonotherapy (Pd-103) or brachytherapy in combination with NHT. Patients receiving Pd-103 combination therapy achieved better results. However, in both studies treatment was selected according to high- and low-risk factors. It is not possible, therefore, to establish whether suggested benefits should be associated with treatment or risk factor.

The nine remaining case series reporting bDFS[55–63] evaluated a number of interventions covering various modalities of brachymonotherapy, brachytherapy with EBRT and/or androgen deprivation or monotherapy and combination therapy. Not all patients received the same treatment within studies and explicit comparisons were not made in those studies evaluating more than one treatment. The median number of cases was 229 (range 100–536).

The most commonly reported outcome was bDFS at 5 years (57%[60] to 94%[56]) and at 10 years (66%[62] to 92%[57]). One study reported bDFS at 15 years (78%[61]) and two studies reported overall actuarial survival at 5 years (77%[55] and 90%[60]). However, some of these ranges report overall bDFS and some report bDFS according to patient subgroup. In addition, definitions of bDFS varied from study to study. Almost all studies commented on the effect of risk factors (T stage, Gleason score, iPSA) on prognosis. Five studies suggested that low-risk factors resulted in better outcomes.[56–58,60,61] Three studies reported using risk factors as criteria for allocating patients to treatments.[58,62,63]

The four systematic reviews reported extremely variable results and commented on the influence of patient selection criteria on this variation. The AFHMR review[41] includes one study which suggests

that intermediate- and high-risk patients may achieve better biochemical outcomes with EBRT or RP than with brachytherapy. Similar results were found in the studies by Brachmann and co-workers[45] and Stokes,[46] published since the AFHMR review and included in the current review. However, none of the systematic reviews was able to draw firm conclusions regarding the effectiveness of brachytherapy in terms of survival compared with current treatments or other forms of radiotherapy, or in terms of brachytherapy technique.

Of nine primary studies reporting morbidity, five reported general health-related quality of life (HRQoL) and/or disease-specific quality of life/functional outcomes (evidence levels 1 and 3)[47,48,53,54,64] and four studies (evidence level 5) reported treatment-related complications (sexual, gastrointestinal and genitourinary).[52,55,60,61]

Of the five studies reporting QoL, two RCTs compared I-125 and P-103 brachymonotherapy.[53,54] Wallner and colleagues[54] reported only preliminary results and is not considered here. The remaining QoL studies compared cohorts undergoing a number of treatments with age-matched healthy controls. Treatments included brachymonotherapy,[47,48,64] brachytherapy in combination with EBRT and/or androgen deprivation,[47,48,64] EBRT[48] and RP.[47,48] Two studies reported between-treatment comparisons.[47,48]

The comparison between I-125 and P-103[53] measured short-term sexual function and found no difference between the two groups.

Brandeis and colleagues[47] compared general and disease-specific QoL for brachytherapy (with and without EBRT) or RP with controls (follow-up 3–17 months). No overall differences were reported in general HRQoL. Urinary symptoms and bowel function in brachytherapy patients were worse than in controls. Sexual function was worse in both treatments than in controls. General and disease-specific QoL was worse in all domains for those receiving brachytherapy with EBRT than brachytherapy alone. However, this group had higher PSA and Gleason scores.

Joly and colleagues[64] compared late sequelae in terms of general and disease-specific QoL for brachytherapy in combination with EBRT with age-matched controls. No significant differences were reported for general HRQoL. Significant differences were observed for level of sexual activity, urinary incontinence and cystitis, which were reported as persistent problems for subjects receiving treatment. No major gastrointestinal complications were observed.

Wei and colleagues[48] compared disease-specific QoL for brachytherapy, 3D conformal EBRT or RP with age-matched controls. EBRT was associated with adverse bowel HRQoL, RP with adverse urinary HRQoL, and brachytherapy with adverse urinary, sexual and bowel HRQoL. However, subjects were well matched with controls but not between treatments in terms of clinical stage, Gleason score or PSA.

Of the four case series reporting treatment-related complications, three reported cases of brachytherapy with or without EBRT and/or androgen deprivation[52,55,60] and one reported brachytherapy with EBRT only.[61] Three studies reported sexual complications,[52,55,61] three reported genitourinary complications[52,55,60] and two reported gastrointestinal complications.[52,55] Most complications (mainly urinary and bowel) were short term. Impotence ranged from 15%[52] to 29%[61] of those who were sexually active before treatment. No long-term gastrointestinal complications were reported. Incontinence (4%[60] to 5%[52]) was associated with patients undergoing transurethral resection of the prostate (TURP) before treatment.

The AHFMR review[41] found that brachytherapy results in equivalent or fewer side-effects than either EBRT or RP. It was found that long-term complications are rare, restricted to a low percentage of patients, and similar to those experienced with EBRT or RP. Incontinence is usually 6% or less and most long-term genitourinary morbidity is seen in fewer than 5% of patients through all treatment modalities. The range for impotence is 5–38%. Crook and co-workers[42] report acute urinary retention of 1–14%, long-term sequelae of less than 5% and sexual potency maintained in 86–96% of patients.

Evaluation of the effectiveness of brachytherapy is hampered by the diversity of different techniques used, patient population selection criteria (clinical stage, Gleason score, pretreatment serum PSA), use of adjuvant therapies such as EBRT and ADT, and different lengths of follow-up. Despite a very large literature identified at the outset, few studies met the inclusion criteria of this review and the majority of these were case series of varying quality.

The primary studies identified and included in the current review report similar results to existing

systematic reviews in terms of disease control, but results relating to morbidity are mixed.

Studies reporting outcomes over 5 years are rare and the majority of studies use proxies for DFS based on serum PSA measurements. Comparisons between brachytherapy and standard treatments are rare and find little difference in outcomes (usually bNED). For patients of low risk as defined by T stage, Gleason score or initial PSA, brachytherapy appears to perform as well as RP or standard EBRT, but this appears not to be the case for intermediate- and high-risk patients, for whom radiotherapy or RP appears to perform better.

The evidence in terms of complications is mixed. Existing systematic reviews suggest that brachytherapy results in rates of complications similar to or lower than standard treatments. The rates of complications reported in these reviews are similar to the level 5 primary studies (descriptive case series) presented in the current review. However, two matched case–control series[47,48] suggest that disease-specific QoL is lower among brachytherapy patients than patients receiving standard treatments when compared with a healthy population. General HRQoL has been shown to be comparable to standard treatments and similar to age-matched healthy controls. Impotence rates for brachytherapy appear to be better than rates of 50% reported for RP.[65]

3D-CRT

3D-CRT is a relatively new technology and a modification of standard four-field box EBRT. It is a method of shaping the radioactive beams to the target volume, defined through a 3D imaging study that determines target volumes and organs at risk on a slice-by-slice basis. The distribution of the overall dose is achieved by shaping the incident beam apertures so that the beam contours match the shape of the target and radiation beams of uniform intensity are delivered across the field or may be modified by devices such as wedges or compensating filters.[66]

The aim of 3D-CRT is to target radiation therapy better to maximise the dose to the tumour and minimise radiation to normal tissue.

In total, 50 papers were identified evaluating 3D-CRT, the majority of which were case series (evidence level 5). It was decided to exclude all level 5 studies with fewer than 100 patients and with a follow-up of less than 3 years. The remaining 25 studies fell into category levels 1 (n = 4), 3 (n = 1) and 5 (n = 20). The median number of subjects was 277 (range 101–1306). Details of included studies are given in Appendix 5 (*Table 41*). Conclusions based on included studies are summarised in *Table 6*.

Three studies compared 3D-CRT with conventional EBRT at the same or a similar dose.[67–69] Two studies compared proton with photon radiation,[70,71] one study compared 3D-CRT with IMRT[72] and one with brachytherapy.[73] One study compared subjects with a healthy population.[74] Seven studies,[75–82] two of which included a comparison between 3D-CRT and EBRT,[75,77] compared different doses. A further four studies stratified results by dose.[71,72,76,83] Six studies evaluated outcomes according to prognostic variables alone.[84–89] A further two studies considered the appropriateness of surrogate end-points.[90,91] Although of interest, these two studies do not allow conclusions to be drawn regarding the effectiveness of 3D-CRT *per se*. For this reason they are are not considered in detail here but are summarised in Appendix 5 (*Table 41*).

TABLE 6 *3D-CRT summary table*

	Level						
Total incl. studies	**Sys. revs**	**1**	**2**	**3**	**4**	**5**	**Inclusion criteria**
25	–	4	–	1	–	20	Sys. revs All levels 1–4 Level 5 ($n \geq 100$, follow-up ≥ 3 years)
Conclusions: No good-quality evidence was identified addressing the key questions as to whether 3D-CRT can achieve increased survival and reduced treatment-related morbidity compared with standard radiotherapy. Higher doses appear to achieve better disease control, although patient characteristics are often reported as independent prognostic indicators. RCT evidence that 3D-CRT achieves significantly fewer gastrointestinal complications than standard radiotherapy.							

Seventeen studies evaluated effectiveness in terms of actuarial, clinical and biochemical disease control/survival.[69–73,76,78–80,84–91] Sixteen studies evaluated effectiveness in terms of treatment-related morbidity.[67–75,77,79,81–83,87,88] Level 1 evidence reporting treatment-related morbidity was identified in the form of four RCTs. The assessment of effectiveness in relation to morbidity is restricted to these four studies.[67,68,75,77] Details of all other studies reporting morbidity are summarised in Appendix 5 (*Table 41*).

One retrospective randomly matched pair analysis (evidence level 3)[78] and eight case series (evidence level 5)[69–73,76,80,92] being considered in detail here measured survival.

In a non-randomised case series comparison Perez and colleagues[69] compared 3D-CRT with standard radiotherapy (SRT) at similar doses in patients with comparable prognostic factors. bDFS at 5 years was 91% (T1c) and 96% (T2) for 3D-CRT, and 53% and 58% for SRT, respectively. 3D-CRT performed significantly better according to all prognostic variables with the exception of Gleason score 5–7, where no significant difference was observed.

In a large case series (n = 1100) Zelefsky and colleagues[72] compared 3D-CRT with IMRT, a development of 3D-CRT that further maximises the potential for increasing the dose and reducing the risk of morbidity (see next subsection). Subjects were stratified into favourable, intermediate and unfavourable risk groups according to pretreatment PSA, Gleason score and stage. Five-year bNED across all subjects was 85%, 58% and 38% for favourable, intermediate and unfavourable risk groups, respectively. Radiation dose as opposed to technique was the more important variable influencing bNED, with higher dose rates (75.6–86.4 Gy) resulting in statistically significantly better bNED rates than lower doses (64.8–70.2 Gy) for all risk groups.

Slater and colleagues report two case series[70,71] of patients receiving 3D planned conformal radiation doses with protons alone or combined with photons. No significant differences between the two groups in either case series were reported for bNED, and initial PSA stage and post-treatment PSA nadir were independent prognostic predictors of bNED control.

A retrospective comparison of two case series reported a comparison of 3D-CRT and I-125 transperineal brachytherapy in 'favourable risk' patients.[73] At 5 years no significant differences were reported between the two groups in terms of PSA RFS rates (88% 3D-CRT and 82% I-125).

The four remaining studies reporting survival compared the effectiveness of radiation dose and not of 3D conformal planning techniques.[76,78–80]

In a large (n = 1306) retrospective randomly matched pair analysis,[78] patients matched on independent prognostic variables and receiving high-dose (> 74 Gy) and low-dose (< 74 Gy) 3D-CRT were compared. Significantly better results were reported for high-dose 3D-CRT in terms of bNED, freedom from distant metastasis, cause-specific survival and overall survival.

Hanks and co-workers[79] reported a consecutive case series to test dose response in dose escalation from 68 to 79 Gy. No dose response in terms of bNED was observed for patients with a pretreatment PSA <10 ng/ml. Dose response was observed for bNED survival for pretreatment PSA groups of 10–19.9 ng/ml and ≥ 20 ng/ml. The dose associated with 50% bNED survival at 3 years was 64 Gy and 76 Gy, respectively. The slope of the dose response was 13 and 9%, respectively.

Hanks and colleagues[80] and Pinover and colleagues[76] report case series comparing dose levels (< 72.50, 72.50–75.99 and ≥ 76 Gy) aimed at identifying dose responses in favourable and unfavourable patient subgroups. The paper by Hanks and colleagues[80] further divides groups by pretreatment PSA levels. At 5 years significant improvements in bNED ranged from 22 to 40% at higher doses and were seen in three out of six subgroups (unfavourable < 10 ng/ml, unfavourable 10–19.9 ng/ml and favourable > 20 ng/ml groups). The paper by Pinover[76] stratifies subjects into 'poor' and 'good' prognosis groups. Five-year bNED control rates of 73, 86 and 89% were reported for doses of < 72.50, 72.50–75.99 Gy and ≥ 76 Gy, respectively (p = 0.12). However, prognosis group was shown to be the only independent predictor of bNED control. For the poor prognosis group alone dose response was seen for those receiving ≥ 76 Gy, compared with the two lower dose groups (94 vs 75 vs 70; p = 0.0062) and dose was shown to be the only independent predictor of improved bNED control.

Of the six studies evaluating outcomes according to prognostic variables alone,[84–89] one reported preliminary results only and is not reviewed here.[88] The remaining five studies reported 3D-CRT as resulting in better bNED control in

'favourable' (lower risk) patient groups, with four studies reporting significantly better outcomes. However, not all studies specified optimal dose in the definitions of 'favourable', and populations varied from study to study in terms of stage, grade and pretreatment PSA (definitions of 'favourable' according to study are shown in Appendix 5, *Table 41*). It is therefore not appropriate to make between-study comparisons or to draw conclusions from these studies regarding the benefits or otherwise of 3D-CRT in terms of survival.

Four RCTs assessed treatment-related morbidity. Two compared conventional and conformal radiotherapy at the same dose,[67,68] and two compared high and low doses using conventional radiotherapy at the lower dose conformal radiotherapy at the higher dose.[75,77] All four assessed gastrointestinal and genitourinary morbidity and one[75] reported impotence. Two reported acute morbidity[68,77] and three reported 'late' morbidity, defined as > 3 months after treatment[67] and 2 years.[75,77] Three graded toxicity according to the RTOG scale.

Dearnaley and colleagues[67] compared conventional EBRT with 3D-CRT, both at 64 Gy. At 3 months' minimum follow-up significantly fewer men had developed gastrointestinal complications (proctitis and bleeding) in the conformal group than in the conventional group (37 vs 56% ≥ grade 1, $p = 0.004$; 5 vs 15% ≥ grade 2, $p = 0.01$). There were no differences between groups in bladder function.

Koper and colleagues[68] compared conventional EBRT with 3D-CRT, both at 66 Gy. No difference in urological toxicity between the two groups was found. A greater reduction in acute gastrointestinal toxicity was observed in the 3D-CRT group (32 and 19% grade 2 toxicity for conventional and conformal radiotherapy, respectively; $p = 0.02$).

Nguyen and colleagues[75] conducted a patient-reported questionnaire at 2 years' follow-up to an RCT comparing 70 Gy (EBRT) with 78 Gy (3D-CRT). Similar incontinence rates were seen in both groups (overall rate of persistent incontinence 29%, with 36% reporting urgency-related and 8% stress-related incontinence). Although 78% of patients reported no or mild changes in bowel function overall, significantly more urine leakage and moderate to major changes in bowel function were reported in the EBRT than in the 3D-CRT group. Potency was reported as 51% overall compared with 80% before radiotherapy.

Storey and colleagues[77] compared a high dose (78 Gy using conformal radiotherapy) with a lower dose (70 Gy using conventional radiotherapy). No significant differences were seen between groups for acute bladder or rectal complications. At 5 years 37% of patients receiving either treatment to more than 25% of the rectum had grade 2 or higher complications, compared with 13% of those receiving treatment to 25% or less of the rectum ($p = 0.05$).

Most of the evidence relating to 3D-CRT assesses the effectiveness of dose rather than treatment planning. Higher dose radiotherapy appears to achieve better disease control than lower doses. However, most studies report biochemical surrogate end-points for disease-free survival and patient characteristics are often reported as independent prognostic indicators of disease control. 'Favourable' or low-risk characteristics as indicators of better biochemical disease control at higher doses are often, although not consistently, reported in studies that assessed dose response according to patient subgroup. No higher quality evidence was identified that compared 3D-CRT with standard RT at the same or similar dose and which reported disease control as an outcome.

RCT evidence of treatment-related morbidity reported significantly fewer grade 1 or 2 gastrointestinal complications in patients receiving 3D-CRT at the same dose as standard radiotherapy. Although differences were observed, urinary toxicity was similar in 3D-CRT and standard radiotherapy whether delivered at the same or different doses.

No higher quality evidence was identified that addressed the key question as to whether 3D-CRT can achieve increased survival through higher doses and reduced morbidity through better targeting of treatment to the tumour. In addition, no evidence was identified relating to acceptability of treatment to patients. Further research is required to establish the clinical benefits of 3D-CRT and patient preferences in the trade-off between the potential side-effects and benefits of treatment.

Intensity-modulated radiotherapy

IMRT is an advanced form of 3D-CRT. In addition to 3D shaping of the beam, IMRT modulates the beam intensity across the target area. Intensity modulators divide the treatment beam into a small set of 'beamlets', the intensity of which can vary from 0 to 100% independent of the other beamlets. IMRT aims to achieve nearly any

dose distribution, notably an abrupt decrease in the dose at the limit between the tumour volume and adjacent normal tissue. The anatomical contours of the target volume, the desired dose and the degree of inhomogeneity acceptable in the tumour volume are planned before treatment and several target volumes can be distinguished (e.g. primary tumour, lymph nodes). Total dose and dose per session to each target volume can be modulated.[66]

In total, six papers were identified for IMRT. One review was found but excluded because it was not systematic.[66] No randomised trials or level 2–4 studies were found, and of five level 5 case series papers one[93] was later excluded because it contained too high a proportion of locally advanced and salvage cases, leaving a total of four studies included here for review. Details of studies are given in Appendix 5 (*Table 42*). Conclusions based on included studies are summarised in *Table 7*.

Only one study[72] addressed biochemical freedom from disease (bNED) as well as complications of treatment; the other three[94] dealt exclusively with morbidity and QoL.

The large case series by Zelefsky and colleagues reported in the previous section compared 3D-CRT with IMRT, with subjects stratified into favourable, intermediate and unfavourable risk groups.[72] Five-year bNED across all subjects was 85, 58 and 38% for favourable, intermediate and unfavourable risk groups, respectively. Radiation dose as opposed to technique was the more important variable influencing bNED, with higher dose rates (75.6–86.4 Gy) resulting in statistically significantly better bNED rates than lower doses (64.8–70.2 Gy) for all risk groups.

The same study reported 3- and 5-year actuarial rates of morbidity.[72] Treatment with IMRT significantly reduced the incidence of grade 2 rectal toxicity at 3 years compared with 3D-CRT at the same dose of 81 Gy (2 vs 14%; $p = 0.005$). IMRT did not affect the incidence of urinary toxicity.

Two studies by Kupelian and co-workers[95,96] report morbidity for short-course intensity-modulated therapy (SCIM-RT) (dose 70 Gy in 28 fractions) compared with 3D-CRT (dose 78 Gy in 39 fractions). One study reported actuarial late grade 2 rectal toxicity at 18 months as being similar between the two groups (10% SCIM-RT vs 12% 3D-CRT).[96] The second study[95] reported preliminary results only for complications. It also compared QoL of SCIM-RT, finding overall physical and mental QoL scores similar to those reported for a general healthy US population.

Shu and colleagues[94] report the actuarial 2-year toxicity profile of two small groups of patients treated with either 3D-CRT or IMRT at a high dose of 82 Gy or more. No significant difference in acute genitourinary toxicity between 3D-CRT and IMRT was noted, although a significantly higher incidence of acute gastrointestinal toxicity was noted in the IMRT group. The 2-year actuarial rates for freedom from late gastrointestinal and genitourinary morbidity across both groups were 77.1% (95% CI 60.4 to 87.5%) and 79.5% (95% CI 62.7 to 89.3%), respectively.

Few studies were found evaluating the effectiveness of this advanced form of radiotherapy. In the largest study, the only study to evaluate both disease control and morbidity, higher dose rates were associated with better biochemical disease control.[72] In the same study IMRT was associated with reduced rectal toxicity. Other smaller studies did not report the same benefits in terms of toxicity.

The quality and paucity of evidence and the reliance on the reporting of surrogate end-points do not allow conclusions to be drawn regarding the relative effectiveness of IMRT compared with 3D-CRT. The existing evidence suggests that potential benefits would warrant further research.

TABLE 7 *IMRT summary table*

	Level						
Total incl. studies	**Sys. revs**	**1**	**2**	**3**	**4**	**5**	**Inclusion criteria**
4	–	–	–	–	–	4	Sys. revs All levels 1–5
Conclusion: Evidence from one large case series to suggest that IMRT may reduce late gastrointestinal toxicity compared with 3D-CRT at the same dose.							

TABLE 8 *Cryotherapy summary table*

Total incl. studies	Level						Inclusion criteria
	Sys. revs	1	2	3	4	5	
12	–	–	–	–	–	12	Sys. revs All levels 1–4 Level 5 ($n \geq 30$, follow-up ≥ 1 year)
Conclusions: Most studies report cryotherapy as a salvage procedure. Some evidence to suggest that complication rates, particularly impotence, are high.							

Cryotherapy

Cryosurgical ablation aims to reduce the prostate tumour by the application of subzero temperatures, administered via the perineum using cryoprobes. A potential benefit of this technique is the rapidity of treatment, and as a consequence the possibility of treatment on a day-case basis. Further development of the technique, particularly with regard to temperature control, should aim to reduce complication rates. Cryotherapy is often reported as a salvage procedure in patients who have failed conventional treatment, including radiotherapy.

Seven reviews and 22 evidence level 5 studies were identified. None of the seven reviews was systematic and all were excluded. Of the 22 remaining papers only those that had a sample size of 30 or more and a median follow-up period of 1 year or more were included. Details of the 12 included studies are in Appendix 5 (*Table 43*). Conclusions based on included studies are summarised in *Table 8*.

All but three of the studies were retrospective reviews of cases treated with cryosurgery at single institutions. The three remaining papers were prospective non-randomised uncontrolled studies.[97–99] Sample sizes in all studies ranged from 48 to 643 and most studies included patients with TNM stages 1–3. Four studies included patients with T1–T4 disease.

Mack and colleagues[100] studied 66 patients with T1–T3 disease and found that for all patients the overall survival rate was approximately 90% at 5 years. Four studies gave results for bDFS, as defined by low levels of serum PSA (usually < 1.0 ng/ml).[97,101–103] In two of these studies[101,103] patients were followed up for 5 years and bDFS ranged from 45% for high-risk to 80% for low-risk patient groups (based on PSA levels, Gleason grade and TNM stage).

In the main, the remaining studies reported the rate of positive biopsies at follow-up after treatment. Follow-up periods were short, ranging from 3 to 36 months, and the rate of positive biopsies ranged from 2 to 16%. One study[104] gave biopsy results at 6 months post-treatment for T1, T2 and T3 patients separately; the rates were 14, 16 and 33%, respectively.

Most studies reported complication rates after 6 and 12 months. The most commonly reported adverse events were impotence and outlet obstruction. Rates for the former varied between 47 and 93% and for the latter the range was 9–15%.

The bDFS rates at 5 years were good for low-risk patients. Complication rates, particularly for impotence, were high. However, the quality of the evidence relating to cryosurgery is not good. Most studies are retrospective case series. Many of the patients received androgen deprivation before undergoing cryosurgery, and some had already failed radiation therapy. In none of the studies were patients randomised to treatment groups. Furthermore, patients were not matched with controls from other therapy groups. RCTs with long-term follow-up are therefore required to draw conclusions regarding the relative effectiveness of cryotherapy.

High-intensity focused ultrasound

HIFU is a non-invasive method that attempts to destroy tissue in deep-seated targets in the body, without damage to adjacent or overlying tissues.[105] This is done through the concentration of an ultrasound beam on a defined target to destroy cells within a specific area. This is still a largely experimental technique being used in a few specialist centres in The Netherlands, Germany and France. Often more than one session is performed, either as day surgery or as an outpatient procedure.

TABLE 9 *HIFU summary table*

Total incl. studies	Level						Inclusion criteria
	Sys. revs	1	2	3	4	5	
8	–	–	–	–	–	8	Sys. revs All levels 1–5
Conclusions: Most studies report HIFU as a salvage procedure. Insufficient evidence to draw conclusions regarding the effectiveness of this intervention.							

No randomised trials or level 2–4 studies were identified. One non-systematic review was excluded. In total, eight level 5 case series were included for review.[106–113] Details of included studies are given in Appendix 5 (*Table 44*). Conclusions based on included studies are summarised in *Table 9*.

In two case series Beerlage and co-workers[106] report results for a small group of 14 patients who received HIFU before undergoing RP and a larger cohort (n = 111) for whom surgery was not an option and who received HIFU alone. A negative biopsy was reported for 60% and bNED for 55% in the HIFU-only group and approximately 29% of the combined HIFU and RP group. Patient characteristics varied widely and no formal length of follow-up was specified.

Chaussy and Thuroff[108] report freedom from cancer rates through sextant biopsies of 80% over 3 years, and bNED of 61%, with tumour mass reduced by >90% in those with residual cancer. In studies reported by Gelet and colleagues[109] overall clinical and bNED rates ranged from 56% at 24 months[109] to 66% at 19 months;[111] or 40–83% at 17 or 19 months according to pretreatment risk group defined either by biopsy or by iPSA and Gleason score.[111] Combined clinical and bNED of 68.7% over a 15-month median follow-up are reported by Kiel and colleagues.[113]

Reported complications of HIFU include temporary obstruction, mild stress incontinence and decreased sexual potency. Beerlage and colleagues[106] report that around 12% of patients developed postoperative complications, including rectourethral fistulae, urethral stenosis and stress incontinence.

Chaussy and Thuroff[108] report that no severe side-effects of fistulae, grade 2 or 3 incontinence, or rectal mucosal burn were seen, and QoL scores did not change significantly following primary HIFU. Gelet and colleagues[112] report asymptomatic urinary tract infections, elimination of small necrotic debris, urgency and nocturia as common in first weeks after HIFU. Acute urinary symptoms were common in first 2 months after HIFU, but were transitory. Stress incontinence was observed in 13% and total incontinence in 4%.

Gelet and colleagues[112] report loss of potency of 23% of previously potent patients. Chaussy and Thuroff[108] and Beerlage and co-workers[106] both report a loss of erectile function associated with global treatment.

HIFU is a relatively new procedure. The studies reviewed here refer to prototype devices. Study populations are small and consist mainly of patients who refused RP, were elderly or were otherwise deemed unsuitable for surgery. Most of the series include patients who have also had some hormonal deprivation therapy, or who are undergoing the HIFU as a salvage procedure. The follow-up periods reported by these studies are very brief and cannot be compared with other treatments where longer follow-up has been reported. Formal studies comparing outcomes with other treatments and longer follow-up periods are required.

Interstitial microwave thermal therapy

IMTT delivered through percutaneously inserted microwave radiating helical antennae under TRUS guidance aims to heat the whole prostatic region to a cytotoxic temperature of 55–70°C, while protecting sensitive adjacent organs such as the rectum, bladder and urethra.

This is a new treatment modality and has been used experimentally as a salvage therapy to treat patients for whom first-line treatment has failed. Only two papers were identified for the IMTT technique. One was a non-systematic review and was excluded; the other was an evidence level 5 Phase I/II trial.[114] Details of this study are given in Appendix 5 (*Table 45*). Conclusions are summarised in *Table 10*.

TABLE 10 *IMTT summary table*

Total incl. studies	Level						Inclusion criteria
	Sys. revs	1	2	3	4	5	
1	–	–	–	–	–	1	Sys. revs All levels 1–5
Conclusions: The only study identified reports IMTT as a salvage procedure. Insufficient evidence to draw conclusions regarding the effectiveness of this intervention.							

TABLE 11 *RITA summary table*

Total incl. studies	Level						Inclusion criteria
	Sys. revs	1	2	3	4	5	
2	–	–	–	–	–	2	Sys. revs All levels 1–5
Conclusion: Insufficient evidence to draw conclusions regarding the effectiveness of this intervention.							

Sherar and colleagues[114] report outcomes for a series of 25 patients who had failed primary EBRT. At 24 weeks post-treatment, bNED was achieved in 52% of patients and an additional 40% with PSA 0.51–4 ng/ml and a negative biopsy rate of 64%. No major complications of treatment were observed. Minor complications were resolved within 3 months.

IMTT is a new procedure in the treatment of prostate cancer which needs further evaluation with larger patient groups and longer follow-up before conclusions regarding its effectiveness can be drawn.

Transperineal radiofrequency interstitial tumour ablation

Transperineal RITA has been used in the treatment of cancers such as hepatocellular carcinoma and metastatic tumours to the liver. It has also been used in the treatment of benign prostate hyperplasia via a transurethral approach, and has been used as an outpatient procedure under spinal or local anaesthesia. In the treatment of prostate cancer the aim is to generate a central hot core in a localised area. The entire organ is destroyed and the targeted tissue is ablated through coagulative necrosis via needles, usually placed transperineally under TRUS guidance. The prostatic tissue is destroyed through direct heating from the electrode and by conduction, with an energy wave generated through a collision of particles produced through ionic and molecular agitation. In these early stages of the development of this technology the ablated gland is removed for histological examination via RP up to a week after the procedure.

Two papers were identified both of which were evidence level 5 case series.[115,116] Details of these studies are given in Appendix 5 (*Table 46*). Conclusions based on included studies are summarised in *Table 11*.

Djavan and co-workers report a small case series of ten patients undergoing RITA for localised prostate cancer.[115] Histopathological examination of tissue removed after RP confirmed necrosis, but no further follow-up, or standard clinical or biochemical outcomes are reported. No rectal discomfort, or internal or external haemorrhage was reported. Postoperative MRI revealed no alterations of the rectum, neurovascular bundle (NVB) or region of the external urethral sphincter. Zlotta and colleagues[116] report a case series of 15 patients. With the exception of one patient residual cancer on histopathological examination of the tissue is reported for all cases. No complications of treatment are reported. Longer term results are not reported.

Evidence is extremely limited and conclusions cannot be drawn regarding the effectiveness of this technology.

Laser photocoagulation

The aim of laser photocoagulation, using a neodymium–yttrium aluminium garnet (Nd-YAG)

TABLE 12 *Laser photocoagulation summary table*

Total incl. studies	Level						Inclusion criteria
	Sys. revs	1	2	3	4	5	
1	–	–	–	–	–	1	Sys. revs All levels 1–5
Conclusion: Insufficient evidence to draw conclusions regarding the effectiveness of this intervention.							

TABLE 13 *Gene therapy summary table*

Total incl. studies	Level						Inclusion criteria
	Sys. revs	1	2	3	4	5	
2	–	–	–	–	–	2	Sys. revs All levels 1–5
Conclusion: Insufficient evidence to draw conclusions regarding the effectiveness of this intervention.							

laser, is to irradiate the prostatic cavity following TURP.

One paper (evidence level 5) was identified.[117] Details of the study are given in Appendix 5 (*Table 47*). Conclusions are summarised in *Table 12*.

Andersson and co-workers report outcomes for a series of 20 patients.[117] Sixteen patients (80%) had residual cancer or recurrent cancer tissue at follow-up within 12 months. Three patients were reported as being cancer free. Few side-effects of treatment are reported.

Evidence is extremely limited and conclusions cannot be drawn regarding the effectiveness of this intervention.

Gene therapy

The purpose of gene therapy is to introduce novel genetic material into the malignant cell in an attempt to bring about either restoration of normal cellular function or, more commonly, tumour cell death. Gene therapy as a treatment for early localised prostate cancer is at an early stage. Most of the trials that are underway are Phase I/II and their aim is to improve survival for patients with advanced and metastatic disease.[118]

Two studies were identified that looked at toxicity in small samples of patients, including some patients with early localised disease. The first study had 30 patients, 13 of whom were low risk and who were treated with a mixture of gene and radiation therapy.[119] The second study was of 33 patients, eight of whom had early localised cancer.[120] They were also treated with gene therapy and radiotherapy. Both studies report toxicity results in terms of flu-like symptoms and fever grades. The conclusion of each study is that gene therapy is safe and well tolerated. No evidence of clinical effectiveness has yet been gathered. Details of both studies are given in Appendix 5 (*Table 48*). Conclusions based on included studies are summarised in *Table 13*.

Five reviews were identified, none of which was systematic. They were therefore excluded, but are useful in that they present up-to-date information on progress with Phase I/II trials.[118,121,122]

The focus of gene therapy at this early stage of development has been on advanced or metastatic disease. More recently, gene therapy has been used for patients with early localised cancers who are receiving radiotherapy. Results have shown that in the short term this therapy is relatively safe and well tolerated. Larger trials, however, are required to examine longer term toxicity and clinical effectiveness.

Assessment of effectiveness

The purpose of this review has been to identify new and emerging technologies in the treatment of early, localised prostate cancer, to identify best available evidence and, where the evidence allows, to draw conclusions regarding clinical effectiveness.

In all, 15 types of intervention were considered. Some are new technologies (e.g. HIFU, RITA and

gene therapy) and some are refinements of existing techniques (e.g. radiotherapy treatments such as brachytherapy and 3D-CRT). Brachytherapy retrieved the largest number of studies (more than 150). However, this evidence consisted largely of case series, the poorest quality evidence considered for inclusion in this review. The best quality evidence, in the form of RCTs, was included in the review of complications for 3D-CRT and in the review of NHT. However, all but one of the RCTs in the review of NHT considered NHT before RP, a treatment option that is not relevant to current clinical practice. The availability of evidence was extremely limited for most of the newer treatments. This is reflected both in the quality of the evidence, which consisted of case series of small patient numbers, and in the selection of patients, where the technology under evaluation was used not as a primary therapy but in patients for whom standard treatments either were unsuitable or had failed. As a result of this wide variation in quantity and quality of evidence between treatments, it is not possible to compare like with like and therefore not appropriate to draw conclusions across interventions.

Despite the large number of papers identified at the outset, the overall quality of evidence that constituted best available evidence across all interventions was not high. The majority of studies included in the review took the form of descriptive case series, the lowest level of evidence in the quality inclusion criteria. The median number of patients reported in the 104 included papers was 180, with only five studies reporting results for more than 1000 patients.[34,45,48,72,78]

Observational data such as are presented in descriptive case series are susceptible to bias. Strong consideration to this and other possible forms of bias relating to study design should be given in interpreting the evidence presented in this review.

Although details of patient characteristics are described at some level in most papers, little information is reported regarding patient selection, with the possibility of bias towards selecting more promising patients for treatment or for inclusion in a published case series. Such bias would exaggerate the benefits of the intervention and would also make between-treatment comparisons difficult. For example, patients selected for brachytherapy alone are considered among the fittest of prostate cancer patients and have the smallest volume disease, whereas patients selected for watchful waiting may be the least favourable (Mason M, University of Wales College of Medicine, Personal communication, 2002). Many studies included in the review stratify results by patient risk factors (in terms of stage, Gleason score and PSA levels). Although this is helpful in trying to identify which patients would be most likely to respond well to treatment, a number of studies report that such variables are independent prognostic indicators of outcome. It is difficult, therefore, to establish whether observed benefits should be attributed to treatment or to the characteristics of the patient group. Other studies report that patients are assigned to treatments according to risk factors.

The source of reporting of most case series, large specialist centres, may limit the generalisability of results. There is evidence to suggest that outcomes in terms of complications are affected by the volume of procedures undertaken by a hospital or by an individual surgeon.[123] This issue is considered in the forthcoming NHS guidance on urological cancers, which specifies that surgery should be undertaken by specialist teams carrying out more than 50 such procedures a year and radiotherapy should be undertaken by oncologists from specialist centres.[124] This issue is also relevant in the interpretation of RCT evidence and consideration should be given to the undertaking of complementary research to assess the generalisability of RCT evidence to routine clinical practice.

Given the developmental nature of the interventions included in the review, follow-up to treatment is of necessity relatively short. Where possible, a minimum of 5 years follow-up was set as the inclusion criterion, but this criterion had to be modified for most treatments. In addition, studies that met the criterion of 5 years or more often did not achieve complete follow-up. Few data regarding overall or disease-free survival or mortality were reported. Given the extended natural history of prostate cancer, such data reported in such relatively short-term follow-up periods are of limited value in terms of interpreting clinical effectiveness.

As a consequence of short-term follow-up, studies concentrate on reporting disease progression, which is thought to give some indication of longer term survival. Disease progression is measured using surrogate end-points based on clinical biopsies or serum PSA levels. The majority of studies use measurements of biochemical failure or freedom from disease, which causes two problems in interpreting results. First, there is a variation in the criteria used to define biochemical success or failure, with the result that it is difficult to compare

like with like between studies. Second, the validity of this measurement as an indicator of survival is open to question.[41,90,91]

All interventions in the treatment of early prostate cancer, including those in this review, and the standard treatments of RP and radiotherapy are associated with complications. Any development in treatment should ideally aim both to improve clinical outcome in terms of survival and to reduce treatment-related morbidity, thus improving the QoL of the patient. All studies in this review evaluate survival (usually using proxy outcomes as described above), complications or both, and several consider QoL.

The availability of evidence for newer treatments, namely HIFU, IMTT, RITA, laser photocoagulation, hormonal monotherapy and gene therapy, is extremely limited and of poor quality. No conclusions can be drawn regarding the clinical effectiveness of these treatments in terms of survival or morbidity.

Data are also limited for cryotherapy and IMRT. However, what evidence exists suggests that these interventions may warrant further investigation. Cryotherapy achieved favourable results in terms of bDFS in low-risk patients, but high rates of impotence. Evidence relating to complications was mixed for IMRT. However, one large case series comparing IMRT with 3D-CRT[72] suggests that high doses of radiation without an increase in complications may be achievable with IMRT.

The availability of evidence for the remaining interventions under consideration was more substantial. However, as already stated, the overall quality of evidence was poor and open to the sources of bias and limitations of study design described above. There were very few comparative data, particularly in the form of RCTs, both within the treatments included in the review and between these and standard current treatments. With the exception of a small number of RCTs, comparisons were indirect and often based on poorly matched patient cohorts.

In many studies overall results were reported for a number of treatment modalities or variations on a single modality. For example, within a cohort of patients receiving brachytherapy some might receive brachytherapy alone, others in combination with EBRT or ADT and some with both adjuvant therapies. In evaluations of 3D-CRT and standard radiotherapy some studies were clear comparisons of radiotherapy technique or of radiation doses. In other studies, however, subjects were assigned to the different radiotherapy techniques and to receive different radiation doses. In many uncontrolled case series a range of radiation doses was used across all subjects. Given the importance of dose on both survival and morbidity in the assessment of the effectiveness of radiotherapy, it is difficult to draw conclusions from these studies.

In studies of NHT no difference in terms of survival was observed in the comparisons NHT and RP with RP alone. However, as stated above, this is not a relevant comparison and therefore these results are of limited value on these grounds alone. The evidence for AHT was mixed in terms of survival in comparisons with standard and 3D radiotherapy. However, a lower QoL in terms of sexual function was observed in patients receiving AHT and EBRT compared with EBRT alone. RCTs of clinically relevant comparisons with longer term follow-up are required to establish whether NHT and AHT can improve survival outcomes.

No overall differences in survival were observed between brachytherapy and standard treatments. The wide variation in results can be attributed to the different techniques evaluated and to the influence of patient selection from study to study. Both existing systematic reviews and the current review present evidence to suggest that brachytherapy may perform worse than standard treatments for intermediate- and high-risk patients.[41,45,46]

The evidence for brachytherapy with regard to treatment-related morbidity is mixed. Existing systematic reviews suggest that brachytherapy performs at least as well as and possibly better than standard treatments in terms of morbidity. The rates of reported complications are low and are similar to those reported in more recent uncontrolled case series presented in the current review. However, this review also presents three matched case–control series (level 3 evidence) that suggest that brachytherapy may result in lower disease-specific QoL in terms of sexual function and urinary and bowel complications than EBRT or RP, compared with an age-matched healthy population.[47,64,125] There are possible reasons for these discrepancies. The evidence from existing systematic reviews and more up-to-date case series report complication rates, whereas the matched case–control series report the QoL associated with complications. Therefore, like is not being compared with like. What is perceived as being acceptable in terms of rates of complications may not be acceptable in terms of impact on QoL.

Limitations in study design in the matched case–control series may limit the interpretation of the results of these studies. There is no direct comparison between the treatment modalities, only between treatments and healthy controls. In one study,[48] although subjects were well matched with healthy controls there was a wide variation in patient characteristics between treatments.

The evidence for brachytherapy with regard to survival varies widely and is influenced by differences in treatment and in patient selection. The evidence relating to morbidity is mixed. Long-term studies are required that control for patient selection bias and assess the impact of complications.

In the evaluation of 3D-CRT, higher radiation doses rather than technique were associated with better biochemical control in terms of no evidence of disease. Although definitions varied from study to study, better rates of control were in the main achieved for patient subgroups defined as 'low risk' or 'favourable'. Many studies reported patient prognostic variables as being independent predictors of outcome. Future studies should control for differences in patient characteristics. Higher doses are also associated with increased complication rates. However, there is good RCT evidence that when delivered at the same dose 3D-CRT significantly reduces grade 1 and 2 gastrointestinal complications. Further studies with long-term follow-up and which control for patient selection bias are required to establish the optimal use of 3D-CRT in terms of dose and planning.

Very few studies reported HRQoL.[47,64,95,125] These studies suggested that general HRQoL was similar to that of a healthy population. There were some differences in disease- or symptom-specific QoL, as described above. No evidence was identified in assessing patient preference or the acceptability to patients of treatment. In an area where potential benefits in terms of survival are achieved to such an extent at the risk of treatment-related complications, evidence of the trade-offs made by patients or of the value placed on QoL associated with the different types of complication is of particular importance. The economic analysis accompanying this review has identified a relatively large body of utility evidence in relation to prostate cancer. This may be useful in informing this aspect of the review (see Chapter 4, Utilities subsection).

The evidence presented in this review is of poor quality overall and subject to weaknesses in study design. The value of evidence is extremely limited in terms of making recommendations for clinical practice, and strong consideration should be given to the possible sources of bias and to the limitations of study design in interpreting results. No overall long-term comparative benefits have been established for any of the interventions reviewed here in relation to standard treatment options. Although no conclusions can be drawn in relation to the newer technologies such as IMTT and HIFU, the short-term evidence for other technologies suggests that further research is warranted.

Chapter 4
Economic analysis

Methods for economic analysis

Overview

A comprehensive literature search to identify the costs, QoL, utility and cost-effectiveness of treating and caring for prostate cancer patients revealed almost no relevant UK evidence on the costs and cost-effectiveness of prostate cancer treatments. A model was therefore developed to examine the cost-effectiveness of new and emerging cancer treatments compared with the standard treatments of active monitoring, RP and EBRT, from a UK NHS perspective. A literature search was also undertaken for reports of previous prostate cancer models to inform the current work.

The intended approach was to draw on previous modelling work comparing the clinical effectiveness of the traditional treatments to develop a cost-effectiveness model that would allow comparison of the newer treatments with the traditional treatments. However, issues were found with the transition probabilities between disease states used in previous models.[126–128] Although it is not the purpose of the current study to compare the traditional treatments with each other, to attempt to compare the cost-effectiveness of newer treatments with traditional treatments it is necessary to establish a plausible baseline for the comparison. Analysis showed that it was impossible to reconcile metastasis-free survival, disease-specific survival (from meta-analyses of RP and watchful waiting data) and the assumption that once metastases occur progression is independent of tumour grade and treatment. Relaxation of the latter assumption gave an apparently arbitrary variation in metastatic progression rates, which for some tumour grade–treatment combinations were outside the limits of what the data indicated as plausible ranges. These issues are discussed in more detail in the Model subsection of this chapter.

The approach adopted for the analysis of the new treatments is that assumed by previous authors, that is to match progression-free survival from the meta-analyses of RP and watchful waiting, and to assume that progression rates after the development of metastases are independent of tumour grade and previous treatment. The resulting discrepancies between modelled survival and those of the meta-analyses are shown in *Table 14*. They are particularly acute for poorly graded tumours on watchful waiting.

Given the lack of certainty in making comparisons between even the traditional treatments, and the lack of metastasis-free and DFS data for the newer treatments, the approach adopted was to assume that new treatments are as effective as RP. If this assumption is made, how do their varying incidences of adverse effects impact on patient quality-adjusted life-years (QALYs)? Further to this, given the paucity of evidence relating to adverse effects for many of the new and emerging technologies considered in this review, a decision was made to restrict the economic analysis to brachytherapy, cryotherapy and 3D-CRT. The aim of the economic analysis therefore is to assess the potential cost-effectiveness of brachytherapy,

TABLE 14 *Metastasis-free and disease-specific survival for watchful waiting and radical prostatectomy*

	Active monitoring			RP		
Differentiated	**Well**	**Moderately**	**Poorly**	**Well**	**Moderately**	**Poorly**
Metastasis-free survival						
5 years	0.93	0.84	0.51	0.93	0.84	0.73
10 years	0.81	0.58	0.26	0.87	0.68	0.52
Disease-specific survival						
5 years	0.98	0.97	0.67	0.99	0.96	0.91
10 years	0.87	0.87	0.34	0.94	0.80	0.77

Data from Chodak *et al.*[129] and Gerber *et al.*[130]

cryotherapy and 3D-CRT compared with traditional treatments, based on an assessment of the impact of adverse effects on patient QALYs and the assumption that all treatments are equally effective in terms of disease-free survival.

In this section, after a summary of the results of the literature search, the prostate cancer model developed is described. This includes the structure of the model, the disease and treatment parameters, and the cost and utility values. The results of the analysis are shown in the following section.

Literature search

A comprehensive literature search was undertaken to identify the costs, utility and cost-effectiveness of treating and caring for prostate cancer patients. Papers reporting prostate cancer models were also sought. In addition, a search was undertaken to identify research on different prostate cancer outcome measures, and how they relate to each other. The latter proved unsuccessful and papers were identified opportunistically from the literature identified by the other searches. The search strategies are shown in Appendix 3.

Costs

The literature search identified only one UK study, a previous HTA review[2] which included costs. Some costs for traditional cancer treatments are also included in Appendix 1 of the National Institute for Clinical Excellence (NICE) guidance on urological cancers.[124]

Utilities

Although the literature on prostate cancer utilities is not extensive, there has been considerably more research into the utility of prostate cancer patients than many other disease areas. Eleven papers and one abstract report prostate cancer utilities elicited using recognised techniques. The literature is described in the Utilities subsection of this chapter.

Cost-effectiveness

No UK studies were identified on the cost-effectiveness of any of the treatments considered in this review.

Models

There has been considerable interest in prostate cancer modelling. This is probably due to the lack of conclusive clinical evidence on the best treatment for localised prostate cancer, combined with the growing number of men who are diagnosed with the disease. Existing modelling studies can in general be divided into two groups: those that investigate the desirability of prostate cancer screening, and those that compare treatment strategies for localised prostate cancer. The former usually include only very simple models of the effectiveness of treatment, and were not of interest. However, models of treatment efficacy, usually comparing RP with watchful waiting, were useful to inform the current modelling work. In particular, a series of papers was identified that describe the development of a model originally reported by Fleming and colleagues.[126] The model is a Markov model and was used to compare the QALY outcomes of radical treatment (prostatectomy and radiotherapy) with watchful waiting. In addition to other developments, Beck and colleagues[128] incorporated evidence from a meta-analysis of patients whose treatment intention was watchful waiting,[129] and Kattan and Miles[127] added a similar analysis for patients treated by RP.[130] This previous modelling work was used as the basis for the development of a model to compare the specified newer treatments with the traditional approaches.

Model

The basic structure of the Markov disease model is that described by Fleming.[126] Patients are assumed to be in one of five disease states: metastasis free, hormonally responsive metastases, hormonally refractory metastases, prostate cancer death and death from other causes. With the exception of the transition to death from other causes, which may occur from any of the other living disease states, it is assumed that the patients can only progress to the next sequential disease state in any one time interval, as illustrated in *Figure 2*.

Within the metastasis-free state patients may suffer from different adverse effects from their treatment.

Progression to metastases

The meta-analyses of watchful waiting and RP by Chodak and colleagues[129] and Gerber and co-workers,[130] respectively, were used by Kattan and Miles[127] to determine progression rates to metastases. The Chodak study has been criticised for potential selection bias due to patient selection within some of the data series included within the meta-analysis.[131,132] However, another large analysis of patients treated by watchful waiting reported by Albertsen and colleagues[133] concluded that his data "are remarkably consistent with those reported by … Chodak *et al*.". The Albertsen analysis was based on a retrospective analysis of

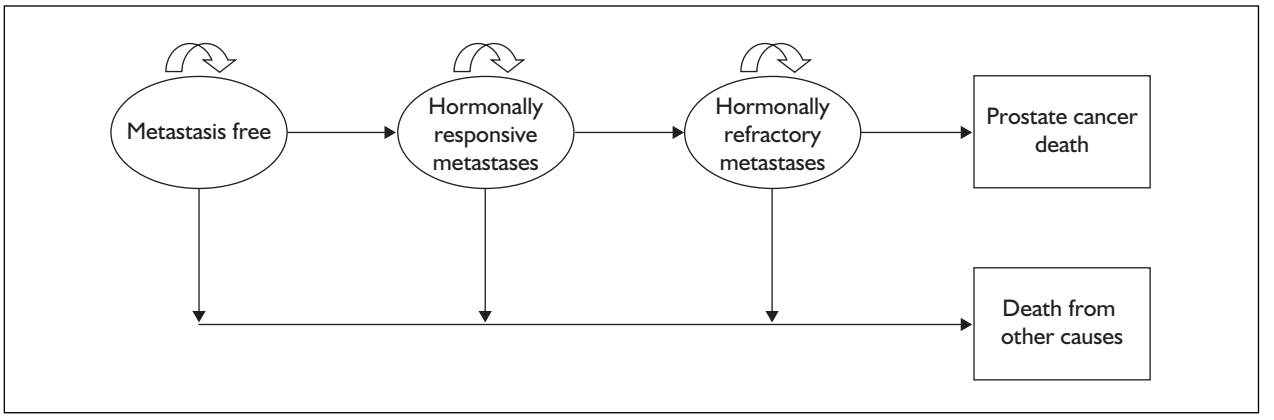


FIGURE 2 *The Markov model structure of prostate cancer*

patients registered with the Connecticut Tumor Registry. The analysis only reports actuarial survival, and not metastasis-free survival. The Chodak analysis was, therefore, also used for the current model. It should be noted, however, that all historical series of watchful waiting may underestimate survival from an initial waiting approach, as PSA testing now allows a more active approach to patient follow-up (active monitoring) and potential identification of patients who may later have radical treatment.

A more recent analysis of RP than that of Gerber has been reported by Pound and co-workers,[134] based on surgeries between 1982 and 1987. The surgeries included in the Gerber analysis took place between 1970 and 1993. Pound does not report mortality by tumour grade, but in his predominantly moderately differentiated cohort (89%) disease-specific survival at 10 years was 94% compared with 80% for Gerber. However, not only is the series more recent than Gerber, it is also from a single (highly experienced) surgeon at a single institution, and hence may not be generalisable. As discussed by Pound, patient selection may also have influenced the results. Gerber found significant heterogeneity between some of the different case series included in his meta-analysis. The advantage of a meta-analysis is that it is more likely to be generalisable. However, in the comparison of RP with watchful waiting the possibility that RP may yield considerably better results than those reported by Gerber should be considered. As long as the basis of treatment comparisons relies on case-series data there will continue to be considerable uncertainty. Meta-analyses currently offer the best available evidence of the efficacy of watchful waiting and RP.

On this basis the meta-analyses of watchful waiting by Chodak and co-workers[129] and RP by Gerber and colleagues[130] provide the best data currently available on actuarial metastasis-free survival and disease-specific survival for these treatments. Both studies used patient-level data from different countries, and analysed the effects of age, grade and stage on survival. Both found that grade was the most significant determinant of survival, and show survival by well, moderately and poorly differentiated tumour grade. A summary of their results is shown in *Table 14*. Note that the 5-year results for RP were estimated from published Kaplan–Meier curves.

Annual progression rates to metastases were calculated for watchful waiting and RP for well-, moderately and poorly differentiated tumours, initially using the 10-year data reported by Gerber[130] and Chodak.[129] This was the approach adopted by Beck[128] and Kattan and Miles.[127] However, it was found that for watchful waiting in particular, assuming a uniform annual progression rate for 10 years did not allow the reported survival rates to be matched. Different progression rates from no metastases to hormonally responsive metastases were calculated for 0–5 years and 5–10 years. For well- and moderately differentiated tumours on watchful waiting the progression rates for 5–10 years were approximately double those for 0–5 years. It is uncertain whether this is a real effect, or a product of the data available for the meta-analysis. Chodak[129] commented that some of the individual data series within the meta-analysis had more favourable outcomes than others. With few patients having been followed for 10 years the 10-year results could be biased by the data available.

With no similar analyses for either traditional radiotherapy or any of the newer treatments, it was assumed that progression to metastases was the same for these as for RP. This assumption seriously limits the scope of the analysis.

TABLE 15 *Annual metastatic transition probabilities*

Transitions	Baseline	Range
Responsive to progressive disease		
with minimal disease	0.20	0.10–0.35
with severe disease	0.36	0.24–0.52
Progressive disease to death	0.50	0.43–0.65

Data from Hillner *et al.*[135]

Progression from hormonally responsive to hormonally refractive metastases and from hormonally refractive metastases to prostate cancer death

Fleming and colleagues[126] used data from a trial of hormonal therapy for metastatic cancer to determine the progression probabilities from hormonally responsive to hormonally refractive metastases and from hormonally refractive metastases to prostate cancer death. These were 0.36 and 0.8 per year, respectively, for patients with tumours of all differentiation. Beck and colleagues[128] and possibly Kattan and Miles[127] also used these probabilities, although the latter study does not specify. However, it was found using these metastatic transition probabilities in combination with a uniform transition probability to metastases for 0–10 years, as used by Beck[128] and Kattan,[127] that 10-year survival for patients on watchful waiting was underestimated by 15% for moderately differentiated tumours and overestimated by 12% for poorly differentiated tumours compared with the Chodak results.[129] In other words, using the Chodak data on metastasis-free survival to calculate progression to metastases, combined with the Fleming[126] rates of progression through metastatic cancer to death, does not even closely match the Chodak[129] survival rates for moderately and poorly differentiated tumours. This has potentially significant implications when modelling comparisons between other treatments and watchful waiting. Even when the progression rates to metastases were modified to allow different rates for 0–5 and 5–10 years, as described in the previous paragraphs, survival for patients on watchful waiting was underestimated by 10% for moderately differentiated tumours and overestimated by 12% for poorly differentiated tumours. Similarly, for patients treated by RP with poorly differentiated tumours survival is underestimated by 8%.

Three different approaches to tackling this issue were made, and the effects on cost and QALY outcomes compared. All the results tables in the following section are for men aged 65 years.

Method 1

Further data on the progression probabilities from hormonally responsive to hormonally refractive metastases and from hormonally refractive metastases to prostate cancer death were sought. The search for modelling literature had identified a cost-effectiveness model for metastatic cancer reported by Hillner and colleagues.[135] This model uses progression rates from the Intergroup 0036 trial of medical or surgical castration with or without flutamide. The annual progression probabilities from Hillner (without flutamide) are shown in *Table 15*.

Analysis was carried out with different probabilities for progression both from hormonally responsive to hormonally refractive metastases and from hormonally refractive metastases to prostate cancer death. Using the midpoint of the Hillner[135] annual progression probabilities for minimal and severe disease (0.28) and his death rate from hormonally refractive cancer to prostate cancer death (0.5) appeared to give the best overall fit to the data, although a combination of values which fitted all the treatment/grade metastatic and disease survival data could not be found. In particular, poorly differentiated tumours on watchful waiting appeared to progress through metastatic disease considerably more quickly than any of the other tumour treatment/grades. However, the sensitivity analysis showed that varying these progression probabilities across a wide range of plausible values, but assuming that for each scenario they are constant across both treatments and all tumour grades, gives only a small variation in QALY and cost differences between RP and watchful waiting, as shown in *Table 16*.

Method 2

As no single set of values for hormonally responsive to hormonally refractive metastases and from hormonally refractive metastases to prostate cancer death fits tumours of all treatments/grades, another approach taken was to calculate for each treatment and tumour grade the progression rates

TABLE 16 *Variation in QALY and cost differences between RP and watchful waiting (WW) when metastatic progression probabilities are varied for a man aged 65*

Metastatic progression probabilities per year	Fleming	Hillner mild metastases	Hillner severe metastases	Hillner mid mild/severe	Hillner/ Fleming mid
Responsive to refractory	0.36	0.2	0.36	0.28	0.28
Refractory to death	0.8	0.5	0.5	0.5	0.65
QALY difference (RP – WW)					
Well differentiated	0.26	0.21	0.25	0.23	0.24
Moderate differentiation	0.44	0.38	0.43	0.41	0.41
Poor differentiation	1.55	1.38	1.53	1.47	1.48
Cost difference (RP – WW)					
Well differentiated	£4,689	£4,581	£4,689	£4,644	£4.644
Moderate differentiation	£4,553	£4,396	£4,553	£4,489	£4,489
Poor differentiation	£3,685	£3,171	£3,685	£3,479	£3,479
ICER					
Well differentiated	£18,366	£22,151	£18,817	£20,015	£19,726
Moderate differentiation	£10,307	£11,708	£10,504	£10,942	£10,820
Poor differentiation	£2,382	£2,290	£2,412	£2,363	£2,345

ICER: incremental cost-effectiveness ratio.

that best fitted the metastasis and disease survival data. However, for well and poorly differentiated tumours on watchful waiting it was not possible to find a combination of progression probabilities from hormonally responsive to hormonally refractive metastases and from hormonally refractive metastases to prostate cancer death that was within plausible ranges, as indicated by the Hillner[135] and Fleming[126] data. Nor was any pattern found indicating, for example, that patients with poorly differentiated tumours had lower metastatic survival rates than those with well-differentiated tumours. Despite these issues the advantage of this approach is that it allows the results of the Chodak[129] and Gerber[130] meta-analyses to be matched on both metastasis-free survival and survival. Not unexpectedly, given the differences between modelled survival and the results of the meta-analyses when the same metastatic progression rates are assumed for all grades and treatment, when survival rates are matched there is some considerable variation in the estimates of QALY differences between treated and untreated patients. See *Table 17*, methods 1 and 2.

Method 3

Yet another approach to the lack of agreement between the different data is to assume the same metastatic progression rates for all tumour grades and treatments, and to calculate back from the survival data the progression probabilities to metastases. The same progression probability to metastases for years 0–10 has been assumed for this scenario. This scenario yielded quite different results again, as shown in *Table 18*.

The conclusion of these analyses is that considerable uncertainty remains in the parameters for disease progression in a prostate cancer model, even for the established treatments. For men aged 65 years, on the basis of comparisons between two different meta-analyses of case series, *Table 18* shows that there only seems to be a clear indication that men with poorly differentiated tumours may benefit from RP, as opposed to watchful waiting. For moderate tumours the estimate of treatment benefit varies from –0.93 to +0.41 QALYs, depending on which two of the three data elements described earlier in this section are matched. This conclusion differs from that of Kattan and Miles;[127] that study was based on the same meta-analyses of metastasis and disease survival, but used method 1 exclusively. They concluded that RP yields QALY benefits for all men aged under 75 years.

For the analyses of the new treatments method 1 is used, except for poorly differentiated tumours on watchful waiting, discussed below. Method 1 matches the metastatic-free survival from the meta-analyses, and assumes the same metastatic progression rates for all tumour grades and initial treatment. This is the method used by Beck[128] and Kattan,[127] albeit with different metastatic progression probabilities. As it is assumed for the purposes of the analysis that the new treatments (and traditional radiotherapy) are all equally as

TABLE 17 *Variation in QALY and cost differences between RP and WW when different state survival data are matched*

	Method		
Metastatic progression probabilities per year	**1**	**2**	**3**
Responsive to refractory	0.28	Various	0.28
Refractory to death	0.5	Various	0.5
QALY difference (RP – WW)			
Well differentiated	0.23	0.42	–0.14
Moderate differentiation	0.41	0.03	–0.93
Poor differentiation	1.47	2.37	3.20
Cost difference (RP – WW)			
Well differentiated	£4,644	£5,099	£5,043
Moderate differentiation	£4,489	£3,400	£5,820
Poor differentiation	£3,479	£6,332	£1,799
ICER			
Well differentiated	£20,015	£12,219	NA
Moderate differentiation	£10,942	£114,174	NA
Poor differentiation	£2,363	£2,673	£562

1: Progression to metastases as meta-analyses, common metastatic progression probabilities across treatments and grades.
2: Progression to metastases as meta-analyses, progression probabilities across treatments and grades calculated to match disease survival for each.
3: Progression to metastases calculated to match disease survival for each treatment and grade, common metastatic progression probabilities.
NA: not applicable.

TABLE 18 *Difference between modelled and meta-analysis results for disease-specific survival using method 1*

	Differentiated		
Absolute difference in % disease-specific survival	**Well**	**Moderately**	**Poorly**
WW	5.4	–4.5	0.0[a]
RP	–0.5	4.6	–2.0

[a] 22% if the same method is used as for other treatment-differentiation combinations.

effective as RP, the comparisons with RP and radiotherapy will be relatively unaffected. However, this is not true for comparisons with watchful waiting, particularly for poorly differentiated tumours. For these patients, modelled survival is overestimated by 22% if method 1 is used, thereby leading to considerable underestimation of the benefits of radical treatment. For this reason, method 3 is used for poorly differentiated tumours treated by watchful waiting.

The differences between modelled and meta-analysis results for disease-specific survival are shown in *Table 18*, and should be taken into consideration when interpreting the results.

Deaths from other causes

As prostate cancer is a disease affecting older men it is essential to take into account deaths from other causes. Deaths by age were from standard life tables corrected for prostate cancer deaths.[136]

Adverse effects of treatment

All radical treatments for prostate cancer can result in long-term adverse affects. The most significant include impotence, incontinence and other urinary problems, and bowel injury. Short-term effects of treatment were ignored, as these would have a very minor effect on total QALYs. For the three standard treatments estimates of the central values and ranges of the incidence of long-term adverse effects were calculated as patient-number weighted means taken from the systematic reviews by Selley and colleagues,[4] except where more recent large studies or meta-analyses were reported in the NHS guidance.[124] For the new treatments estimates of the incidence of adverse effects were calculated as patient-number weighted

TABLE 19 *Incidences of adverse effects of prostate cancer treatments*

		Impotence			Urinary symptoms			Bowel injury		
Treatment		**Central**	**Low**	**High**	**Central**	**Low**	**High**	**Central**	**Low**	**High**
Active monitoring	1	0	0	0	0	0	0	0	0	0
RP	2	0.58	0.44	0.6	0.15	0.05	0.25	0	0	0
Radical radiotherapy	3	0.31	0.29	0.36	0.2	0.09	0.23	0.15	0.08	0.26
3D-CRT	1	0.36	0.32	0.39	0.2	0.09	0.23	0.05	0.02	0.12
Brachytherapy	2	0.18	0.04	0.51	0.14	0.14	0.3	0.03	0.01	0.05
Cryotherapy	3	0.86	0.67	0.93	0.18	0.14	0.46	0.004	0.004	0.005

means from the literature used in the clinical review (see Appendix 6). As papers were excluded from this review that had been included in other reviews, the results from the latter were also taken into consideration.

Several difficulties arise in making comparisons between treatments. First, none of the comparisons between treatments, with the exception of the comparison between 3D-CRT and traditional radiotherapy, is based on RCT evidence. All the estimated incidences are based on different case series, and therefore should be treated with caution. The definitions of a particular adverse effect also vary considerably between trials, as do the time intervals from treatment when adverse effects are reported. These factors will contribute to the wide ranges of incidences of adverse effects reported for the same treatment.

One particular problem is that while incontinence rates for RP are usually specified, in many studies of radiotherapy the incidence of all urinary problems is grouped. This was also the case for some of the reports of adverse effects of the newer treatments. It is also not possible to differentiate between incontinence and other urinary problems in the utility literature (see subsection on utilities below). Incontinence and other urinary problems were therefore treated as the same, with the same utility assigned to both. This may adversely affect the QALYs for radiotherapy and other treatments where other, possibly more minor, urinary problems can occur.

The incidences of adverse effects used in the model are shown in *Table 19*. The data sources used are detailed in Appendix 6.

Note that for NHT and AHT the adverse effects of the primary treatment were assumed, except for impotence, which was assumed to affect all patients for the duration of treatment. In all analyses it is assumed that patients are free of any of these problems before treatment.

For RP mortality as a result of treatment was included, with a central estimate of 0.5% (range 0.2–1.2%).[4]

Utilities

To adjust survival in the model for the QoL of patients, utility values of the different disease states are needed. Utility values usually range between 1, representing perfect health, and 0, representing death.

The literature search included terms to identify the literature on utility values in prostate cancer. In addition, some of the modelling papers reported utility values. Until recently models often relied on judgements of relative utilities by clinicians (e.g. Fleming[126] and Gottlieb[137]). While these assessments are of some value in the absence of better evidence, they are considered unreliable both because of their lack of use of a standard proven technique to elicit utilities [usually time trade-off (TTO) or standard gamble (SG)] and because physicians often value health states more highly than either patients or the general public. For these reasons these papers were excluded from the review of utilities. Two further studies, both by Chapman and co-workers,[138,139] were rejected although of good methodological quality. The prostate cancer states that Chapman used as the basis of these studies are not comparable with those used in the other studies, and are not appropriate for the model structure. In total, nine papers and one abstract were accepted into the review of utility data for prostate cancer. Two of the nine papers reported some of the same result.[140,141] The abstract by Cowen[142] reported a pilot study, which led to a more comprehensive piece of work reported later by the same author.[143] This left eight separate studies of prostate cancer utilities to be considered.

Not all of the studies consider the same health states. Three cover the symptoms of localised prostate cancer and/or its treatment,[144–146] three report utilities for metastatic cancer,[140,141,147] and

two show results for both.[143,149] A summary of the results of the studies is shown in Appendix 7. It can be seen that the results vary considerably, especially for metastatic cancer. There are several reasons for these differences. These include the method of determining utilities, the definition of 'perfect health', definitions of the health states, and the subjects who were asked to determine the utilities. These will be discussed below.

Method of determining utilities

All except for Rosendahl[147] used the TTO method to determine utilities. This method is often considered more reliable than SG, as it is thought to be easier for participants to understand. Souchek[148] compared TTO results with SG and a rating scale and found the differences between different metastatic cancer states to be similar for all three methods, but that TTO gave results between 10 and 20% higher than the other methods. Studies in other disease areas have often found TTO to give lower results than SG. Rosendahl[147] used a QoL instrument for which an algorithm for assigning utilities had previously been developed.

Definitions of the health states

Differences may arise both in the categorisation of health states and in the descriptions that are used to define apparently similar states. An example of varying categorisation can be seen in the categorisation of urinary problems. Cantor[144] distinguishes between incontinence and bladder outlet obstruction, whereas Albertsen[145] groups urinary troubles. Krahn[149] distinguishes between complete and partial incontinence, in contrast to the other studies that just state utility values for incontinence. In some studies patients were given QoL questionnaires to develop the health state descriptions that were used as the basis of the utility assessments, whereas in others the researchers developed the definitions. Using either method the definition of a problem such as incontinence can cover a wide spectrum of disability from a minor irritation to a more serious problem with major QoL implications. Most studies do not show the health state descriptions that they used, and therefore the states on which subjects were asked to base their utility assessments may vary considerably between studies. This is likely to be a particular issue with metastatic cancer, a category in which patients may range from stable, and able to carry out many of their usual activities, to close to death.

Definition of 'perfect health' or utility of 1

'Perfect health', the reference point defined as a utility of 1, is not defined as such in all studies. Some authors implicitly assume that men without the specific treatment or disease problems considered have a utility of 1.[144,149] In this case 'perfect health' is the average health of men of that age, excluding prostate cancer. Saigal[146] and Albertsen[145] also effectively use this definition. The population utility norms by age and gender published by Kind and colleagues,[150] albeit derived using a different instrument, the EQ5D, show that for men aged 55–74 years mean utility is 0.78, falling to 0.75 for men aged over 75. For this reason studies that implicitly, or explicitly, assume that men of the age being considered are in perfect health (or that ideal health for that age group is the relevant comparator) are likely to result in higher utility values than those that do not. Of the eight utility studies three state that a utility of 1 is defined as perfect health: Cowen,[143] Bennett[140,141] and Souchek.[148] The Q-tility instrument used by Rosendahl[147] is not described and it is therefore not clear how a utility of 1 is defined.

The subjects who were asked to determine the utilities

The results of utility studies for a particular disease usually differ depending on who is asked to assess utility. Patients and medical staff usually assign higher utilities to a particular state than the general public. It is thought that this is because patients often adapt to their new circumstances, and medical staff have experience of this. While there is continuing debate as to which perspective should be used, that of the general public is generally accepted as being the more relevant. Only one of the utility studies used men in good health to determine utilities,[144] but the results are based on a sample of only ten. Cowen[143] used men without prostate cancer attending a general medicine clinic, whereas Saigal[146] used men waiting for a prostate biopsy. The highest utility scores for the symptoms and effects of treatment for localised prostate cancer were from Albertsen[145] (prostate cancer patients) and Krahn[149] (physicians). Apart from Cowen[143] and Rosendahl,[147] all of the utility studies for metastatic cancer were based on physician or patient assessments. The Rosendahl[147] results, based on a scoring of patient QoL assessments, yield surprisingly high scores for metastatic cancer. The results of Cowen[143] are, however, in general lower than the physician and patient assessments. Bennett[141] reported on the differences in utilities according to whether they were assessed by physicians or by prostate cancer patients. The physicians rated all states more highly than patients, particularly for advanced metastatic cancer, where the physicians rated it at

0.42, in contrast to patients who assigned it a utility of only 0.05.

Utilities: discussion and conclusion

Despite the many differences between the studies some patterns do emerge. In all studies where comparison is possible, with the exception of Saigal,[146] impotence was found to have a higher utility score than incontinence. In other words, on average the subjects in the utility studies were more willing to trade life-years for continence than for potency. The results for bowel injury are less conclusive, with the results from Cantor[144] and Saigal[146] showing bowel injury to have a utility approximately 0.2 lower than incontinence, whereas Albertsen[145] shows a higher utility. Cowen[143] did not include bowel injury in his study, as previous modelling by Fleming[126] and Beck[128] showed that it was not a significant factor in determining the choice of treatment between watchful waiting and prostatectomy, as patients were considered to have a very low risk of sustaining bowel injury.

Only Cowen[143] and Krahn[149] studied utility values across localised and metastatic cancer. Both showed metastatic cancer to have lower utilities than any patients with localised cancer. The range of utility values for metastatic cancer varies from 0.05 to 0.92 depending on how advanced the cancer, the subjects (physicians or patients) used in the assessment, and the method for determining utilities. If the perspective of the general public is adopted the Cowen[143] values of 0.45 for hormonally responsive metastatic cancer and 0.15 for refractory cancer seem the most plausible. Modelling will, however, include sensitivity analysis to examine the effect of higher utility values for metastatic states.

The results of the Cowen[143] studies are used as the baseline utility values for the model. The study uses a proxy for the general public, with patients attending a general medicine clinic without cancer, it is based on a reasonable sample (n = 63), and the values were derived using a recognised technique (TTO). Furthermore, the study provides the most comprehensive and plausible set of values across the problems associated with treatments for localised cancer and morbidity from metastatic cancer. However, there are still some utility values required in the model that Cowen[143] does not include. The most important of these is the utility of patients who have had radical treatment but are not suffering from any side-effects. None of the studies considers this state, but all of the models identified assume that treated patients without adverse effects of treatment have a higher utility than untreated patients, although Kattan[127] included a sensitivity analysis to this effect. As a baseline value for treated prostate cancer the Kind[150] utility for all men aged 55–74 years will be used, but as this was derived from a different study using a different instrument it is slightly arbitrary. This value (0.78) is higher than the Cowen[143] value for watchful waiting (0.73). Kattan[127] used a value of 0.84, derived from the Beaver Dam study for men aged 65–74 years. This value will be used in a sensitivity analysis, as will a scenario where the utility is the same for treated patients (without toxicities) as for patients on watchful waiting.

Another state that Cowen[143] did not consider was bowel injury. The difference between the utilities of common states (impotence, incontinence) and bowel injury from other studies were subtracted from the Cowen values for those states to give an estimated utility for bowel injury. This gave a range of values from 0.37 to 0.59. The average value, used as the central estimate, is 0.47.

Table 20 summarises the utility values used as the baseline in the modelling, and the sensitivity analyses undertaken.

Costs

The costs have been calculated from an NHS perspective and therefore the costs to patients, their carers and other parties are not included. These other potential indirect costs are discussed in Chapter 5. All costs have been inflated to the year 2002 using the Hospital and Community Health Services (HCHS) pay and prices indices,[151] with the exception of 2001–2, where the figure is not yet available and the retail price index (RPI) for 2001 has been used.[152] All costs have been discounted at 6%, and benefits by 1.5%.

Initial treatment costs

Treatment costs have been derived from a variety of sources including the literature and NHS trusts. The initial treatment costs are shown in *Table 21*. These do not include the costs of continued patient monitoring, which are discussed below. Total treatment costs are shown in *Table 22*.

The central cost of RP was taken as £5042 (Calvert N, Fourth Hurdle Consulting Ltd, personal communication). The mean cost of the health resource group (HRG), which includes prostatectomy, is £2079 (50% range £1502–2433),[153] but an RP is more complex than most procedures in the group. For sensitivity analysis the upper interquartile range of the HRG cost is used. The costs of conformal and traditional radiotherapy were sourced from the

TABLE 20 *Utility value scenarios*

Scenario	Baseline	Radical treatment as Kattan	Radical treatment as active monitoring	Metastatic cancer + 0.15	Bowel injury low	Bowel injury high
	1	2	3	4	5	6
Active monitoring	0.73	0.73	0.73	0.73	0.73	0.73
Radical treatment, no side-effects	0.78	0.84[a]	0.73[a]	0.78	0.78	0.78
Impotence	0.70	0.70	0.70	0.70	0.70	0.70
Incontinence	0.60	0.60	0.60	0.60	0.60	0.60
Bowel injury	0.47	0.47	0.47	0.47	0.37[a]	0.59[a]
Other						
Metastatic cancer						
Hormonally responsive	0.44	0.44	0.44	0.59[a]	0.44	0.44
Hormonally refractory	0.15	0.15	0.15	0.30[a]	0.15	0.15

[a] Changed from baseline.

TABLE 21 *Initial costs of treatments for localised prostate cancer*

	Treatment costs (£)		
Treatment	Central	Low	High
Active monitoring	0	0	0
RP	5042	2484	6302
Radical radiotherapy	563	422	703
3D-CRT	779	584	1251
Brachytherapy	5556	5504	6946
Cryotherapy	7000	5250	8750
NHT (+ primary)	794	387	1,177
AHT (+ primary)	2477	743	3567

TABLE 22 *Costs of caring for patients with hormonally responsive metastases*

Cost item	Medical castration (central)	Surgical castration (low)
Initiation costs (£)		
Outpatient visit[a]	55	55
Bone scan[b]	178	178
Orchiectomy[c]		635
Initial total	233	868
Annual cost (£)		
Outpatient visits[d]	713	110
Zoladex[e]	1590	
Annual total	2302	110

[a] National reference costs 2001, urology outpatient follow-up attendance with no investigation.[153]
[b] Mean cost from three NHS trusts.
[c] National reference costs 2001, activity weighted cost of elective inpatient and day-case episodes for HRG L43.[153]
[d] As note *a*, 13 per year for medical castration, two per year for surgical castration.
[e] British National Formulary, 43, March 2002, 3.6 mg every 4 weeks.[154]

NICE report 'Improving outcomes in urological cancers'.[124] The cost of conformal therapy varies depending on whether it is delivered using older machines using Cerrobend blocks (high cost) or newer multileaf collimators (MLCs). The latter are gradually replacing older machines, and the MLC cost is used as the central figure. Brachytherapy costs were sourced from the Christie Hospital, Manchester (Wylie J, Christie Hospital NHS Trust, personal communication). They are shown in more detail in Appendix 8. Only an approximate cost for cryotherapy was obtained. Where cost ranges were not available the central cost was varied by ±25%. For adjuvant and neoadjuvant therapy, where sufficient information was available, the costs of therapy for each trial were calculated. They varied considerably according to the regimen and its duration. Further details are given in Appendix 9.

Active and post-treatment monitoring

Active monitoring and post-treatment monitoring were costed assuming two PSA tests and GP check-ups per year, giving an annual cost of £45. For a high costing it was assumed that the checks took place in an outpatient clinic, at a cost of £129 per year.

Hormonally responsive metastatic cancer

Two alternative costs for hormonally responsive metastatic cancer are available in the model. The central option assumes that patients are treated with the luteinising hormone-releasing hormone (LH-RH) analogue goserelin. A lower cost, but less popular option is orchiectomy, or surgical castration. It is assumed for both options that patients will have an outpatient appointment and a bone scan before initiation of treatment. The initiation cost for the orchiectomy option will also include the cost of the surgery. The costs used are shown in *Table 22*. The time-dependent state costs are also shown in the table. It has been assumed that patients attend an outpatient clinic for their 4-weekly injections of goserelin.

Hormonally refractory metastatic cancer

As a proxy for the costs of terminal care it has been assumed that on average patients have one course of palliative radiotherapy, an inpatient stay and community nurse support. These costs are shown in *Table 23*.

Results

QALY

Baseline results

In the interpretation of QALY and cost-effectiveness results it is essential to remember the key limitation of the analysis: with the exception of watchful waiting it is assumed that all treatments are equally as effective as RP in terms of progression to metastases, and hence disease survival. The differences between treatments in QALYs arise from differences in the incidences of the possible adverse events. For this reason the differences in QALYs between treatments are not considerable: a maximum range of 0.72 and 0.55 QALYs for well- and moderately differentiated tumours, respectively, as can be seen from *Table 24*. The Chodak[129] and Albertsen[133] data showed that poorly differentiated tumours on watchful waiting had relatively poor survival, and this is reflected in

TABLE 23 *Costs of caring for patients with hormonally refractive metastases*

Cost item	Cost (£)
Palliative radiotherapy[a]	277
Inpatient stay[b]	1638
Community nurse support[c]	254
Total	2169

[a] National reference costs 2001, HRG W04.[153]
[b] National reference costs 2001, non-elective inpatient HRG L31.[153]
[c] National reference costs 2001, NHS Trusts, service code N21.[153]

TABLE 24 *QALYs for different treatments for a man aged 65*

Treatment	Differentiated		
	Well	Moderately	Poorly
WW	8.88	7.52	3.99
RP	8.93	7.78	6.83
Radical radiotherapy	8.56	7.47	6.57
3D-CRT	8.89	7.75	6.81
Brachytherapy	9.28	8.07	7.07
Cryotherapy	8.66	7.56	6.65

the low QALYs for these tumours compared with radical treatments.

Of the radical treatments brachytherapy yields the greatest QALYs and radical radiotherapy the least in this analysis. However, there is some evidence that brachytherapy may not be as effective as prostatectomy for more severe tumours, which is important to consider in any comparison between the treatments.

The reason for the lower number of QALYs for radiotherapy is the relatively high incidence of radiation proctitis (15%). Of all the localised cancer disease states, bowel injury had the lowest utility of 0.47, compared with a utility of 0.78 for patients unaffected by adverse events and 0.7 for impotence. Thus, although the central estimate of the incidence of impotence after prostatectomy is considerably higher (58%) than that for radiotherapy (31%), the QALYs for prostatectomy are greater. Conformal therapy has been shown in four RCTs[67,68,75,83] to reduce significantly the incidence of bowel injury compared with traditional radiotherapy, and the utility results indicate that patients treated with conformal therapy have a similar utility to those treated with RP.

NHT, assumed to cause loss of potency in all patients for 3 months, results in a loss of 0.02 QALYs. As adjuvant treatment is given after primary therapy, when a proportion of patients have become impotent as a result of that treatment, the QALY loss is dependent on the incidence of impotence following the primary therapy. If adjuvant therapy is added to RP the loss of QALYs ranges from 0.01 to 0.04, depending on the duration of treatment, and the equivalent range for radiotherapy is 0.01–0.06.

Effect of variation in the incidence of adverse effects of treatment

In making QALY comparisons between treatments, albeit on the assumption of equal survival, it must be emphasised that almost all the data on the incidence of adverse effects are derived from different case-series data, and the range of incidences of a particular adverse event following a treatment is wide. The utilities for different adverse event scenarios are shown in *Table 25*.

Figure 3 is a graphical representation of *Table 25*, and clearly shows that the variation in QALYs is greater between different scenarios for the same treatment than between the various treatments.

For this reason apparent QALY differences between treatments need to be treated with caution. For example, the possible range of QALY benefit of brachytherapy over RP for a man aged 65 years with a moderately differentiated tumour ranges from +0.67 to –0.64, depending on the incidences of adverse effects assumed for each treatment. Note that a maximum–minimum comparison is not relevant to the comparison of 3D-CRT with traditional radiotherapy, as the differences in adverse events between the treatments have been established by RCTs. For this reason the variation in QALY difference between the two treatments varies only from +0.17 to +0.42.

Effect of variation of utility values

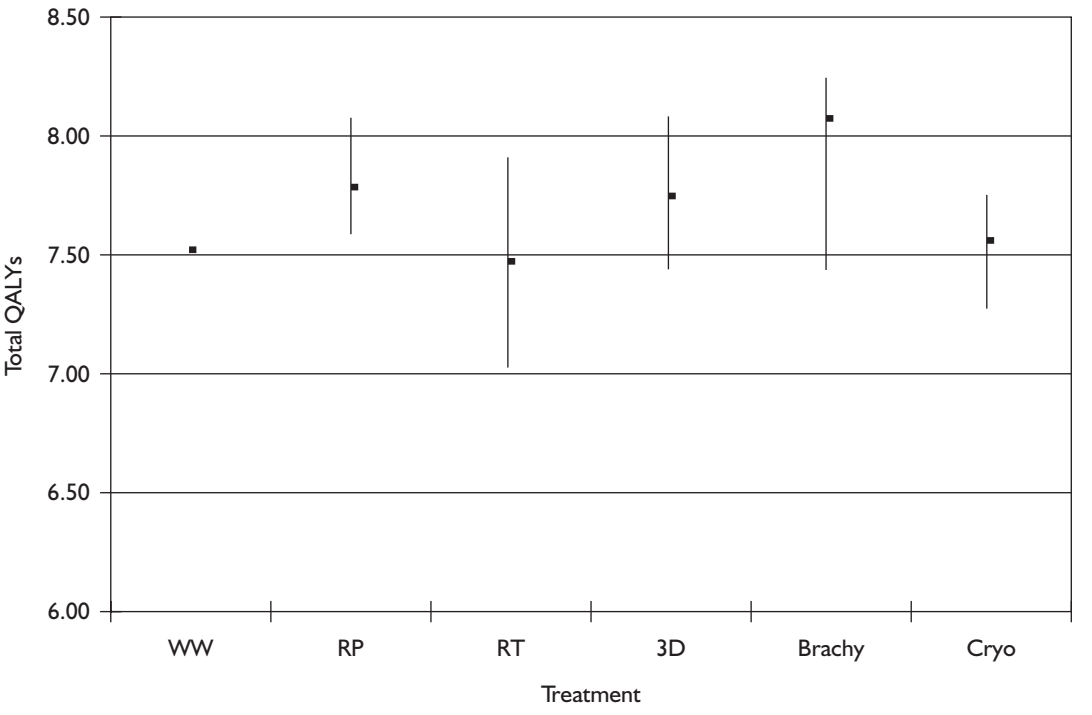
The upper part of *Table 26* shows the effect of different utility scenarios on QALYs for men aged 65 years, with tumours of moderate differentiation. The scenario that has the greatest effect on all treatments, with the exception of brachytherapy, is scenario 4, in which the utility of metastatic cancer is increased by 0.15. However, the effect is the same for all of the radical treatments: an addition of 0.24 QALYs. The figure of 0.31 for watchful waiting differs from that for radical treatments as disease progression is modified.

When comparing treatments, however, it is the effect of different utility scenarios on the QALY differences between treatments that is of interest. The lower part of Table 26 shows the effect of different utility scenarios on QALY differences of the various treatments with RP. The comparison of watchful waiting with RP is, not unexpectedly, sensitive to the gain in utility that is assumed from having had radical treatment. The QALY benefit from RP compared with watchful waiting for a man aged 65 years with a moderately differentiated tumour varies from 0.43 to 0.13. As the utility gain for radical treatment over watchful waiting has not been measured, but rather it has been assumed that the utility of treated patients is the same as for men of the same age without prostate cancer, it is a significant uncertainty in the debate of the merits of radical treatment compared with watchful waiting.

Other radical therapies are also sensitive to this parameter. This is because the proportion of patients not suffering from any adverse effects varies between treatments. It is only these patients who are affected by changing the utility assumed for a ‘cure’: the adverse effects they are suffering determine the utility of other patients. Thus, brachytherapy is most sensitive to the utility value

TABLE 25 *Variation in QALYs with low/high adverse event incidences for men aged 65, with tumours of moderate differentiation*

Treatment	Adverse event incidences		
	Central	Low	High
WW	7.52	7.52	7.52
RP	7.78	8.08	7.58
Radical radiotherapy	7.47	7.91	7.03
3D-CRT	7.75	8.08	7.45
Brachytherapy	8.07	8.25	7.44
Cryotherapy	7.56	7.75	7.28



WW: watchful waiting; RP: radical prostatectomy; RT: traditional radiotherapy; 3D: 3D conformal radiotherapy; Brachy: brachytherapy; Cryo: cryotherapy.

FIGURE 3 *Variation in QALYs with low/high adverse event incidences for men aged 65 years, with tumours of moderate differentiation*

assumed for patients treated with radical therapy, but not suffering from adverse effects (scenarios 2 and 3), as it has been assumed (for the central scenario) that the total incidence of adverse effects is lower for brachytherapy than for other treatments. In contrast, cryotherapy is not sensitive at all to scenarios 2 and 3, as all patients suffer from adverse effects, principally impotence.

The central set of utility values was taken from one study,[143] apart from the utilities for treated patients and bowel injury. This gives more uncertainty in the utilities of these latter states compared with those in the Cowen study. As previously discussed, traditional radiotherapy has a relatively high incidence of bowel injury compared with other treatments, and this state has a high morbidity. When the utility of bowel injury is varied across a plausible range of values the QALY difference with RP varies from –0.46 to –0.12.

The utility of bowel injury also affects the comparison of newer forms of radiotherapy (including brachytherapy) with traditional treatments, as shown in *Table 27*.

TABLE 26 *Effect of different utility scenarios on QALYs and QALY difference with radical prostatectomy for men aged 65, with tumours of moderate differentiation*

QALYs	Baseline	Radical treatment as Kattan	Radical treatment as active monitoring	Metastatic cancer + 0.15	Bowel injury low	Bowel injury high
	1	2	3	4	5	6
WW	7.52	7.52	7.52	7.83	7.52	7.52
RP	7.78	7.95	7.64	8.02	7.78	7.78
Radical radiotherapy	7.47	7.68	7.30	7.72	7.32	7.66
3D-CRT	7.75	7.99	7.55	7.99	7.70	7.81
Brachytherapy	8.07	8.47	7.74	8.32	8.04	8.11
Cryotherapy	7.56	7.56	7.56	7.80	7.55	7.56
QALY difference with RP						
WW	–0.26	–0.43	–0.13	–0.19	–0.26	–0.26
RP						
Radical radiotherapy	–0.31	–0.26	–0.35	–0.31	–0.46	–0.12
3D-CRT	–0.03	0.04	–0.09	–0.03	–0.08	0.03
Brachytherapy	0.29	0.53	0.09	0.29	0.26	0.33
Cryotherapy	–0.22	–0.39	–0.08	–0.22	–0.23	–0.22

TABLE 27 *Effect of different utility scenarios on QALY differences between newer forms of radiotherapy and traditional radiotherapy for men aged 65, with tumours of moderate differentiation*

QALY difference with radiotherapy	Baseline	Radical treatment as Kattan	Radical treatment as active monitoring	Metastatic cancer + 0.15	Bowel injury low	Bowel injury high
	1	2	3	4	5	6
3D-CRT	0.28	0.31	0.25	0.28	0.38	0.15
Brachytherapy	0.60	0.79	0.44	0.60	0.72	0.45

For the comparison of 3D-CRT with traditional radiotherapy the utility of bowel injury is the most important uncertainty in the utility value sensitivity analysis. Variation of bowel injury utility also affects the comparison between brachytherapy and traditional radiotherapy, but assumptions about the utility of the treated patient have a slightly greater effect.

Effect of patient age on QALYs

As most men diagnosed with prostate cancer die of other causes, younger men in general live longer with prostate cancer and the consequences of its treatment than men diagnosed in advanced old age. There will therefore be differences in the utility gain (or loss) between new and standard treatments for patients of different ages, as illustrated in *Table 28*.

Whereas patients aged 55 years enjoy on average between 9 and 10 QALYs after diagnosis with localised prostate cancer, this is reduced by almost half for patients aged 75. The potential benefit from treatments with fewer adverse effects is therefore age dependent, and will affect the cost-effectiveness of treatments.

Cost-effectiveness

The lack of clinical evidence demonstrating differences in survival between treatments necessarily limits the scope of the economic analysis. The study should be viewed as an exploratory analysis of the potential cost-effectiveness of new treatments, assuming they are as effective as RP. QALY differences between treatments are limited to variations in the adverse events resulting from different treatments.

Total treatment costs

The total treatment costs for patients are shown in *Table 29*. The costs are greater for patients with poorly differentiated tumours as more of them

TABLE 28 *Variation in QALYs by age and treatment, for tumours of moderate differentiation*

Treatment	Age (years)		
	65	55	75
Active monitoring	7.52	9.17	5.49
RP	7.78	9.91	5.48
Radical radiotherapy	7.47	9.52	5.26
QALY difference with RP			
3D-CRT	–0.03	–0.04	–0.02
Brachytherapy	0.29	0.37	0.21
Cryotherapy	–0.22	–0.28	–0.16
QALY difference with radiotherapy			
3D-CRT	0.28	0.35	0.20
Brachytherapy	0.60	0.76	0.43
Cryotherapy	0.09	0.11	0.06

TABLE 29 *Total treatment costs (£) by tumour differentiation for a man aged 65 at diagnosis*

Treatment	Differentiated (£)		
	Well	Moderately	Poorly
WW	1714	3061	6481
RP	6359	7549	8521
Radical radiotherapy	1886	3083	4060
3D-CRT	2103	3299	4276
Brachytherapy	6880	8077	9054
Cryotherapy	8324	9520	10497

TABLE 30 *Total treatment costs by cost scenario for a man aged 65 at diagnosis with a moderately differentiated tumour*

Treatment	Total treatment costs (£)		
	Central	Low	High
WW	3061	1225	3670
RP	7549	3542	9458
Radical radiotherapy	3083	1485	3875
3D-CRT	3299	1647	4423
Brachytherapy	8077	6567	10118
Cryotherapy	9520	6313	11922

progress to metastatic disease. Neoadjuvant treatment adds between £387 and £1177, dependent on the regimen, and adjuvant therapy adds between £743 and £3567, dependent on both the regimen and the duration of therapy.

The total costs of the three different traditional approaches to localised prostate cancer vary from £3061 for active monitoring to £7549 for RP, for a man aged 65 years with a moderately differentiated tumour.

Table 30 shows that total treatment costs vary for a particular therapy depending on whether high- or low-cost scenarios are assumed. The high-cost scenario assumes, as well as high initial treatment costs, that patients attend outpatient clinics for monitoring and those with metastatic disease are treated with medical castration (the latter as for the central scenario). The low-cost scenario includes low initial treatment costs and GP monitoring (as for the central scenario), and assumes that those with metastatic disease are treated with surgical castration.

As the low treatment costs assume that patients are treated with surgical rather than medical castration, which is a less costly but also less

TABLE 31 *ICER (£) of new treatments compared with radical prostatectomy and traditional radiotherapy for a man aged 65*

Treatment	Differentiated (£)		
	Well	Moderately	Poorly
Comparator: WW			
3D-CRT	26766	1030	NA[a]
Brachytherapy	12828	9059	834
Cryotherapy	NA[b]	159712	1513
Comparator: RP			
3D-CRT	NA: costs less than RP		
Brachytherapy	2021	2363	2760
Cryotherapy	NA: QALYs less than RP		
Comparator: radiotherapy			
3D-CRT	683	796	929
Brachytherapy	8575	9994	11660
Cryotherapy	111316	129741	151373

[a] Total cost of 3D-CRT less than WW.
[b] Cryotherapy QALYs less than WW.

popular option, it is representative of the lower cost estimate for patients who choose orchiectomy, but not of the average cost for all patients.

Total treatment costs also vary by age, as on average patients diagnosed at a younger age live longer with their disease than do older patients. For example, the average total costs for a patient treated with RP vary from £8224 to £6719 for men aged 55 and 75 years, respectively.

Cost-effectiveness

The incremental cost-effectiveness ratios (ICERs) for the new treatments compared with RP and traditional radiotherapy are shown in *Table 31*. Note that, as the basis of the analysis is equal survival for all treatments, and neoadjuvant and adjuvant therapy results in reduced QALYs, an ICER is not appropriate. The same is true for the comparison of cryotherapy with RP. Conformal radiotherapy costs less than RP and therefore there is no incremental cost.

The results of the central scenarios show that brachytherapy and 3D-CRT may be considered as within the bounds of what is normally considered to be cost-effective, on the basis of a reduced incidence of adverse effects. For a tumour of moderate differentiation, the ICER for brachytherapy compared with prostatectomy and radiotherapy is £2363 and £9994, respectively. 3D-CRT appears to be highly cost-effective compared with traditional radiotherapy, with an ICER of £796 for a moderate tumour. A small additional cost results in a small, but significant reduction in patient morbidity. The current data on adverse events resulting from cryotherapy, principally high levels of impotence (central 86%), suggest that it would have to be considerably more effective in improving survival compared with RP to be considered either clinically effective or cost-effective as a primary treatment. Cryotherapy is currently used principally as a salvage treatment for patients who have progressed after other treatments, or who are unsuitable for them.

The sensitivity analyses on utilities and costs earlier in this section show that the results need to be treated with caution, even within the limited scope of this analysis. With the range of treatments and variability in different parameters a considerable number of permutations of the ICER analysis is possible. However, two different treatment comparisons are perhaps of the most interest. These are the comparisons of 3D-CRT with traditional radiotherapy, and brachytherapy with RP. Extreme value sensitivity analysis was undertaken. To obtain a minimum ICER the utility differences between the new and traditional treatments were maximised and the cost differences minimised, and vice versa for the maximum ICER. The previously described sensitivity analyses were used to ascertain how to achieve these scenarios.

The sensitivity analysis demonstrated that the utility scenario assumed for treated patients without toxicities was the most sensitive in the comparison of all treatments with prostatectomy, with the exception of radiotherapy. Thus, utility scenarios 2 and 3 (increased and decreased utility for treated patients) were used in the comparison between brachytherapy and prostatectomy. In

TABLE 32 *ICER sensitivity analysis for selected treatment comparisons*

Treatment	ICER of 3D-CRT compared with traditional radiotherapy		ICER of brachy compared with RP	
	Min.	Max.	Min.	Max.
Scenarios				
Adverse event scenario	High	Low	High brachy, low RP	Low brachy, high RP
Utility value scenario	5	6	3	2
Cost scenario	Low	High	Central	Low
Results				
Utility new treatment	7.32	8.11	8.75	
Total costs new treatment	£1647	£4423	£8077	
Utility traditional treatment	6.76	8.01	7.67	
Total costs traditional treatment	£1485	£3875	£7549	
Utility difference	0.56	0.09	1.08	Negative
Cost difference	£162	£548	£527	
ICER	£288	£5929	£490	Dominated by RP

Brachy, brachytherapy.

contrast, the utility of bowel injury was found to affect the comparison between 3D-CRT and radiotherapy the most, and therefore for this comparison utility scenarios 5 and 6 (low and high bowel injury) were used.

The sensitivity analysis on the incidences of adverse effects was found to have the greatest effect on utility differences for all treatment comparisons, except for that between 3D-CRT and radiotherapy, where RCT evidence is available. Depending on the incidences assumed for the adverse effects of brachytherapy and prostatectomy, brachytherapy may lead to lower utilities than for prostatectomy. In this case the prostatectomy dominates brachytherapy, which is effectively the result for the maximum ICER scenario.

Rather than use extreme cost difference scenarios (high-cost therapy 1 to low-cost therapy 2) the maximum and minimum cost differences between treatments within the central-, high- and low-cost scenarios were used. This is more relevant as different ongoing and metastatic treatment options are included, as well as variation in the initial treatment costs. The scenarios used in the analyses, together with the results, are shown in *Table 32*.

The ICER for 3D-CRT compared with traditional radiotherapy ranges from £288 to £5929, with a central value of £796. While this is a wide range, it confirms that 3D-CRT is cost-effective, assuming that it is as clinically effective as traditional radiotherapy. The greatest uncertainty in the analysis is the incidence of bowel toxicity.

Although a significant difference in the incidence of bowel toxicity between the two treatments has been shown by more than one RCT, there is still some uncertainty in both the absolute incidences and the difference in bowel toxicity. To a certain extent this reflects the variation in toxicity with radiation dose. The next most important variable is the utility of bowel toxicity.

The results of the comparison of brachytherapy with RP are shown to be less secure than the comparison between 3D-CRT and traditional radiotherapy. While the ICER of brachytherapy over RP may be as little as £490, the utility difference is not always positive, indicating that even if survival after brachytherapy equals that for prostatectomy, adverse effects may make the treatment less desirable. The greatest uncertainty in brachytherapy toxicity in the incidence of impotence, for which the average of the studies included in this review is 18%, but has been reported to be as high as 53%.[73] There are also few studies that report urinary toxicities.

The results in the utility analysis are heavily dependent on the underlying assumption that survival is the same for all radical treatments. The maximum difference in QALYs between radical treatments for patients aged 65 years with moderately differentiated tumours is 0.51. Assuming that the average utility for a treated patient, taking toxicities into consideration, is approximately 0.7, a difference between treatments in mean survival of 9 months would dominate the maximum QALY difference between any radical treatments on the basis of adverse effects alone.

Discussion and conclusions

The intended approach to the economic analysis was to develop a model based on previous clinical effectiveness models designed to compare the standard treatments. While the model developed owes much to preceding models, the analysis undertaken as part of the model verification showed that there were anomalies in the data for disease progression for watchful waiting and RP, despite good-quality meta-analyses of case-series data for each treatment. This raises questions about the security of the conclusions of previous modelling studies.

The fact that such questions arise in the comparison between treatments that have been established highlights the difficulty in reaching firm conclusions on the relative effectiveness of even well-established treatments in this field and the need for RCTs.

Given the lack of certainty in comparing even the traditional treatments, and the lack of metastasis-free and disease survival data for the newer treatments, the approach adopted was to assume that new treatments are as effective as RP. If this assumption is made, how does the incidence of adverse effects associated with different treatments impact on patient QALYs and therefore on the potential cost-effectiveness of treatment? As stated in the overview to the economic analysis, owing to a paucity of evidence relating to adverse effects for many of the newer treatments, the assessment of cost-effectiveness was restricted to three of the treatments considered in the review of clinical effectiveness, these being brachytherapy, 3D-CRT and cryotherapy.

The central results of the analysis suggest that brachytherapy, if assumed to be as effective as RP, is cost-effective when compared with either prostatectomy or traditional radiotherapy because of reduced morbidity from adverse events. However, this conclusion was shown not to be robust, mainly because of the uncertainty in the incidence of adverse effects following brachytherapy. The conclusion that conformal radiotherapy is cost-effective compared with traditional radiotherapy is not sensitive to variations in parameters, although the range of estimated ICER ranges from £288 to £5929, with a central value of £796. However, the ICER estimates are dependent on the assumption of equal clinical efficacy. Of the new treatments included in the economic analysis, only cryotherapy appears unpromising as a primary treatment owing to the high incidence of impotence following therapy. However, interpretation of these results must consider the underlying assumption of the analysis; that the ICER estimate is dependent on the assumption that treatments are equally effective in terms of survival.

All of the results in the utility analysis are heavily dependent on the underlying assumption of the analysis that survival is the same for all radical treatments. Conclusive evidence of differences in survival between prostate cancer treatments is difficult to obtain. Most patients survive for many years after their prostate cancer diagnosis and die of other causes. Therefore, trials need to include relatively large numbers of patients to be adequately powered and to follow patients for several years to detect survival differences. PSA measures play an important role, but to date an adequate interim measure with a clear relationship to survival has not been identified. RCT evidence of the effectiveness or otherwise of the newer treatment in terms of survival is needed. In the short term, patients and their carers are faced with difficult choices between treatments and have only limited evidence of the incidence of treatment-related morbidity.

This analysis has highlighted the need for more RCTs to compare the adverse effects of treatments, using standardised definitions of adverse effects, such as the RTOG scale developed to compare different forms of radiotherapy. Such trials can be achieved within much shorter timescales and with fewer patients than trials designed to detect survival differences.

The other area of uncertainty in the economic analysis is the utility value attributed to each state. While there is more literature on prostate cancer utilities than many other disease areas, a major gap is the utility of patients treated with radical therapy. All studies identified have assumed that the utility of this state is equal to that for men without prostate cancer, and that patients on watchful waiting have a lower utility. To what extent this is true is likely to depend on a patient's belief that they have been cured. Given the continuing uncertainty as to the benefits of radical treatment for patients without poorly differentiated tumours, and the fact that some patients receiving surgery will have local spread detected, the assumption of a 'cure' seems unfounded. While most critical in the comparison of radical treatments and active monitoring, the utility of the treated state without adverse effects also influences comparisons between treatments where different proportions of patients are unaffected by adverse events.

Chapter 5

Implications for other parties

There are considerable differences between radical treatments in the amount of time that patients typically spend undergoing or recovering from treatments. Not only does this affect the convenience of the treatments to patients and their families, but for patients of working age it may lead to financial loss either to themselves or to their employers. Taking into consideration average male earnings, employment rates and full- or part-time status, all for men of the relevant age, as well as typical times that patients may be off work, the average lost earnings for treatments can be calculated. These are shown in *Table 33*.

As radiotherapy treatment (traditional, conformal, IMRT) is usually given 5 days a week over a period of 6–7 weeks, the inconvenience to the patient, his family and his employer is likely to be greater than for therapies that involve only a single treatment. However, as men may continue to work part time during treatment it has been assumed that time lost from work is similar to that for prostatectomy. Travel costs will also be far greater for radiotherapy.

The community palliative care costs from the National Reference Costs[153] that have been used in the economic model only include the NHS cost element. Services provided by charities such as Marie Curie and Macmillan are not included. These charities also provide hospice care.

The model uses average utility values for different patient states. Research has shown that there is very wide variation in the different valuations attributed by patients to different prostate cancer states.[143] Given the lack of clear evidence as to the superiority of any one treatment it is essential that patient preferences are taken into consideration when determining the optimum treatment for a patient.

TABLE 33 *Average lost earnings*

Age (years)	RP and radiotherapy[a] (3 weeks off work)	Brachytherapy (1 week off work)
50–59	1098	366
60–64	838	279
≥ 65	66	22

[a] Radiotherapy treatment is normally given over 6–7 weeks, but men may continue to work during this time. It has therefore been assumed that time lost is similar to that for prostatectomy.

Chapter 6

Factors relevant to the NHS

Given the lack of evidence of clinical effectiveness and the variation in estimated treatment costs presented in the economic analysis, it was not considered appropriate or possible to estimate the overall cost of the technologies to the NHS in England and Wales.

The evidence presented in this review considers technologies only in terms of clinical and cost-effectiveness and does not consider matters relating to implementation. Implications of implementation other than clinical effectiveness and cost-effectiveness are outlined in the NHS guidance on urological cancers, issued under the auspices of NICE.[124] The guidance states that centres should aim to provide conformal radiotherapy and that radical surgery should only be undertaken by teams performing at least 50 such procedures per year. All patients for whom radical treatment may be appropriate should have the opportunity for a joint meeting with a urologist, an oncologist and a specialist nurse. The role of the specialist nurse is emphasised in providing patients with information about treatments and in supporting them in their decision.

Chapter 7

Discussion and conclusion

The review of clinical effectiveness identified evidence on emergent technologies and on more established technologies undergoing further development. It is difficult to draw conclusions on the benefits or otherwise of the newer technologies owing to the lack of substantive evidence of any quality. Evidence of actuarial survival is comparable across the more established technologies, although it is not possible to make comparisons with traditional treatments owing to a lack of long-term follow-up. The results of the clinical effectiveness review should be viewed in the context of the quality of the available evidence. Very few RCTs were identified, with the majority of included studies being descriptive case series, open to patient selection bias and measuring surrogate end-points with relatively short-term follow-up.

Owing to the lack of disease-free survival data both for the treatments included in the review and for traditional treatments, cost-effectiveness estimates were based on the impact of adverse events. Of the new treatments included in the analysis only cryotherapy appeared not to be cost-effective compared with traditional treatments owing to the associated high incidence of impotence. The economic analysis is based, however, on the assumption that newer and traditional treatments are equally effective in terms of survival, and results are sensitive to the estimate of adverse events and utility values.

Given the lack of high-quality clinical evidence with long-term follow-up and the uncertainty surrounding the assumptions in the economic analysis, the following areas are recommended for further research:

- RCTs with sufficient follow-up to measure benefits in terms of overall survival, to include QoL measurement to establish trade-offs between potential adverse events and benefits of treatment.
- The identification of prognostic risk factors among men diagnosed with early prostate cancer.
- QoL studies to compare the utility of health states between patients on active monitoring, patients receiving treatment and the comparable healthy population.
- The relationship between surrogate end-points and survival.
- The adoption of standard definitions for adverse events.

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All responsibility for the contents of the report remains with the authors.

Contributions of authors

Silvia Hummel carried out the economic analysis, Elizabeth Currie and Anne Morgan undertook the review of clinical effectiveness, Naomi Brewer undertook the electronic literature searches and Suzy Paisley was project lead.

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Appendix 1

Electronic databases searched

1. Biological Abstracts
2. CCTR (Cochrane Controlled Trials Register)
3. CDSR (Cochrane Database of Systematic Reviews)
4. CINAHL
5. EBM Reviews – ACP Journal Club
6. EMBASE
7. HEED (Health Economic Evaluations Database)
8. HMIC (Health Information Management Consortium, comprising DH-Data, the King's Fund Database and Helmis)
9. MEDLINE
10. NHS DARE (Database of Assessments of Reviews of Effectiveness)
11. NHS EED (Economic Evaluations Database)
12. NHS HTA (Health Technology Assessment)
13. PreMedline
14. Science Citation Index
15. Social Sciences Citation Index

Appendix 2

Other sources searched

1. AHRQ (Agency for Healthcare Research and Quality), USA
2. Bandolier
3. Cancer BACUP
4. Cancer Research UK
5. CCOHTA (Canadian Coordinating Office for Health Technology Assessment)
6. CHE (Centre for Health Economics), York
7. CMA (Canadian Medical Association) InfoBase
8. Comprehensive Cancer Center, University of Michigan, USA
9. eBNF (electronic British National Formulary)
10. eGuidelines
11. Health Evidence Bulletin, Wales
12. HSRU (Health Services Research Unit), Aberdeen
13. INAHTA (International Network of Agencies for Health Technology Assessment) Clearinghouse
14. National Cancer Institute, USA
15. National Center for Chronic Disease Prevention and Health Promotion
16. National Guidelines Clearinghouse
17. NCCHTA (National Co-ordinating Centre for Health Technology Assessment)
18. NHS CRD (Centre for Reviews and Dissemination), University of York
19. Prostate Cancer Research Institute, Los Angeles, CA, USA
20. Research Findings Register
21. Royal Pharmaceutical Society
22. ScHARR Library catalogue
23. SIGN (Scottish Intercollegiate Guidelines Network)
24. The Prostate Cancer Charity, UK
25. Trent Working Group on Acute Purchasing
26. TRIP (Turning Research into Practice) Database
27. Wessex DEC (Development and Evaluation Committee) Reports
28. Wessex Institute Steer Reports
29. West Midlands Regional HTAC (Health Technology Assessment Collaboration) reports
30. York Centre for Health Economics Discussion & Occasional Papers

Appendix 3

Search strategies

Biological abstracts

1992–2002
SilverPlatter WebSPIRS
Search undertaken April 2002

#1 Prostate-Cancer
#2 Prostatic-Carcinoma
#3 Prostate-Carcinoma
#4 #1 or #2 or #3
#5 Neoplasm
#6 Carcinoma
#7 Adenocarcinoma
#8 #5 or #6 or #7
#9 PROSTATE
#10 (Prostat*) near2 (disease*)
#11 #9 or #10
#12 #8 and #11
#13 (Carcinoma* or neoplasia* or neoplasm* or adenocarcinoma* or cancer* or tumor* or tumour* or malignan*) near3 (prostat*)
#14 #12 or #13
#15 RITA
#16 (Intensit* modulat*) near2 (radiotherap*)
#17 IMRT
#18 (Neutron*) near2 (therap* or treatment*)
#19 (Hadrono*) near2 (therap*)
#20 (Antineoplastic*) near3 (agent*)
#21 (Antiandrogen*) near3 (antagonist*)
#22 Immunotherap*
#23 (Gene*) near3 (therap*)
#24 Proton*
#25 Brachytherap*
#26 Interstitial irradiation
#27 Transperineal interstitial permanent prostate brachytherap*
#28 (Computer assist*) near3 (radiotherap*)
#29 3D radiotherap*
#30 Conformal radiotherap*
#31 (Three dimensional) near2 (radiotherap*)
#32 Intensity modulat* conformal radiotherap*
#33 External beam radiotherap*
#34 High-linear energy transfer radiation
#35 Radiofrequency interstitial tumo* ablation*
#36 (Radionuclide) near2 (therap* or treatment*)
#37 Ultrasound radiotherap*
#38 (Particle beam radiation) near2 (therap* or treatment*)
#39 (Somatostatin based radioactive tumo* target*) near2 (therap* or treatment*)
#40 (Proton) near2 (therap* or treatment*)
#41 (Thermal*) near2 (therap* or treatment*)
#42 (Interstitial microwave* thermal) near2 (therap* or treatment*)
#43 (Microwave*) near2 (therap* or treatment*)
#44 Microwave* hypothermia
#45 Laser* surger*
#46 (Laser*) near2 (therap* or treatment*)
#47 Cryotherap*
#48 (Cryotherap*) near2 (ablation*)
#49 Cryoablation*
#50 High intensity focus* ultrasound
#51 (Neoadjuvant androgen) near2 (deprivat* or suppress*) near2 (therap* or treatment*)
#52 Flutamide monotherap*
#53 (Antiandrogen) near2 (LHRH or luteini* hormone releas* hormone)
#54 Dexamethasone*
#55 Satraplatin*
#56 JM216
#57 EMS182751
#58 BMY45594
#59 (Cell based) near2 (therap* or treatment*)
#60 Monoclonal antibod*
#61 Human antibod*
#62 T-lymphocyte*
#63 Dendritic cell*
#64 Prostat* specific enhancer*
#65 Toxic* gene*
#66 Cell lytic gene*
#67 Suicid* gene*
#68 Photochemotherap*
#69 (Photodynamic) near2 (therap* or treatment*)
#70 Photosensiti* agent*
#71 Photofrin
#72 (Dihematoporphyrin) near2 (ether* or ester*)
#73 5 aminolevulinic acid
#74 Stereotactic radiosurg*
#75 #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or#61 or #62 or #63 or #64

or #65 or #66 or #67 or #68 or #69 or #70 or#71 or #72 or #73 or #74
#76 #14 and #75

CDSR and CCTR

2001, Issue 4
The Cochrane Library, Update Software (CD-ROM version)
Search undertaken January 2002

#1 PROSTATIC-NEOPLASMS*:ME
#2 PROSTATIC-DISEASES*:ME
#3 PROSTATE*:ME
#4 #1 OR #2 OR #3
#5 BRACHYTHERAPY*:ME
#6 INTERSTITIAL IRRADIATION
#7 TRANSPERINEAL INTERSTITIAL PERMANENT PROSTATE BRACHYTHERAP*
#8 3D RADIOTHERAP*
#9 THREE DIMENSIONAL RADIOTHERAP*
#10 DIMENSIONAL RADIOTHERAP*
#11 INTENSITY MODULATED CONFORMAL RADIOTHERAP*
#12 EXTERNAL BEAM RADIOTHERAP*
#13 HIGH-LINEAR ENERGY TRANSFER RADIATION
#14 (RADIONUCLIDE) NEAR2 (THERAP* OR TREATMENT*)
#15 ULTRASOUND RADIOTHERAP*
#16 PARTICLE BEAM RADIATION
#17 SOMATOSTATIN BASED RADIOACTIVE
#18 PROTON
#19 INTERSTITIAL MICROWAVE THERMAL
#20 MICROWAVE HYPERTHERMIA
#21 LASER SURGERY
#22 CRYOTHERAP*
#23 CRYOABLATION
#24 HIGH-INTENSITY FOCUS ULTRASOUND
#25 CHEMOTHERAP*
#26 NEOADJUVANT ANDROGEN DEPRIVATION
#27 NEOADJUVANT ANDROGEN SUPPRESSION
#28 FLUTAMIDE MONOTHERAP*
#29 (ANTIANDROGEN) NEAR2 (LHRH OR LUTEINIZING HORMONE-RELEASING HORMONE)
#30 DEXAMETHASONE
#31 SATRAPLATIN
#32 JM216
#33 EMS182751
#34 EMS 182751
#35 BMY 45594
#36 BMY45594
#37 CELL-BASED
#38 MONOCLONAL ANTIBOD*
#39 HUMAN* ANTIBOD*
#40 T-LYMPHOCYTE
#41 DENDRITIC CELL*
#42 GENE THERAP*
#43 PROSTAT* SPECIFIC ENHANCER*
#44 TOXIC GENE*
#45 CELL LYTIC GENE*
#46 SUICID* GENE*
#47 PHOTOCHEMOTHERAP*
#48 PHOTODYNAMIC
#49 PHOTOSENSITI*
#50 PHOTOFRIN
#51 (DIHEMATOPORPHYRIN) NEAR2 (ETHER* OR ESTER*)
#52 5-AMINOLEVULINIC ACID
#53 STEREOSTATIC RADIOSURG*
#54 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53
#55 #4 AND #54

CDSR and CCTR – for terms decided upon after initial searches

2002, Issue 1
The Cochrane Library, Update Software (CD-ROM version)
Search undertaken March 2002

#1 PROSTAT*
#2 RITA
#3 INTENSIT* MODULAT* AND RADIOTHERAP*
#4 IMRT
#5 NEUTRON* THERAP*
#6 NEUTRON* TREATMENT*
#7 #5 OR #6
#8 HADRONOTHERAP*
#9 ANTINEOPLASTIC-AGENTS-HORMONAL*:ME
#10 ANDROGEN-ANTAGONISTS*:ME
#11 IMMUNOTHERAPY*:ME
#12 GENE-THERAPY*:ME

#13 PROTONS*:ME
#14 #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
#15 #1 AND #14

CINAHL

1982–2001
Ovid Biomed
Search undertaken February 2002

1 Prostate Neoplasms/
2 Neoplasms/
3 Carcinoma/
4 Adenocarcinoma/
5 or/2-4
6 Prostatic diseases/
7 Prostate/
8 or/6-7
9 5 and 8
10 ((Carcinoma or neoplasia or neoplasm$ or adenocarcinoma or cancer$ or tumor$ or tumour$ or malignan$) adj3 (prostat$)).tw
11 1 or 9 or 10
12 Brachytherapy/
13 Brachytherap$.tw
14 Interstitial irradiation.tw
15 Transperineal interstitial permanent prostate brachytherap$.tw
16 Conformal radiotherap$.tw
17 3D radiotherap$.tw
18 ((Three dimensional) adj2 (radiotherap*)).tw
19 Intensity modulated conformal radiotherap$.tw
20 External beam radiotherap$.tw
21 High-linear energy transfer radiation.tw
22 Radiofrequency interstitial tumo$ ablation.tw
23 ((Radionuclide) adj2 (therap$ or treatment$)).tw
24 Ultrasound radiotherap$.tw
25 ((Particle beam radiation) adj2 (therap$ or treatment$)).tw
26 ((Somatostatin based radioactive tumo$ target$) adj2 (therap$ or treatment$)).tw
27 ((Proton) adj2 (therap$ or treatment$)).tw
28 ((Thermal) adj2 (therap$ or treatment$)).tw
29 ((Interstitial microwave$ thermal) adj2 (therap$ or treatment$)).tw
30 ((Microwave$) adj2 (therap$ or treatment$)).tw
31 Microwave$ hyperthermia.tw
32 Exp laser surgery/
33 Laser$ surger$.tw
34 ((Laser$) adj2 (therap$ or treatment$)).tw
35 Exp cryotherapy/
36 Cryotherap$.tw
37 ((Cryotherap$) adj2 (ablation).tw
38 Cryoablation$.tw
39 High-intensity focus$ ultrasound.tw
40 Neoadjuvant therap$.tw
41 ((Neoadjuvant androgen) adj2 (deprivation or suppression) adj3 (therap$ or treatment$)).tw
42 Flutamide monotherap$.tw
43 ((Antiandrogen) adj2 (LHRH or luteinizing hormone-releasing hormone)).tw
44 Dexamethasone/
45 Dexamethasone$.tw
46 Satraplatin.tw
47 JM216.tw
48 EMS182751.tw
49 BMY 45594.tw
50 ((Cell-based) adj2 (therap$ or treatment$)).tw
51 Monoclonal antibod$.tw
52 Human antibod$.tw
53 T-lymphocyte$.tw
54 Dendritic cell$.tw
55 Prostat$ specific enhancer$.tw
56 Toxic gene$.tw
57 Cell lytic gene$.tw
58 Suicid$ gene$.tw
59 Exp photochemotherapy/
60 Photochemotherap$.tw
61 ((Photodynamic) adj2 (therap$ or treatment$)).tw
62 Photosensiti$ agent$.tw
63 Photofrin.tw
64 ((Dihematoporphyrin) adj2 (ether$ or ester$)).tw
65 5-aminolevulinic acid.tw
66 Stereotactic radiosurg$.tw
67 Or/12-66
68 11 and 67

Citation indexes (science and social sciences)

1992–2002
Web of Science
Search undertaken February 2002

Database limits:
DocType=All document types;
Language=English; Databases=SCI-EXPANDED, SSCI; Timespan=1992+.

'Title' searched for:
Prostate cancer and brachytherapy
Prostate cancer and cryotherapy
Prostate cancer and radiotherapy
Prostate cancer and external beam radiation
((Prostate cancer) and (intensity modulated conformal or high-linear energy transfer))

Prostate cancer and radiofrequency interstitial tumo* ablation*
Prostate cancer and radionuclide
Prostate cancer and ultrasound radiotherap*
Prostate cancer and particle beam radiation
((Prostate cancer) and (somatostatin or proton) and (therap*))
Prostate cancer and microwave
Prostate cancer and laser therap*
Prostate cancer and hormone therap*
Prostate cancer and neoadjuvant androgen
Prostate cancer and flutamide monotherap*
((Prostate cancer) and (antiandrogen) near2 (luteinizing hormone-releasing hormone))
Prostate cancer and dexamethasone
((Prostate cancer) and (satraplatin or JM216 or EMS182751 or BMY 45594))
((Prostate cancer) and (monoclonal antibod* or human antibod*) and (therap*))
Prostate cancer and T-lymphocyte*
((Prostate cancer) and (dendritic cell*) and (therap*))
Prostate cancer and prostat* specific enhancer*
((Prostate cancer) and (toxic or cell lytic or suicid*) and (gene*))
((Prostate cancer) and (photodynamic) and (therap*))
Prostate cancer and photofrin
((Prostate cancer) and (dihematoporphyrin) and (ester* or ether*))
Prostate cancer and 5-aminolevulinic acid
Prostate cancer and stereotactic radiosurger*

CRD databases (NHS DARE, EED, HTA)

CRD website – complete databases
Search undertaken January 2002

Prostate cancer/all fields
Prostate neoplasm/all fields
Prostat tumo/all fields

EMBASE

1980–2001
SilverPlatter WebSPIRS
Search undertaken October 2001

#1 Explode 'prostate-cancer' / all subheadings
#2 Explode 'prostate-tumor' / all subheadings
#3 #1 or #2
#4 Explode 'neoplasm-' / all subheadings
#5 Explode 'carcinoma' / all subheadings
#6 'Adenocarcinoma-' / all subheadings
#7 #4 or #5 or #6
#8 Explode 'prostate-disease' / all subheadings
#9 Explode 'prostate-' / all subheadings
#10 #8 and #9
#11 #7 and #10
#12 ((Carcinoma or neoplasia or neoplasm* or adenocarcinoma or cancer* or tumor* or tumour* or malignan*) near3 (prostat*))
#13 #3 or #11 or #12
#14 Explode 'brachytherapy-' / all subheadings
#15 Brachytherap*
#16 Interstitial irradiation
#17 Transperineal interstitial permanent prostate brachytherap*
#18 'Computer-assisted-radiotherapy' / all subheadings
#19 3D radiotherap*
#20 Conformal radiotherap*
#21 ((Three dimensional) near2 (radiotherap*))
#22 Intensity modulated conformal radiotherap*
#23 External beam radiotherap*
#24 High-linear energy transfer radiation
#25 Radiofrequency interstitial tumo* ablation*
#26 ((Radionuclide) near2 (therap* or treatment*))
#27 Ultrasound radiotherap*
#28 ((Particle beam radiation) near2 (therap* or treatment*))
#29 ((Somatostatin based radioactive tumo* target*) near2 (therap* or treatment*))
#30 ((Proton) near2 (therap* or treatment*))
#31 ((Thermal) near2 (therap* or treatment*))
#32 ((Interstitial microwave* thermal) near2 (therap* or treatment*))
#33 ((Microwave) near2 (therap* or treatment*))
#34 Microwave* hyperthermia
#35 Explode 'laser-surgery' / all subheadings
#36 Laser* surger*
#37 ((Laser*) near2 (therap* or treatment*))
#38 'Cryotherapy-' / all subheadings
#39 Cryotherap*
#40 ((Cryotherap*) near2 (ablation*)
#41 Cryoablation*
#42 High-intensity focus* ultrasound
#43 ((Neoadjuvant androgen) near2 (deprivation or suppression) near2 (therap* or treatment*))
#44 Flutamide monotherap*
#45 ((Antiandrogen) near2 (LHRH or luteinizing hormone-releasing hormone))
#46 'Dexamethasone-' / all subheadings
#47 Dexamethasone*
#48 Satraplatin
#49 JM216
#50 EMS182751

#51 BMY 45594
#52 ((Cell-based) near2 (therap* or treatment*))
#53 Monoclonal antibod*
#54 Human antibod*
#55 T-lymphocyte*
#56 Dendritic cell*
#57 Prostat* specific enhancer*
#58 Toxic gene*
#59 Cell lytic gene*
#60 Suicid* gene*
#61 'Photochemotherapy-' / all subheadings
#62 ((Photodynamic) near2 (therap* or treatment*))
#63 Photosensiti* agent*
#64 Photofrin
#65 ((Dihematoporphyrin) near2 (ether* or ester*))
#66 5-aminolevulinic acid
#67 Stereotactic radiosurg*
#68 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67
#69 #13 and #68
#70 #69 and (PY=1992-2002)

EMBASE – for terms decided upon after initial searches

1992–2002
SilverPlatter WebSPIRS
Search undertaken April 2002

#1 Explode 'prostate-cancer' / all subheadings
#2 Explode 'prostate-tumor' / all subheadings
#3 #1 or #2
#4 Explode 'neoplasm-' / all subheadings
#5 Explode 'carcinoma' / all subheadings
#6 'Adenocarcinoma-' / all subheadings
#7 #4 or #5 or #6
#8 Explode 'prostate-disease' / all subheadings
#9 Explode 'prostate-' / all subheadings
#10 #8 and #9
#11 #7 and #10
#12 ((Carcinoma or neoplasia or neoplasm* or adenocarcinoma or cancer* or tumor* or tumour* or malignan*) near3 (prostat*))
#13 #3 or #11 or #12
#14 RITA
#15 ((Intensit* modular*) near2 (radiotherap*))
#16 IMRT
#17 ((Neutron*) near2 (therap* or treatment*))
#18 ((Hadrono) near2 (therap*))
#19 Explode 'antineoplastic-agent' / all subheadings
#20 Explode 'antiandrogen-' / all subheadings
#21 Explode 'immunotherapy-' / all subheadings
#22 Explode 'gene-therapy' / all subheadings
#23 'Proton-' / all subheadings
#24 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23
#25 #13 and #24
#26 #25 and (PY=1992-2002)

HEED (Office of Health Economics Health Economic Evaluation Database)

CD-ROM version
Search undertaken April 2002

Search terms:

Prostate cancer
Prostatic cancer
Prostate tumour
Prostatic tumour
Prostate tumor
Prostatic tumor
Prostate carcinoma
Prostatic carcinoma
Prostate adenocarcinoma
Prostatic adenocarcinoma
Prostate neoplasm
Prostatic neoplasm

Fields searched:

Quick search – All data

HMIC (Health Management Information Consortium (King's Fund, DH Data and Helmis databases))

CD-ROM version
Search undertaken April 2002

((Prostat*) and (cancer* or tumo* or carcinoma* or adenocarcinoma* or neoplasm*))

MEDLINE

1992–2002
Ovid Biomed
Search undertaken February 2002

#1 Prostate Neoplasms/
#2 Neoplasms/
#3 Carcinoma/
#4 Adenocarcinoma/
#5 or/2-4
#6 Prostatic diseases/
#7 Prostate/
#8 or/6-7
#9 5 and 8
#10 ((Carcinoma or neoplasia or neoplasm$ or adenocarcinoma or cancer$ or tumor$ or tumour$ or malignan$) adj3 (prostat$)).tw
#11 1 or 9 or 10
#12 Brachytherapy/
#13 Brachytherap$.tw
#14 Interstitial irradiation.tw
#15 Transperineal interstitial permanent prostate brachytherap$.tw
#16 Radiotherapy-conformal/
#17 3D radiotherap$.tw
#18 ((Three dimensional) adj2 (radiotherap*)).tw
#19 Intensity modulated conformal radiotherap$.tw
#20 External beam radiotherap$.tw
#21 High-linear energy transfer radiation.tw
#22 Radiofrequency interstitial tumo$ ablation.tw
#23 ((Radionuclide) adj2 (therap$ or treatment$)).tw
#24 Ultrasound radiotherap$.tw
#25 ((Particle beam radiation) adj2 (therap$ or treatment$)).tw
#26 ((Somatostatin based radioactive tumo$ target$) adj2 (therap$ or treatment$)).tw
#27 ((Proton) adj2 (therap$ or treatment$)).tw
#28 ((Thermal) adj2 (therap$ or treatment$)).tw
#29 ((Interstitial microwave$ thermal) adj2 (therap$ or treatment$)).tw
#30 ((Microwave$) adj2 (therap$ or treatment$)).tw
#31 Microwave$ hyperthermia.tw
#32 Exp laser surgery/
#33 Laser$ surger$.tw
#34 ((Laser$) adj2 (therap$ or treatment$)).tw
#35 Exp cryotherapy/
#36 Cryotherap$.tw
#37 ((Cryotherap$) adj2 (ablation).tw
#38 Cryoablation$.tw
#39 High-intensity focus$ ultrasound.tw
#40 Exp neoadjuvant therapy/
#41 ((Neoadjuvant androgen) adj2 (deprivation or suppression) adj3 (therap$ or treatment$)).tw
#42 Flutamide monotherap$.tw
#43 ((Antiandrogen) adj2 (LHRH or luteinizing hormone-releasing hormone)).tw
#44 Dexamethasone/
#45 Dexamethasone$.tw
#46 Satraplatin.tw
#47 JM216.tw
#48 EMS182751.tw
#49 BMY 45594.tw
#50 ((Cell-based) adj2 (therap$ or treatment$)).tw
#51 Monoclonal antibod$.tw
#52 Human$ antibod$.tw
#53 T-lymphocyte$.tw
#54 Dendritic cell$.tw
#55 Prostat$ specific enhancer$.tw
#56 Toxic gene$.tw
#57 Cell lytic gene$.tw
#58 Suicid$ gene$.tw
#59 Exp photochemotherapy/
#60 Photochemotherap$.tw
#61 ((Photodynamic) adj2 (therap$ or treatment$)).tw
#62 Photosensiti$ agent$.tw
#63 Photofrin.tw
#64 ((Dihematoporphyrin) adj2 (ether$ or ester$)).tw
#65 5-aminolevulinic acid.tw
#66 Stereotactic radiosurg$.tw
#67 Or/12-66
#68 11 and 67
#69 Limit 70 to yr=1992-2002

MEDLINE – for terms decided upon after initial searches

1992–2002
Ovid Biomed
Search undertaken March 2002

#1 Prostate Neoplasms/
#2 Neoplasms/
#3 Carcinoma/
#4 Adenocarcinoma/
#5 or/2-4
#6 Prostatic diseases/
#7 Prostate/
#8 or/6-7
#9 5 and 8
#10 ((Carcinoma or neoplasia or neoplasm$ or adenocarcinoma or cancer$ or tumor$ or tumour$ or malignan$) adj3 (prostat$)).tw
#11 1 or 9 or 10

#12 RITA.tw
#13 ((Intensity modulat$) adj2 (radiotherap$)).tw
#14 IMRT.tw
#15 ((Neutron$) adj2 (therap$ or treatment$)).tw
#16 Hadronotherap$.tw
#17 Immunotherapy/
#18 Gene therapy/
#19 Protons
#20 Exp antineoplastic agents, hormonal/
#21 Exp androgen antagonists/
#22 Or/12-21
#23 11 and 22
#24 Limit 23 to yr=1992-2002

MEDLINE – prostate-specific antigen as an outcome measure

1992–2002
Ovid Biomed
Search undertaken February 2002

#1 Prostate Neoplasms/
#2 Neoplasms/
#3 Carcinoma/
#4 Adenocarcinoma/
#5 or/2-4
#6 Prostatic diseases/
#7 Prostate/
#8 or/6-7
#9 5 and 8
#10 ((Carcinoma or neoplasia or neoplasm$ or adenocarcinoma or cancer$ or tumor$ or tumour$ or malignan$) adj3 (prostat$)).tw
#11 1 or 9 or 10
#12 Prostat$ specific antigen.tw
#13 Exp Prostate-Specific Antigen/
#14 ((Prostat$) adj2 (specific) adj2 (antigen)).tw
#15 Or/12-14
#16 Exp "Outcome Assessment (Health Care)"/
#17 Outcome$ measure$.tw
#18 16 or 17
#19 11 and 15 and 18
#20 Limit 19 to (human and English language and yr=1992-2002)

Appendix 4

Methodological search filters in MEDLINE

Systematic reviews/meta-analyses

#1. Meta-analysis/
#2. Exp review literature/
#3. (Meta-analy$ or meta analy$ or metaanaly$).tw
#4. Meta analysis.pt
#5. Review academic.pt
#6. Review literature.pt
#7. Letter.pt
#8. Review of reported cases.pt
#9. Historical article.pt
#10. Review multicase.pt
#11. or/1-6
#12. or/7-10
#13. 11 not 12

Randomised controlled trials

#1. Randomized controlled trial.pt
#2. Controlled clinical trial.pt
#3. Randomized controlled trials/
#4. Random allocation/
#5. Double blind method/
#6. Single blind method/
#7. or/1-6
#8. Clinical trial.pt
#9. Exp clinical trials/
#10. ((Clin$) adj25 (trial$)).ti,ab
#11. ((Singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab
#12. Placebos/
#13. Placebos.ti,ab
#14. Random.ti,ab
#15. Research design/
#16. or/8-15
#17. Comparative study/
#18. Exp evaluation studies/
#19. Follow up studies/
#20. (Control$ or prospective$ or volunteer$).ti,ab
#21. Prospective studies/
#22. or/17-21
#23. 7 or 16 or 22

Economic evaluations

#1. Economics/
#2. Exp "costs and cost analysis"/
#3. Economic value of life/
#4. Exp economics, hospital/
#5. Exp economics, medical/
#6. Economics, nursing/
#7. Economics, pharmaceutical/
#8. Exp models, economic/
#9. Exp "fees and charges"/
#10. Exp budgets/
#11. Ec.fs.
#12. (Cost or costs or costed or costly or costing$).tw
#13. (Economic$ or pharmacoeconomic$ or price$ or pricing).tw
#14. or/1-13

Guidelines

#1. Guideline.pt
#2. Practice guideline.pt
#3. Exp guidelines/
#4. Health planning guidelines/
#5. or/1-4

Quality of life

#1. Exp quality of life/
#2. Qol.tw
#3. Qaly$.tw
#4. Qald$.tw
#5. Qale$.tw
#6. Qtime$.tw
#7. Hye.tw
#8. Hyes.tw
#9. "Well-being".tw
#10. (Utility or utilities).tw
#11. "Life quality".tw
#12. (Sf-36 or sf36).tw
#13. Euroqol.tw
#14. (Eq-5d or eq5d).tw
#15. "Health utilities index".tw
#16. or/1-15

Appendix 5

Included studies

TABLE 34 *Neoadjuvant hormonal therapy (systematic reviews)*

Study	Aims of the study	Study criteria and assessment	Results	Discussion
Chay and Smith (2001, USA)[27]	To explore the efficacy of hormonal and chemotherapy in both the adjuvant and neoadjuvant settings	**Inclusion criteria:** Articles of historical relevance in addition to those using large patient numbers with a randomised design were reviewed preferentially **Exclusion criteria:** There were no explicit exclusion criteria applied. Neither were there explicit assessment criteria for the included studies	For NHT 7 clinical studies were found: 5 looked at NHT with RP and RP alone; 2 looked at NHT with EBRT and EBRT alone The first 5 studies suggest that NHT with RP decreases the rate of positive surgical margins and increases downstaging, but there has been no evidence that NHT has a clinical benefit in terms of survival. Data on survival and long-term follow-up are still being collected, but so far disease-free progression is unchanged. The 2 studies looking at NHT and EBRT suggest that NHT may be beneficial in decreasing recurrence rates after RT for localised disease. Owing to the small size of the trials any increase in survival may be difficult to identify 2 early studies looked at the timing of AHT. 2 retrospective studies supported the results from the early studies that early AHT was better than delayed AHT in terms of disease progression 3 more recent clinical trials showed an improvement in survival for AHT patients compared with those receiving definitive treatment only, but follow-up was short in all studies	Early HT in prostate cancer has been shown to have positive effects in terms of PFS with newer studies showing promise for benefit in overall survival. These studies require long-term follow-up owing to the natural history of the disease. Positive effects need to be balanced by concerns about patient selection, duration of therapy, and the immediate and long-term side-effects of HT NHT before RP has consistently shown a decrease in positive surgical margins, but there has been no clear evidence for a change in DFS or mortality. Before RT, NHT seems to provide a statistically significant improvement in DFS and local control

continued

TABLE 34 *Neoadjuvant hormonal therapy (systematic reviews) (cont'd)*

Study	Aims of the study	Study criteria and assessment	Results	Discussion
Scolieri *et al*. (2000, USA)[155]	To assess randomised prospective articles for NHT before RP	**Inclusion criteria:** The focus was primarily on randomised, prospective studies, but other articles that did not fit these criteria were evaluated when they included specific issues not addressed by the prospective studies The data were analysed for the impact of NHT on the rate of positive margins, seminal vesicle invasion, lymph-node metastasis, and survival or some surrogate of survival	7 randomised prospective trials were found NHT decreased the rate of positive margins in 6 of the 7 randomized prospective studies. In none of 4 randomised prospective series was there an improved rate of seminal vesicle invasion with NHT. Of 4 studies, 3 showed no improvement in the rate of lymph node metastasis after NHT compared with that in controls There was no improvement in PSA-free survival and no significant difference in operative time, intraoperative blood loss, transfusion or hospital stay in patients treated with NHT and controls. In 2 of 3 studies there was no difference in the complication rate	Based on this review they note that despite the apparent benefit of NHT for decreasing the rate of positive surgical margins in clinical stage T2b–c tumours, there is an inconsistent advantage in the rate of seminal vesicle invasion as well as no advantage in the rate of lymph-node metastasis An important finding is that no study to date has shown an improved PSA-free survival or DFS advantage in men who receive NHT, despite a follow-up of up to 4 years

continued

TABLE 34 *Neoadjuvant hormonal therapy (systematic reviews) (cont'd)*

Study	Aims of the study	Study criteria and assessment	Results	Discussion
Vicini *et al*. (1999, USA)[26]	To determine whether any conclusions could be reached on the efficacy of androgen deprivation in combination with RT and the patients most suitable for its application	**Inclusion criteria:** Medical subject headings that were used to search the MEDLINE database were: (a) prostatic neoplasms; (b) prostatic neoplasms/radiotherapy; (c) prostatic neoplasms/androgen deprivation; (d) hormone therapy; (e) English; and (f) 1980 to 1998 **Exclusion criteria:** Reviews were excluded as were studies that discussed treatment issues unrelated to RT results **Data collection and assessment of studies:** Studies were analysed to determine patient stage, pretreatment PSA and Gleason score, total number of patients treated, duration and type of androgen deprivation, end-points used to analyse outcome, statistical methodology, type and dose of RT and median follow-up	Studies were grouped into 2 categories to aid in data analysis: (a) prospective randomised trials and (b) retrospective reports 14 studies reported treatment results combining various forms of hormonal manipulation with RT A total of 6 prospective randomised trials with published results were identified that compared RT treatment alone or in combination with some form of hormonal manipulation Hormonal withdrawal almost uniformly resulted in significant improvements in various interim measures of local/biochemical control and DFS. Only 2 prospective studies were identified that showed a statistically significant improvement in overall survival and only 1 study reported an improvement in cancer-specific survival	These data suggest that despite extremely promising preliminary results with hormonal manipulation given in conjunction with RT, the true impact of this treatment approach on overall or cause-specific survival remains undefined and awaits the published results of several recently initiated and completed prospective randomised trials When all available studies on androgen withdrawal given in conjunction with RT for the definitive treatment of localised prostate cancer are reviewed, no definite conclusions can be reached on the efficacy of this treatment approach

continued

TABLE 34 *Neoadjuvant hormonal therapy (systematic reviews) (cont'd)*

Study	Aims of the study	Study criteria and assessment	Results	Discussion
Bonney *et al*. (1998, USA)[25]	To test a hypothesis that neoadjuvant androgen ablation has a significant effect on pathological stage and tumour in surgical margins using meta-analysis of randomised trials Objectives were to identify the published reports of interest, establish pathological stage and surgical margin as outcome variables, identify independent variables that might explain outcomes differences, study the surgical end-points in relation to the independent variables to identify some factors that influence treatment results and test the hypothesis	**Inclusion criteria:** Randomised clinical trials that provided specific data about variables of interest were identified by MEDLINE search and review of published bibliographies with a publication cut-off date of 31 March, 1997 **Exclusion criteria:** Not explicitly defined 11 variables were identified and data extraction was based on these	The null hypothesis of no true effect of NHT ($p = 0.0001$) on surgical margin was rejected The null hypothesis of no true effect of NHT ($p < 0.0001$) on pathological stage was also rejected	Using the trial as a unit of analysis it was not possible to determine the extent to which the pooled treatment results could be attributed to treatment and other risk factors. This limitation theoretically might be overcome in the meta-analysis of future results by accumulation of pooled patient-level data from several trials As PSA and other clinical evidence of recurrence/progression become available it will be possible to determine whether pathological stage and surgical margin are good surrogates for final treatment outcomes

RT: radiotherapy; HT: hormonal therapy.

TABLE 35 *Neoadjuvant hormonal therapy (primary studies)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Evidence level I					
Aus *et al*. (1998, Sweden)[22]	NHT before RP NHT = gonadotropin-releasing hormone agonist	*n* = 122 (58 NHT + RP, 64 RP only) Stage T1bNxM0 to T3aNxM0 PSA and Gleason grade similar for each group	Multicentre prospective RCT Follow up = 5–60 months, median 38 months Outcomes = treatment failure: lymph-node involvement, PSA > 0.5 ng/ml, or need for postoperative hormonal or radiation adjuvant treatment	No statistical difference between the 2 groups. 34.5% of NHT group experienced treatment failure vs 40.6% in control group (p = 0.48)	Results at 3 months favour the intervention group, but at 38 months follow-up there is no difference between the groups
Bono *et al*. (2001, Italy)[156]	Complete androgen blockade on pathological stage and resection margin status of prostate cancer NHT = Casodex + Zoladex	*n* = 303 (107 RP only, 114 3 months of NHT before RP and 82 6 months of NHT before RP) Stage B–C PSA and age similar for each group Gleason grade not reported	Multicentre, prospective, randomised study Follow-up = immediately postoperation Outcomes = pathological stage and surgical margin status	Pathological organ-confined disease was found in 63.1% of patients with clinical stage B disease treated with 6 months of NHT vs 61% after 3 months of NHT and 37.5% after immediate surgery (p = 0.002) 3 months of NHT produced a significant increase in negative margins in patients with clinical stage B and C disease, but the addition of another 3 months of treatment did not significantly improve this result. A lower degree of benefit was observed in patients with clinical stage C tumours (p = 0.001)	Will require longer term follow-up to investigate survival
Dalkin *et al*. (1996, USA)[14]	NHT before RP NHT = LH-RH agonist	*n* = 56 (28 NHT + RP, 28 RP only) Mean age = 65.5 years in the intervention group and 64.7 years in the control group Stage T1c, T2a and T2b PSA and grade similar for both groups	Prospective RCT Follow-up not applicable Outcome = organ-confined disease as decided histologically	No statistical difference between the 2 groups: 57% of NHT group and 61% of control group had organ-confined disease (p = 1.0)	

continued

TABLE 35 *Neoadjuvant hormonal therapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Debruyne and Witjes (2000, Europe)[23]	NHT before RP NHT = Goserelin and flutamide	*n* = 402 (192 NHT + RP, 210 RP only) Mean age not reported Stage T2 and T3 PSA and grade reported in an earlier study[157]	Multicentre prospective RCT Follow-up = minimum of 4 years Primary outcome = duration of PFS using serum PSA as a surrogate end-point	No statistical difference between the 2 groups. In the NHT group 26% developed disease progression vs 33% in the RP-only group ($p = 0.18$)	2 other published studies from 1997 and 1998 report earlier results for the same study subjects[157,158]
Fair *et al*. (1999, USA)[15]	NHT before RP NHT = Goserelin and flutamide	*n* = 148 (74 NHT + RP, 74 RP only) Mean age = 61.5 years in NHT group and 60.8 years in RP-only group Stage T1–T2 PSA and grade were similar for both groups and details reported in study	Prospective RCT Median follow-up = 35 months Outcomes = organ-confined, margin-negative disease	2 patients in the NHT group and 9 in the RP-only group are no longer in the study. See study for details There was no statistically significant difference between the 2 groups. 70% in the NHT group had organ-confined margin-negative disease vs 59% in the control group ($p = 0.17$)	There was no significant difference in PSA relapse rates between the 2 groups ($p = 0.73$) One other published study from 1997 reports details of trial enrolment for the same study subjects[159]
Gleave *et al*. (2001, Canada)[24]	3-month and 8-month NHT before RP NHT = leuprolide and flutamide	*n* = 547 (273 in 3-month group, 274 in 8 month group) Mean age = 62.5 and 62.7 years in 3-month and 8-month groups, respectively Stage T1 and T2 The 2 groups were similar in stage, grade and baseline PSA. Details reported	Multicentre, prospective RCT Primary outcome = 3 year PSA recurrence rate. Secondary outcomes = differences in biochemistry, pathology and adverse events	44 men withdrew from the study and were not followed up Mean preoperative PSA was 57% lower in the 8 month group ($p = 0.0141$). Postoperation 23% in the 3-month group had positive surgical margins vs 12% in the 8-month group ($p = 0.0106$). Men in the 8-month group had 4.5 new adverse events vs 2.9 in the 3-month group ($p = 0.0001$)	Longer follow-up required before PSA recurrence rate known. Interim results only are presented here One other published study from 2000 also presents interim results for these study subjects[160]

continued

TABLE 35 *Neoadjuvant hormonal therapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Klotz *et al*. (1999, USA)[16]	NHT before RP NHT = cyproterone acetate	*n* = 213 (112 in NHT group, 101 in RP-only group) Mean age = 62.5 and 62.2 years in NHT group and RP groups respectively Stage T1–T2 The 2 groups were well matched for stage, grade and baseline PSA. Details reported	Multicentre, prospective RCT Median follow-up = 36 months Outcome = biochemical progression: 2 detectable consecutive PSAs, retreatment or death from prostate cancer	12 patients have been lost to follow-up: 7 in the NHT group and 5 in the RP group No significant difference in the estimated probability of biochemical progression between the 2 groups (p = 0.3233)	When analysed by pathological stage there was a higher probability of NHT patients having disease progression Two other published studies from 1996 and 1998 also present interim results for these study subjects[161,162]
Hugosson *et al*. (1996, Sweden)[18]	NHT before RP NHT = cyproterone acetate + triptorelin	*n* = 111 (56 in NHT group, 55 in RP only group) Mean age = 67 and 66 years in NHT and RP groups, respectively Stage T1b–T3a PSA, grade and stage reported	Multicentre, prospective RCT Follow-up = immediately postoperation Outcomes = local tumour extension, perioperative blood loss and operation time	In total, 126 patients were randomised and 15 were withdrawn from the study No significant difference in blood loss and operation time. The NHT group had lower frequency of positive margins (41 vs 23%, p = 0.013)	
Labrie *et al*. (1993, Canada)[19]	NHT before RP NHT = flutamide and lupron	*n* = 142 (77 in NHT group, 65 in RP-only group) Mean age = 62.6 and 62.9 years in NHT and RP groups, respectively Stage B0–C2 PSA and grade not reported	Prospective RCT Follow-up = immediately postoperation Outcomes = incidence of positive margins at RP and on histopathological stage at surgery	Cancer positive margins were reduced from 38.5% in control patients to only 13.0% in NHT patients (p = 0.006)	

continued

TABLE 35 *Neoadjuvant hormonal therapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Labrie *et al*. (1997, Canada)[20]	NHT before RP NHT = flutamide and an LH-RH agonist	*n* = 161 (90 in NHT group, 71 in RP-only group) Stage B0–C2 PSA and grade not reported	Prospective RCT Follow-up = immediately postoperation Outcomes = comparison of organ-confined vs specimen-confined disease and comparison of pathological stage with clinical stage at diagnosis χ^2 test for differences	Incidence of positive margins reduced to 7.8% in the NHT group vs 33.8% in the RP-only group ($p = 0.001$) 7.8% of NHT patients had positive margins vs 33.8% of RP-only patients ($p = 0.001$) There was a difference of 54.9% in net upstaging (difference between no. of patients who had upstaging and no. who had downstaging) between the 2 groups, in favour of the NHT group	Another study from 1994[163] (13433) also includes description of this study
Laverdiere *et al*. (1997, Canada)[13]	NHT before EBRT (group 2). Also, hormonal treatment before, during and after EBRT (group 3). Group 1 had EBRT only NHT = LH-RH agonist + a pure antiandrogen. Group 3 also given TAB	*n* = 120 (41 in group 1, 43 in group 2, 36 in group 3) Median age in groups 1, 2 and 3 = 68.9, 70.6 and 71.6 years, respectively Stage B1–C2 PSA, grade and stage reported in detail	3-arm prospective, randomised trial Minimum follow-up = 24 months Outcomes = rate of positive follow-up biopsies and serum PSA	At 12 months 62% of group 1 patients had residual disease vs 30% and 4% of groups 2 and 3, respectively ($p = 0.00005$). At 24 months 65, 28 and 5% of groups 1–3, respectively, had residual disease Median PSA levels: at 12 months the same advantage was seen ($p = 0.0001$); at 24 months the difference between groups 2 and 3 was not statistically significant	

continued

TABLE 35 *Neoadjuvant hormonal therapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Soloway *et al.* (2002, USA)[17]	NHT before RP NHT = leuprolide + flutamide	*n* = 282 (138 in NHT group, 144 in RP-only group) Mean age = 64.9 and 65.4 years in NHT and RP groups, respectively Stage cT2bNxM0 Grade and PSA were similar for both groups. Details reported	Multicentre prospective RCT Minimum follow-up = 5 years Outcomes = biochemical recurrence (PSA > 0.4 ng/ml)	20 patients were lost to follow-up At 5 years PSA was < 0.4 ng/ml in 64.8% of patients in the NHT group and in 67.6% in the RP-only group (p = 0.663)	Another published study from 1995 presents interim results for the same study subjects[164]
Van Poppel *et al.* (1995, USA)[21]	NHT before RP NHT = estramustine phosphate	*n* = 130 (65 in NHT group, 62 in RP-only group) Mean age across both groups = 67 years Stage T2b–T3 PSA, grade and stage were similar for both groups. Details reported	Multicentre prospective RCT Follow-up = immediately postoperation Outcomes = number of positive margins after surgery	2 patients in the NHT group and 1 patient in the RP-only group were unsuitable for surgery Number of positive margins was significantly higher in the control group: 45.9% had positive margins in the posterolateral aspect of the prostate vs 19.4% in the NHT group for stage T2 (p = 0.01). The opposite was true for stage T3, where the NHT group had more positive margins (p-value not reported) No difference in PSA levels between the 2 groups	Study also reports on downstaging after surgery and on PSA levels at 3 months

TABLE 36 *Adjuvant hormonal therapy (systematic reviews)*

Study	Aims of the study	Study criteria and assessment	Results	Discussion
Roach *et al*. (2000, USA)[31]	To assess the impact of short-term and long-term androgen suppression on the disease-specific and overall survival of 2200 men treated with RT in one of five prospective randomised trials when stratified by prognostic risk groups, using meta-analysis of trials	**Inclusion criteria:** Randomised prospective trials that included men with clinically localised prostate cancer Patients were included if they were evaluable, eligible for the trial and if follow-up information was available Patients were put into 4 risk categories based on PSA, stage and Gleason grade, with group 1 as the lowest risk and group 4 as the highest risk **Exclusion criteria:** No explicit exclusion criteria applied	Risk group 2 patients appeared to have a disease-specific survival benefit at 8 years with the addition of 4 months of goserelin and flutamide. Group 3 and 4 patients were noted to have an approx 20% higher survival at 8 years with the addition of long-term HT ($p < 0.0004$)	Based on this meta-analysis of RTOG trials, subsets of patients can be identified who either do not appear to benefit from the use of HT, benefit from short-term HT, or benefit only from long-term hormonal therapy. These observations should be confirmed by prospective randomised trials before they can be considered conclusive. In the meantime, however, these observations provide rational guidelines for deciding who should receive HT and for how long

TABLE 37 *Adjuvant hormonal therapy (primary studies)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Evidence level 1					
Laverdiere *et al*. (1997, Canada)[13]	NHT before EBRT (group 2). Also, HT before, during and after EBRT (group 3). Group 1 had EBRT only NHT = LH-RH agonist + a pure antiandrogen. Group 3 also given TAB	*n* = 120 (41 in group 1, 43 in group 2, 36 in group 3) Median age in groups 1, 2 and 3 = 68.9, 70.6 and 71.6 years, respectively Stage B1–C2 PSA, grade and stage reported in detail	3-arm prospective, randomised trial. Outcomes = rate of positive follow-up biopsies and serum PSA. Follow-up = 24 months	At 12 months 62% of group 1 patients had residual disease vs 30% and 4% of groups 2 and 3, respectively (p = 0.00005). At 24 months 65, 28 and 5% of groups 1–3, respectively, had residual disease Using median PSA levels at 12 months the same advantage was seen (p = 0.0001). At 24 months the difference between groups 2 and 3 was not statistically significant	
Evidence level 3					
Horwitz *et al*. (1999, USA)[32]	3D-CRT and short-term AHT compared with 3D-CRT alone A subset of 67 randomly selected 3D-CRT-only patients were matched with 67 who had 3D-CRT and AHT	*n* = 558 (74 in AHT group and 484 in 3D-CRT-only group) Median age in AHT group = 69 and in 3D-CRT-only group = 70 years Stage T1–T3 Stage, grade and PSA reported	Retrospective study of patients treated at one institution with 3D-CRT and 3D-CRT + AHT. Additional analysis performed with matched case–controls for AHT patients (*n* = 67 in each group) Outcome = bNED Follow-up = 40 months in AHT group and 48 months in 3D-CRT-only group	The 5 year bNED control rate for patients in the 3D-CRT-only group was 66% and for the AHT group it was 68%. The difference was not statistically significant (p = 0.502). Using the matched case–control groups there was a significant difference between the 2 groups: 71% in the AHT group and 43% in the 3D-CRT only group (p = 0.02). There was no statistically significant difference between groups in terms of cause specific survival and overall survival using total no. of patients or the matched case–control groups	

continued

TABLE 37 *Adjuvant hormonal therapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Anderson *et al*. (1997, USA)[33]	RT in combination with adjuvant ADT compared with RT alone Patients matched by stage, grade and pretreatment PSA	n = 112 (56 in ADT group, 56 in RT-only group). 517 patients in total were included in a multivariate analysis of predictors of outcome Age not reported Stage T1–T3 PSA, grade and stage reported in detail	Retrospective, matched case–control study. 56 patients out of 517 treated in one institution received ADT with RT. 56 patients receiving RT alone were matched by PSA, stage and grade Outcome = bNED control (stage, grade and PSA levels) Median follow-up for ADT group = 46 months and for RT-only group = 37 months	5-year actuarial bNED results are presented. Patients in the ADT group had a bNED control of 55% at 60 months vs 31% in the RT-only group. The difference of 24% is statistically significant (p = 0.0088). No overall survival difference was observed	Multivariate analysis using patient details for all 517 patients shows that the addition of ADT is a highly significant independent predictor of bNED control (p = 0.0006)
Evidence level 5					
Chen *et al*. (2001, USA)[36]	HT and its influence on sexual function in men receiving 3D-CRT for prostate cancer HT = LH-RH agonist with or without a non-steroidal antiandrogen	n = 144 patients who received 3D-CRT in one institution. 55 patients also received HT. 21 patients received neoadjuvant + adjuvant, 22 received neoadjuvant alone and 12 had adjuvant alone Median age in HT group = 71 years and in 3D-CRT-only group = 73 years No details of stage, grade or PSA reported	Before and after study 144 men were evaluated before and after 3D-CRT for prostate cancer Primary outcome = total sexual potency (erections firm enough for penetration during intercourse). Secondary outcomes = erectile function, ejaculatory ability and quality of sex life Mean follow-up = 21 months	Men receiving HT had a lower rate of potency at 1 year (31% vs 44% at baseline, p = 0.01). Men receiving 3D-CRT only had a potency rate of 56% vs 71% at baseline Ejaculatory ability was lower at 1 year in the HT group (13% vs 40%, p = 0.003) At 1 year 63% of the HT group were partially satisfied with their sex life vs 42% of the 3D-CRT-only group (p = 0.068)	

continued

TABLE 37 *Adjuvant hormonal therapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
D'Amico *et al*. (2000, USA)[34]	EBRT with or without AST for clinically localised prostate cancer	*n* = 1586 (276 in AST group, 1310 in EBRT-only group) Median age not reported Patients put into low-, intermediate- and high-risk groups based on PSA, stage and grade. Details reported	Retrospective study of all patients treated with EBRT at one institution Primary outcome = RR of PSA failure by treatment and high-, intermediate- and low-risk groups Minimum follow-up = 6 months and maximum = 98 months	No significant difference between treatment groups was found for patients in the low-risk category (RR = 0.5, $p = 0.09$). Intermediate-risk and high-risk patients treated with EBRT + AST had a 5-fold (RR = 0.2, 95% CI 0.1–0.3) and a 2.5-fold (RR 0.4, 95% CI 0.3–1.1) reduction in risk of failure, respectively, compared with patients treated with EBRT alone. These results were statistically significant	Difference in median follow-up favours the AST group, while prognostic factor distribution and PSA failure favour the EBRT-only group
Scherr *et al*. (2002, USA)[35]	The hypothesis that DES can cause androgen deprivation without causing osteoporosis as evidenced by a significantly lower level of urinary collagen type I cross-linked N-telopeptides Androgen deprivation = DES and LH-RH	*n* = 54 prostate cancer patients (20 received EBRT only, 34 received ADT). Of the 34, 20 were given 1 mg of DES only daily and 14 were given LH-RH + DES after a delay. 24 men with BPH were used as controls Mean age =74 years	Prospective non-randomised study Outcome = degree of bone breakdown as measured by urinary collagen type I Cross-linked N-telopeptides Follow-up = 3 months	In the control group of BPH and EBRT the ratio of N-telopeptides/creatinine in the urine was 27 and 25 mM BCE/mM respectively, compared with 22 in the DES-only group and 56 in the LH-RH group. When DES was added to the regimen of the LH-RH group this figure was reduced to 25 ($p = 0.05$)	

AST: androgen suppression therapy; DES: diethylstibesterol acetate.

TABLE 38 *Hormonal monotherapy (primary study)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Evidence level 5					
Leibowitz and Tucker (2001, USA)[40]	Triple androgen blockade therapy for localised prostate cancer where local therapy was refused Patients treated with an LH-RH agonist plus an antiandrogen plus finasteride Median duration of androgen blockade = 13 months	*n* = 110 Mean age 67 years Stage T1–T3 Mean Gleason = 6.6 Mean serum PSA = 13.2	A review of patients from one institution who refused any form of local therapy, and who were subsequently prescribed hormone blockade Outcome = PSA levels Median follow-up = 36 months	During treatment PSA levels decline to ≤ 0.1 ng/ml in all patients, with a median time of 3 months. After a median follow-up of 36 months PSA levels have remained stable in 105/110 patients	

TABLE 39 *Brachytherapy (systematic reviews)*

Study	Treatment(s) reviewed	Included studies	Methods	Outcomes	Results	Comments
Crook *et al*. (2001, Canada)[42]	Effectiveness of brachytherapy over current standard therapies for localised prostate cancer	**Participants:** Men with localised prostate cancer (T1–T2) **Interventions:** Brachytherapy; brachytherapy and neo/adjuvant EBRT **Design:** Cohort studies: case series	**Review question:** Yes **Literature search:** Systematic review of articles from 1988 to April 1999 from MEDLINE and CancerLit databases, combined with a consensus interpretation of evidence in the context of conventional practice **Inclusion criteria:** Series limited to T1/T2; brachytherapy performed under ultrasound or CT; not an abstract	Freedom from biochemical failure (bNED), biopsy results or toxicity	No RCTs comparing brachytherapy with standard treatment; evidence from 13 case series and 3 cohort studies. Rates of bNED varied considerably from one series to another and were highly dependent on tumour stage, grade and pretreatment PSA levels (iPSA) Freedom from biochemical failure ranged from 63% at 4 years ($n = 92$) to 93% at 5 years. This variation is largely due to differences in patient selection criteria Results in patients with favourable tumours (T1/T2) Gleason ≤ 6, iPSA ≤ 10 ng/ml comparable to those undergoing RP Acute urinary retention reported as 1–14% of patients. Long-term sequelae occurred in $< 5\%$ and included urinary incontinence, cystitis, urethral stricture and proctitis. Sexual potency was maintained after implantation in 86–96% of patients Insufficient evidence to recommend brachytherapy over current standard therapy for localised prostate cancer	Only two databases searched No meta-analyses or randomised trials were found

continued

TABLE 39 *Brachytherapy (systematic reviews) (cont'd)*

Study	Treatment(s) reviewed	Included studies	Methods	Outcomes	Results	Comments
Vicini *et al*. (1999, USA)[43]	Different techniques of prostate brachytherapy	**Participants:** Men with clinically localised prostate cancer **Interventions:** Different techniques of brachytherapy **Design:** Any; stratification of subjects by iPSA	**Review question:** Yes **Literature search:** MEDLINE only **Inclusion criteria:** Recent studies (1985–1998) with the largest group of patients treated, or most comprehensive Materials and methods sections	Biochemical disease control as end-point (bNED)	178 articles identified, of which 53 studies discussed evaluable techniques of implantation 3–5-year biochemical control rates ranged from 48 to 100% for iPSA ≤ 4 ng/ml, 55 to 90% for iPSA 4–10 ng/ml, 30 to 89% for iPSA >10 and ≤ 20, and <105 to 100% for iPSA > 20 ng/ml Owing to substantial differences in patient selection criteria (median Gleason score, clinical stage, iPSA), number of patients treated, median follow-up, definitions of biochemical control and time points for analysis, no single technique consistently produced superior results	This is a good and well-constructed study, reviewing the range of different implantation techniques used in prostate brachytherapy. The inclusion criteria are broad in scope. However, it limits itself to a MEDLINE search only

continued

TABLE 39 *Brachytherapy (systematic reviews) (cont'd)*

Study	Treatment(s) reviewed	Included studies	Methods	Outcomes	Results	Comments
Vicini *et al*. (1998, USA)[44]	Optimal therapeutic management by RT	**Participants:** Men with localised prostate cancer **Interventions:** Conventional (EBRT); 3D-CRT; permanent interstitial brachytherapy alone; permanent interstitial brachytherapy with EBRT; temporary interstitial brachytherapy (low and high dose); heavy-particle RT; altered fractionation RT schedules; adjuvant hormonal manipulation **Design:** Not stated/any?	**Review question:** Yes **Literature search:** MEDLINE **Inclusion criteria:** iPSA values recorded and grouped for evaluation; post-treatment PSA values continuously monitored after treatment; definitions given of biochemical control used to evaluate outcome; median follow-up given **Exclusion criteria:** Studies combining clinical recurrence with biochemical failure to calculate disease progression or only reporting percentage of patients achieving a specific PSA nadir were excluded	By biochemical (PSA) control	Of 246 articles identified, only 20 met the inclusion criteria, of which 8 focused on brachytherapy and 4 on 3D-CRT Results for all therapies were extremely variable with the 3–5-year rates of biochemical control for patients with iPSA ≤ 4 ng/ml ranging from 48–100% For iPSA (i) ≤ 4 ng/ml 48–100%; (ii) > 4 and ≤ 10 ng/ml 44–90%; (iii) >10 and ≤ 20 ng/ml 27–89%; (iv) > 20 ng/ml 44–89%. For brachytherapy series: (i) 48–100%; (ii) 55–90%; (iii) 32–89%; (iv) 38–89% For 3D-CRT: (i) 90%; (ii) 71–87%; (iii) 56–87%; (iv) 20–37% No RT option consistently produced superior results	This is a good and well-constructed study, comparing published outcomes of a range of different radiation therapies. The inclusion criteria are tightly defined, but the study limits itself to a MEDLINE search only

continued

TABLE 39 *Brachytherapy (systematic reviews) (cont'd)*

Study	Treatment(s) reviewed	Included studies	Methods	Outcomes	Results	Comments
Wills and Hailey (1999, Canada)[41]	Outcomes for new prostate brachytherapy interventions and comparisons with other therapeutic interventions	**Participants:** Men with localised prostate cancer **Intervention:** Brachytherapy **Design:** Not stated/Any?	**Review question:** Yes **Literature search:** Cochrane Library search; MEDLINE; HealthSTAR; CancerLit; EMBASE and CINAHL Also reference lists from literature retrieved **Inclusion criteria:** 1997–1999 studies	Clinical control by DRE, biopsy, bone scans and CT scans for diagnosis of disease recurrence and biochemical control by serum PSA over a variable follow-up period (± 5 years)	Biochemical control rates range from 95% to as low as 60%, with 10-year follow-up reflecting the diversity of patient populations as well as varying technique Disease recurrence through positive biopsy varied from 5 to 35% according to study protocol and length of follow-up. Non-biochemical outcomes follow these general trends, but biopsy tends to underestimate local recurrence Disease-specific deaths range from 0 to 3%. Overall survival ranges from 65% for studies with long follow-up, to no reported deaths Brachytherapy appears to be a promising intervention for localised prostate cancer in the short term, although its potential for influencing overall outcomes, particularly long-term morbidity and survival, is unknown	This is a very comprehensive and well-structured review, which has used a range of alternative databases for the literature search. The findings support brachytherapy over the short term, but still leave long-term efficacy in question

TABLE 40 *Brachytherapy (primary studies)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Evidence level 1					
Merrick *et al.* (2001, USA)[53]	I-125 or P-103 No supplemental EBRT	*n* = 34 Age = 63 years T1c/T2a PSA ≤ 10 Gleason ≤ 6 I-25I = 20; Pd-103 = 14	1998–1999. Phase III prospective, randomised study Mean and median IIEF questionnaire with hematospermia, orgasmalgia and alteration in intensity of orgasm 13 month median follow-up Clinical parameters evaluated included age, clinical T-stage and elapsed time since implantation. Treatment parameters included NAAD, isotope (I-125, Pd-103) and radiation dose to NVB Pearson's correlation coefficient and *t*-tests to determine strengths of relationships between prostate, dosimetric and clinical parameters, with significance level set at $p < 0.05$	15% with haematospermia, which may persist in 6%; 26% with orgasmalgia, which may persist in 15%; 38% with alteration in intensity of orgasm: effect not time-limited Radiation dose to NVB not associated with development of postbrachytherapy impotence. With medium follow-up of 13 months, 65% of patients maintained sexual function without pharmacological support, and including *sildenafil* responses, 76.5% *sustained* erections suitable for intercourse	Small study population. Prostate brachytherapy does affect sexual function, although in this study the majority of patients maintained adequate sexual function

continued

TABLE 40 *Brachytherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Wallner *et al*. (2000, USA)[54]	Brachytherapy with I-125 (144 Gy) or Pd-103 (125 Gy)	*n* = 182[a] Age = 63 years T1c-T2a PSA = 4–10 ng/ml Gleason = 2–6 I-25I = ?; Pd-103 = ?	2000 prospective, randomised matched controlled study with patients in each arm well matched by prostate volume, AUA score and age Urinary functional outcomes, by questionnaires using AUA and RTOG urinary function criteria 1, 3, 6, 12 and 24-month follow-up. Approx. 10% of all AUA follow-up scores not obtained, mostly at 1 and 3 month. 94% total responses at 6 months. One patient died and was excluded from all follow-up data	AUA scores peaked at 1 month for both isotopes and gradually declined. At 1 month, Pd-103 patients had a mean AUA score of 21 ±9 compared with 18 ±6 for I-125 patients $p = 0.08$). However, average and median AUA scores were lower in the Pd-103 patients, with the difference being more marked at 6 months. Subjects treated with Pd-103 appear to recover from radiation-induced prostatitis sooner than those with I-125	Preliminary results of an in-progress study; planned total of 380 subjects, with a minimum of 172 subjects per treatment arm; subjects still being enrolled. Longer term follow-up to 12 and 24 month awaited. Statistical methodology not recorded

continued

TABLE 40 *Brachytherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Evidence level 3					
Brandeis *et al.* (2000, USA)[47]	Brachytherapy (IMP) with I-125 or Pd-103 (with or without external beam) compared with RP	$n = 256$ Age = 69 ± 7 years Stage ≤ T2 **Brachytherapy**: $n = 48$ I-125 = 25; Pd-103 = 23 Mean PSA = 7.4 ± 2.9 ng/ml Gleason = 6.0 With EBRT: $n = 14$ Without EBRT: $n = 34$ **Prostatectomy**: $n = 74$ Age = 61 ± 7 years PSA = 9.5 ± 3.2 ng/ml Gleason = 6.0 Age-matched healthy controls from literature: $n = 134$ Age = 66 ± 5 years PSA = NA Gleason = NA	1997–1998 retrospective, cross-sectional study Outcomes on general and disease-specific HRQoL RAND 36-item general health survey; University of California Los Angeles Prostate Cancer Index; AUA. symptom index; validated cancer interference with life and family scales; sociodemographic and co-morbidity questionnaires 3–17 months after treatment; average 7.5 month. QoL scores by mean and SD. RP and IMP compared using two-sample *t*-tests, and three groups compared using analysis of variance with $\alpha = 0.05$. Bonferoni and Schiffé tests for which groups were significantly different; two-sample *t*-test for direct comparison between groups. Categorical sociodemographic variables compared with χ^2 analyses	General HRQoL did not differ greatly among the three groups Brachytherapy group had worse urinary function (leakage) than controls, but better than in prostatectomy group; brachytherapy group had more irritative urinary symptoms and worse bowel function than controls. Sexual function and bother worse in both interventions than in controls. Physical function, bodily pain, urinary function and bother, and AUA symptom index scores improved with time with brachytherapy. Those with combined brachytherapy and EBRT performed worse in all general and disease-specific HRQoL domains compared with brachytherapy-alone patients. Prostatectomy group had better physical function. At an average of 7.5 months after treatment general HRQoL of brachytherapy subjects (with or without EBRT) was similar to age-matched controls, although urinary, bowel and sexual problems were reported, which appeared to improve during the first year after treatment. Much of the impairment in disease-specific HRQoL among brachytherapy patients was attributable to pretreatment radiation	Brachytherapy treatment included both I-125 and Pd-103; group included those who had also received EBRT, separated into two subgroups, which were matched for age and co-morbidity, but those who received EBRT had higher PSA and Gleason scores. NHT therapy had also been administered to 23 patients. Unclear whether worse sexual function and bother in brachytherapy group was a result of the seeds, pretreatment radiation therapy or the single 3 month neoadjuvant dose

continued

TABLE 40 *Brachytherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Cha *et al*. (1999, USA)[49]	TPB with either Pd-103 or I-125 Including EBRT and ADT (1992–1997)	n = 648 (222 matched pairs stratified into three risk groups by clinical stage, PSA and Gleason score EBRT: n = 116 Antiandrogen therapy: n = 93 I-125 = 111; Pd-103 = 111	1992–1997 retrospective matched-pair analysis for differences between isotopes Matched by Gleason score, iPSA and stage. PSA RFS at 5 years based on PSA ASTRO Consensus Group definitions of DFS Minimum follow-up = 24 months, median 42 months (24–82 months). 2 lost to follow-up; 10 died Kaplan–Meier actuarial survival curves to assess differences in iPSA and Gleason score. Log-rank test to compare rSA RFS between patients for each isotope. Univariate and multivariate analysis by Cox proportional square hazards model testing	Gleason score, pretreatment PSA and stage as significant factors to predict PSA RFS, but no significant difference in PSA RFS between isotopes used. No difference demonstrated in PSA RFS by subset analysis of either high or low Gleason score. Actuarial PSA RFS at 5 years for all 222 patients is 86.5%. Pd-103 group has a 5 year PSA RFS of 87.1%; I-125 85.9% PSA DFS at 5 years (p = ns) This matched pair analysis failed to demonstrate a difference for I-125 and Pd-103 in PSA RFS for patients undergoing TPB	A well-structured study with robust methodology, good use of statistical analyses and testing. The authors comment that lack of a significant difference in PSA RFS fails to justify the use of Pd-103 as advantageous for higher or I-125 for lower Gleason score tumours

continued

TABLE 40 *Brachytherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Joly *et al*. (1998, France)[64]	Brachytherapy and EBRT with CT planning and dosimetry	$n = 142$ Intervention: $n = 71$; randomly selected age and residence-matched controls: $n = 71$ Mean age = 68 years T1–T3aN0M0	1996 case-controlled study HRQoL and sequelae by Nottingham Health Profile and EORTC QLQ-C30 core questionnaires and EORTC Genitourinary Tract Cancer Cooperative Group Student's *t*-test and Mann–Whitney test used for comparison of means; χ^2 and Fisher's exact tests for proportion comparisons. Linear regression model used to test correlation between general QoL scores and those from prostate module. Multivariate analysis and covariance used for groupwise comparisons	General HRQoL scale general symptom scale scores did not significantly differ between patients and controls. No more late psychosocial sequelae were reported by patients than by controls. No major digestive complications were observed among patients. Statistical differences observed in interest in sex ($p = 0.016$), sexual activity ($p < 0.0010$), urinary incontinence ($p < 0.001$) and cystitis ($p = 0.010$). Late subjective morbidity (dysuria, nocturia, urinary incontinence, pelvic pain) differed slightly. Nocturia reported more by physicians than by patients ($p = 0.0016$): patients reported urinary incontinence and pelvic pain more than physicians (both $p < 0.001$). Survivors from localised prostate cancer treated with brachytherapy and EBRT have a good global health status. However, sexual disorders, urinary incontinence and cystitis can be major persisting problems; digestive disorders are rare	

continued

TABLE 40 *Brachytherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Wei *et al*. (2002, USA)[48]	Transperineal ultrasound brachytherapy I-125, 3D conformal EBRT, RP. All treatment groups with subsets of AHT/NHT; a subset of brachytherapy also with adjuvant EBRT. IMP evaluation by dosimetry	n = 1014 IMP: n = 114 Age = 67.2 years EBRT: n = 203 Age = 70.9 years RP: n = 896 Age = 74.9 years Control: n = 142 Age = 78.9 years T1–T3 Details of iPSA, Gleason score and T stage provided for each treatment group	1995–1999 cross-sectional survey over 4 years with age-matched controls, by percentage response rate RAND 36-item Health Survey 1.0; Functional Assessment of Cancer Therapy-General (FACT-G) and Functional Assessment of Cancer Therapy–Prostate (FACT-P) subscale, Expanded Prostate Cancer Index Composite (EPIC) HRQoL compared between intervention groups and controls using regression models with a range of statistical tests employed, including pairwise comparisons, for differences in demographic characteristics, Fisher's exact test for differences between groups for categorical variables (e.g. Gleason score, clinical T-stage and androgen deprivation therapy). Age differences tested using Student's exact t-test	Compared with controls, each intervention group reported bothersome sexual dysfunction; RP was associated with adverse urinary HRQoL; EBRT with adverse bowel HRQoL; brachytherapy with adverse urinary, bowel and sexual HRQoL (p 0.0002 for each). Hormonal adjuvant symptoms associated with significant impairment (p < 0.002). More than a year after intervention, several HRQoL outcomes were less favourable among subjects after IMP than after EBRT or RP. Progression-free subjects reported better sexual and hormonal HRQoL than subjects with increasing PSA (p < 0.00010) Long-term HRQoL after brachytherapy showed no benefit relative to RP or EBRT and may be less favourable in some domains. Hormonal adjuvants can be associated with significant impairment	Intervention groups matched for age with controls, but not well matched for clinical stage, Gleason score or PSA between therapy groups. An unspecified subset of brachytherapy patients had adjuvant EBRT

continued

TABLE 40 *Brachytherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Evidence level 4					
Schellhammer *et al*. (2000, USA)[50]	Retropubic and TRUS I-125 brachytherapy	$n = 252$ Historical series: $n = 126$ T1b–T3 Present series: $n = 126$ T1b–T2b Some PSA details. No other information	Retrospective case series: 1976–1983 historical brachytherapy series compared with 1995–1999 treated with TRUS brachymonotherapy Clinical freedom from disease; also uses some biochemical (PSA) parameters 15 year follow-up = 15 years Tumour grade and stage compared between cohorts No statistical methodology reported	Patients currently selected for brachytherapy have a lower Gleason score and TNM stage than for historical series patients	Authors note that owing to refinements in histopathological criteria and other differences that limit the ability to match patients across time and institution, historical comparisons such as that attempted in this study are very valid. The two cohorts are not well matched, e.g. there are more locally advanced in the historical series and none in the present comparator

continued

TABLE 40 *Brachytherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Evidence level 5					
Blank *et al*. (2000, the Netherlands)[55]	Transperineal I-125 brachytherapy with TRUS. Some adjuvant external beam and neoadjuvant ADT	*n* = 102 Mean age = 69 years T1c–T2bN0 iPSA = 17 ng/ml	1985–1996 case series Overall survival rates over 5 and 7 years; clinical progression-free survival and biochemical failure. Sexual function, early and late toxicity also assessed Kaplan–Meier actuarial method used to calculate three specified end-points. Multivariate analysis of prognostic factors (e.g. PSA) also carried out and log-rank test used to detect statistical differences	77% 5-year and 63% 7-year actuarial survival (medical 103 months). 10 (9.5%) subjects died from prostate cancer, 29 died from intercurrent disease; 4 alive with recurrence and 59 alive with no clinical evidence of disease 5 and 7 year clinical progression rates were 12% and 17%, respectively; biochemical failure rates were 39% and 44%, respectively. iPSA was a prognostic indicator of clinical and biochemical outcome ($p = 0.0000$), but not of survival, with biochemical control at 6 years 30% for iPSA > 20 ng/ml to 95% for iPSA ≤ 8 ng/ml. 41/49 sexually active patients maintained sexual function after therapy. One patient had complete urinary incontinence. No rectal complications in patients receiving brachymonotherapy	Some mixture with other treatment modalities: 27 patients had EBRT and 5 had had neoadjuvant ADT. Means disguise some wide variations (e.g. age, PSA values)

continued

TABLE 40 *Brachytherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Blasko *et al*. (2000, USA)[56]	Pd-103 brachytherapy with TRUS	$n = 230$ Median age = 69 years T1–T2 Median PSA = 7.3 ng/ml	1988–1995 case series Biochemical outcome at 9 years Kaplan–Meier estimates of biochemical failure on basis of 2 consecutive elevations of PSA. Multivariate risk groups constructed	No patient has yet died of prostate cancer. Overall biochemical control at 9 years was 83.5%, with 3.0% local failures, 6.1% distant; PSA progression only 4.3%. PSA >10 ng/ml and Gleason sum ≥ 7 were significant risk factors. 5 year biochemical control for patients with no risk factors was 94%, with one risk factor 82%, and with both risk factors 65%	
Brachman *et al*. (2000, USA)[45]	I-125 or Pd-103 brachymonotherapy and EBRT	$n = 2222$ Brachymonotherapy: $n = 695$ Median age = 74.3 years EBRT: $n = 1527$ Median age = 73.7 years T1–T2cNx–N0	1988–1995 case series comparison FFS at 5 years, defined by ASTRO criteria, by initiation of hormonal management, by positive post-treatment biopsy, by PSA rising to ≥ 10 ng/dl despite lack of 3 consecutive elevations, by development of distant metastases, or by death from prostate cancer Median follow-up 45 months; EBRT = 41.3 months (1–114.7 months); brachymonotherapy = 51.3 months (1–116.2 months) Pairwise log-rank tests; χ^2 and Kaplan–Meier actuarial methods	FFS at 5 years 69% for EBRT and 71% for brachymonotherapy ($p = 0.91$). No significant difference in FFS for T-stage between EBRT and brachymonotherapy for T1 (78 vs 83%, $p = 0.47$) or T2 (67 vs 67%, $p = 0.89$). Superior outcomes for Gleason 8–10 treated with EBRT vs brachymonotherapy (52 vs 28%, $p = 0.04$); For lower Gleason grade lesions outcomes do not vary significantly. Patients with iPSA 10–20 ng/ml have improved FFS with EBRT vs brachymonotherapy at 5 years (70 vs 53%, $p = 0.001$). Outcomes for patients with an initial PSA of 0–4 ng/dl, >4–10 ng/dl and >20 ng/dl did not differ significantly by treatment. All Gleason score combinations within iPSA range > 10–20 ng/dl had superior outcomes with EBRT compared with brachymonotherapy, with statistical significance in Gleason scores 2–4 (72 vs 58%, $p = 0.026$), Gleason 7 (67 vs 28%, $p = 0.002$) and Gleason 8–10 (63 vs 23%, $p = 0.05$). For low-risk patients, brachymonotherapy and EBRT are equally efficacious in FFS at 5 years; for intermediate- and higher risk patients, brachymonotherapy produces significantly poorer FFS outcomes than EBRT	

continued

TABLE 40 *Brachytherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Critz *et al*. (1999, USA)[57]	Retropubic and transperineal I-125 brachytherapy followed by EBRT; no adjuvant/ neoadjuvant intervention	*n* = 489 Median age = 66 years (45–84 years) Transperineal: *n* = 143 with T1–T2Nx Retropubic: *n* = 346 with T1–T2N0 Median PSA = 8.3 ng/ml (0.3–188 ng/ml)	1984–1994 retrospective case series DFS: PSA nadir of 0.2 ng/ml 5-year minimum follow-up (5–15 years), median 6 years. DFS calculated by Kaplan–Meier method from time of implant with 95% CIs DFS curves compared by log-rank test and McNemar's test. Multivariate analysis calculated by Cox proportional hazards model	After minimum 5 year follow-up, 336 men had a non-rising PSA, of whom 107 had undergone simultaneous irradiation by transperineal implant technique; 97% of this subgroup had a PSA nadir of 0.2 ng/ml and 3% 0.3–1.0 ng/ml. Of the 489 subjects, those with a PSA nadir of 0.2 ng/ml had a 92% non-rising PSA rate (p = 0.001) 10 years after treatment, compared with a 41% rate for those with nadirs of 0.3–1.0 ng/ml. All subjects with nadir > 1.0 ng/ml had recurrence. Median time to a PSA nadir of 0.2 ng/ml = 27 months (3–102 months)	Focus of the study is the subgroup of 143 men receiving transperineal implants from an overall cohort of 489, 346 of whom received retropubic implants. Results are presented both for the overall cohort (mixed treatments) and then for 107 men with transperineal implants and a non-rising PSA. No clear information is presented for this group separately (including failures), and comparison between these two groups appears to be of limited value
Galalae *et al*. (1999, Germany)[58]	HDRIr-192 brachytherapy and EBRT. Some adjuvant ADT	*n* = 189 Median age = 69 years (44–84 years) T1–T2 = 127 T3 = 62	Prospectively recorded case series Survival by bNED, morbidity and prognostic variables Mean follow-up = 6 years (12–143 months) Total planned dose by EBRT = 50 Gy in small pelvis; 40 Gy in prostate by dose modification. HDRIr-192 in 2 fractions of 15 Gy for target Univariate analysis of prognostic indicators for survival outcomes. Non-random stratification for treatment with adjuvant ADT	76.7% of patients survived for a mean of 6 years and the bNED rate was 78%. Univariate survival analysis revealed low stage (T1–T2), low grade (G1–G2), normal PSA status after radiation therapy, no adjuvant hormonal treatment associated with long survival. In multivariate analysis, PSA status was the only independent prognostic factor in survival terms	Too little information from this data summary. Higher risk patients received adjuvant hormonal deprivation; unclear what additional influence this had on outcomes

continued

TABLE 40 *Brachytherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Grimm *et al*. (2001, USA)[59]	I-125 brachymonotherapy, preplanned, TRUS 'Seattle technique' no adjuvant/ neoadjuvant therapy	*n* = 125 Median age = 70 years T1–T2b T2a = 85.6% iPSA = 10 ng/ml Gleason 6 = 76.8%	1988–1990 prospective, consecutively treated case series Biochemical (PSA) PFS defined as 2 consecutive rises in serum PSA Median PSA follow-up 82 months;10 year overall follow-up includes 5 subjects < 2 years, who died with no evidence of disease within 3 years of therapy Cross-sectional analyses. Cumulative survival functions by Kaplan–Meier. Log-rank for differences in biochemical RFS functions, and influence of single covariates on PSA PFS. Cox regression for influence of multiple covariates on PSA PFS	At 10 years, the overall PFS PSA was 87%. 47% patients followed beyond 7 years, 51 (86%) had PSA < 0.5 ng/ml; 48 (81%) < 0.2 ng/ml. 35 local and 3% distant failures. No patients died of prostate cancer Proportion of patients with PSA 0.2 ng/ml continued to increase until at least 7–8 years post-therapy. Subjects from this cohort had statistically improved PFS compared with an earlier cohort (1986–1987) independent of patient selection (p = 0.0002), suggesting that maturation of the technique resulted in improved biochemical control	Study also includes a second consecutive cohort of 97 patients treated earlier, between 1986 and 1987. Good range of statistical tests applied to data
Percarpio *et al*. (2000, USA)[60]	TRUS I-125 brachytherapy. Some neoadjuvant EBRT. Some neoadjuvant ADT	*n* = 100 Age = 71 years (46–82 years) iPSA = 12 ng/ml (1.6–87 ng/ml) T1 = 15% T2a = 41% T2b = 44% Gleason provided Brachymonotherapy = 54% (Gleason 6) Brachytherapy + EBRT = 46% Neoadjuvant hormonal deprivation = 12%	1992–1997 case series Overall survival and DFS (bNED) by PSA at 5 years Median follow-up 63 months (40–94 months) QoL/morbidity outcomes over 12–24 months postimplantation, by RTOG criteria No statistical methodology reported	Overall actuarial survival of entire group is 90% at 5 years. Biochemical freedom from relapse is 57% at 5 years. Patients with iPSA < 10 ng/ml = 80%, > 10 20 = 55%, > 20% = 38% Secondary malignancies in 7 subjects. Side-effects of nocturia, urinary frequency, dysuria and proctitis transient and decreased to < 10% 12–24 months post-therapy. Only patients with prior TURP (4%) experienced urinary incontinence	Patients divided by PSA analytical subgroups only; but no clear attempt to disaggregate patients by different interventions (i.e. with or without EBRT or androgen deprivation) to assess likely influence of different treatment modalities

continued

TABLE 40 *Brachytherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Puthawala *et al*. (2001, USA)[61]	Low-dose temporary iridium-192 brachytherapy and EBRT. No adjuvant/neoadjuvant ADT	*n* = 536 Age = ?? years T1b,c = 31 (6%); T2a = 113 (21%); T2b,c = 263 (49%); T3a–c = 129 (24%) Gleason: by well, moderately, poorly differentiated. sPSA available for only 231 patients	1980–1995 case series Cumulative DFS including bDFS at 10 and 15 years. DFS defined as absence of local, distant or biochemical failure (bNED). bNED defined as increasing PSA on 3 successive follow-ups from nadir (cf. ASTRO). QoL/morbidity outcomes. Actuarial survival curves by Kaplan–Meier with SPSS; log-rank test to make comparisons between subgroups defined by prognostic factors. Multivariate analysis with Cox proportional hazards model. Stepwise backward algorithm to select independent predictors of survival	Cumulative DFS including DFS for T1b,c was 78% at 10 years and 72% at 15 years; for T2a 78% at both 10 and 15 years; for T2b,c 68% at 10 years and 66% at 5 years. Cause-specific survival and for entire group (including later stages T3a–c) was 89% at 10 years and 87% at 15 years. 60–70% of patients experienced mild, self-limiting symptoms for 2–3 weeks post-treatment; severe complications occurred only in the early developmental stage of the study; 29% of sexually potent patients became impotent following treatment at a median follow-up of 24 months. Clinical stage, histological grade, iPSA, lymph-node status and results of repeat post-treatment biopsy all independently significant prognostic factors	Study represents a mixture of local to locally advanced, with inclusion of patients with D stage, one or more positive lymph nodes (18%). Good use of a range of statistical tests employed and presented to disaggregate outcomes by prognostic groups (sPSA, Gleason score, etc.). Outcomes also presented for later stages T3a–c. Some discussion of treatment complications

continued

TABLE 40 *Brachytherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Ragde *et al*. (2001, USA)[51]	I-125 or Pd-103 brachymonotherapy. No AHT/NHT	*n* = 769 Median age = 69 years (43–92 years) T1c–T2b (range T1–T3) Low–high Gleason score 1. low risk = 542 (125I) 2. high risk = 227 (103) by clinical stage and Gleason score	1987–1997 prospectively followed case series 13 years bDFS; median follow-up 71 month (18–156 months) bDFS defined as 3 consecutive PSA rises with value of third PSA rise > 0.5 ng/ml	137 patients lost to follow-up; 13 died of non-cancer causes within 18 months of the implant leaving *n* = 619 (group 1 = 441, group 2 = 178) bDFS at 3, 5, 10 and 13 years was 85, 80, 77 and 77%, respectively. bDFS of the 441 lower risk I-125 patients at 3, 5, 10 and 13 years was 84, 79, 76 and 76%, respectively. Of the 178 higher risk patients treated with Pd-103 the bDFS outcomes at 3, 5, 10 and 13 years were 87, 82, 80 and 80%, respectively	Statistical methodology not reported, but seems limited. Some treatment-related morbidity reported. bDFS outcome of high-risk group appears marginally more favourable in this study
Ragde *et al*. (2000, USA)[62]	I-125 TRUS transperineal brachytherapy Neoadjuvant EBRT for high-risk subjects No adjuvant/neoadjuvant ADT. Postoperative CT dosimetry	*n* = 229 Mean age = 70.5 years T1–T2b,c (T1a–T3a range) Group 1, low risk = 147 (64%); group 2, high risk = 82 (36%) by clinical stage and Gleason score	1987–1989 case series Median follow-up 122 months (18–144 months) for biochemical freedom from disease by ASTRO definition of biochemical failure	14 (6%) patients lost to follow-up and excluded from survival analysis, 7 from each treatment group within 18 months of therapy, leaving 215 for complete evaluation. Using the ASTRO definition of biochemical failure resulted in minimal change in survival compared with previous study using PSA level > 0.5 ng/ml. Observed 10 year DFS for entire cohort was 66%; for higher risk patients treated with EBRT was 79%. No patients followed-up between years 10 and 12 failed. Only 25% of failures occurred > 5 years after treatment. No patient failed after 115 months	Represents an update of an earlier 10-year follow-up brachytherapy study (Ragde and Korb, 2000,[63] see below), with a further 77 patients (> 50%) and an increase of 2 years to the original 10 year follow-up. Statistical methodology not reported, but seems limited

continued

TABLE 40 *Brachytherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Ragde and Korb (2000, USA)[63]	I-125 TRUS transperineal brachytherapy and neoadjuvant EBRT. No adjuvant/neoadjuvant ADT. Postoperative CT dosimetry	*n* = 152	1987–1988 case series	See previous study	See Ragde *et al*.[62]
Sharkey *et al*. (2000, USA)[52]	Transperineal ultrasound Pd-103 brachytherapy. Some neoadjuvant ADT	*n* = 780 Mean age = 72.6 year (48–88 years) Pd-103 monotherapy = 299; Pd-103 + neoadjuvant ADT = 481; previous TURP = 236 (30.5%) iPSA average = 7.2 ng/ml (0.0–93.0 ng/ml) 84% stage T2; 78% Gleason < 7	1991–1999 retrospective case series Follow-up yearly for 5 years Biochemical control by PSA level (< 1.5 ng/ml) and negative biopsy at 1 and 2 years post-therapy Markov process estimates of proportion of patients free from PSA failure at 3 months and 1–5 years	14 patients lost to follow-up at 1 year. 166 patients with evaluable data remaining at 5 years. At 1 year, 86% of 766 patients had stable PSA of 1.5 ng/ml; at 5 years 86% of 166 patients with available data had stable PSA of 1.5 ng/ml. Biopsies were negative in 92% of patients studied at 2 years. Patients with iPSA <10 ng/ml had best outcomes and those treated with Pd-103 plus hormone ablation achieved PSA reduction more rapidly than those with monotherapy, although subjects were not randomised to treatments, but chosen on basis of risk. Principal morbidity was short-term bladder and bowel irritation. Approx. 15% of patients developed impotence, and incontinence developed in 5% of those with a history of TURP	A large number of the original study population of 780 seem to be lost to follow-up by year 5. Statistical tests for relationship between different variables and outcomes appear limited to using the Markov process for biochemical (PSA) failure. Definition of acceptable level of biochemical control as sPSA of < 1.5 ng/ml seems a little high compared with other studies using stricter criteria (see Grado *et al*. 1998[165]). Some discussion of treatment complications given

continued

TABLE 40 *Brachytherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Stokes (2000, USA)[46]	TRUS-guided I-125 brachytherapy, RP, EBRT No adjuvant/neoadjuvant ADT	n = 540 I-125 brachytherapy: n = 186 EBRT: n = 132 RP: n = 222 **I-125 group:** Median age = 74 years Mean iPSA = 7.6 ng/ml, median = 10.56 ng/ml (0.7–66.7 ng/ml) Stage T1c–T2a,b	1988–1994 retrospective case series bDFS 2–10 years follow-up Patients retrospectively stratified by pretreatment risk groups (low, intermediate and high) by iPSA, clinical T-stage and Gleason score for post-treatment PSA recurrence Actuarial bDFS with Kaplan–Meier survival curves. p-Values on log names (Mantel–Haenzel) statistics	Of 186 patients undergoing I-125, 112/147 low to intermediate risk (76%) obtained nadir of < 1.0 ng/ml; 20/39 (51%) high-risk patients obtained nadir PSA of < 1.0 ng/ml. The bDFS for patients with low or intermediate risk at 5 years is 80 and 70%, and 35% for high risk, with no significant difference between patients treated with I-125 brachytherapy, EBRT and RP. For patients with high-risk disease, there is no significant outcome difference between TRUS implant and EBRT, but RP provides a significantly improved bDFS	Study compares treatment outcomes between therapies, but patients not randomly allocated to intervention and not matched across a range of variables. Treatment modalities have been selected depending on risk criteria, patient/clinician choice, etc. The present review concentrates on the outcomes for brachytherapy intervention

[a] Number in each intervention reported unclear. AUA: American Urological Association; TPB: transperineal brachytherapy; ns: not significant.

TABLE 41 *Three-dimensional conformal radiotherapy (primary studies)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Evidence level 1					
Dearnaley *et al*. (1999, UK)[67]	Conventional EBRT and 3D-CRT	n = 225 EBRT: n = 114 Median age = 69 years 3D-CRT: n = 111 Median age = 68 years T1–T3	1988–1995 randomised study Late GI and GU morbidity, defined as > 3 months after treatment. Median follow-up = 3.6 years χ^2 test for linear trends, Kaplan–Meier, log rank test for differences between groups	Significantly fewer men developed radiation-induced proctitis and bleeding in the 3D-CRT group than the EBRT (37 vs 56% ≥ grade 1, p = 0.004; 5 vs 15% grade 2, p = 0.01) No differences between groups in bladder function (53 vs 59% grade 1, p = 0.34; 20 vs 23% grade 2, p = 0.61) After 3.6 years' median follow-up, there was no significant difference between groups in local tumour control (3D-CRT = 78%, EBRT = 83%)	
Koper *et al*. (1999, The Netherlands)[68]	Conventional EBRT and 3D-CRT	n = 266 Mean age = 69 years T1–T4	1994–1996 randomised study GI and GU acute morbidity All patients received a dose of 66 Gy with same planning procedure. Patient and tumour characteristics equally distributed between both groups	Max. GI toxicity = 57% grade 1 and 26% grade 2; GU toxicity = 47% grade 1, 17% grade 2 and 2% > grade 2 For grade 2 GI toxicity: conventional EBRT = 32%, 3D-CRT = 19% (p = 0.02) Strong correlation between exposure of the anus and anal toxicity. No difference in urological toxicity between treatment arms	

continued

TABLE 41 *Three-dimensional conformal radiotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Nguyen *et al*. (1998, USA)[75]	Conventional EBRT and 3D-CRT	*n* = 101 EBRT: *n* = 50 T1–T2 = 72% T3–T4 = 28% **3D-CRT**: *n* = 51 T1–T2 = 67% T3–T4= 33%	Randomised dose–response study comparing 70 Gy EBRT and 78 Gy 3D-CRT Late complications evaluated by questionnaire	Similar urinary incontinence rates seen in both groups. 3D-CRT reported less leakage of urine (33 vs 63%, $p = 0.044$). Majority (78%) had no or mild change in bowel function. EBRT group had more moderate or major changes in bowel function (34 vs 10%), more frequent bowel movements (47 vs 27%) and more urgent bowel movements (37 vs 18%, $p = 0.040$ for all 3)	
Storey *et al*. (2000, USA)[77]	Conventional 4-field or conventional 4-field followed by 3D-conformal 6-field RT	*n* = 189 **70 Gy**: *n* = 98 Median age = 68 years Median iPSA = 9.6 ng/ml T1c–T2c = 78.6% **78 Gy**: *n* = 91 Median age = 69 years Median iPSA = 10.1 ng/ml T1c–T2c = 69%	1993 randomised prospective trial Minimum follow-up = 2 years Patients stratified by iPSA All patients received 4-field box to an isocentre dose of 46 Gy at 2 Gy per fraction. Subjects then randomised to receive 70 or 78 Gy. In the 70 Gy arm, treatment continued to a reduced volume with a 4-field box technique. In the 78 Gy arm treatment continued to a reduced volume using a conformal 6-field arrangement Treatment complications on a 1–4 scale adapted from RTOG and Late Effects Normal Tissue Task Force criteria	No significant differences in acute rectal or bladder toxicity between the 2 arms ($p > 0.6$ for all comparisons). 5 year Kaplan–Meier risks of grade 2 or higher late bladder toxicity were 20 and 9% for 70 and 78 Gy, respectively (log-rank, $p = 0.8$). 5-year risks of ≥ grade 2 late rectal toxicity were 14% and 21% for 70 and 78 Gy, respectively ($p = 0.4$). DVH analysis of 78 Gy subjects showed a significant correlation between the percentage of rectum irradiated to ≥ 70 Gy and the likelihood of developing late rectal complications. Patients with > 25% of rectum receiving ≥ 70 Gy had a 5-year risk of ≥ grade 2 complications of 38%, compared with 13% with ≤ 25% ($p = 0.05$). All 3 grade 3 complications occurred when > 30% of the rectum received 70 Gy or more	Generally a well-constructed study. Patients in both arms well matched, except that 78.6% of the 70 Gy arm were within T1c–T2c, vs 69% in the 78 Gy arm, and there were more locally advanced (T3a/c) in the 78 Gy than in the 70 Gy arm. However, as the study addressed treatment complications this is not too important

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TABLE 41 *Three-dimensional conformal radiotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Evidence level 3					
Hanks *et al*. (1999, USA)[78]	3D-CRT with dose escalation. No adjuvant/neoadjuvant ADT	*n* = 1,306 Group I: *n* = 592 Group II: *n* = 714 Group I/3D-CRT > 74 Gy = 296 Group I/3D-CRT < 74 Gy = 296 Group II/3D-CRT > 74 Gy = 357 Group II/3D-CRT < 74 Gy = 357 Median age = 68–71 years across 4 groups Median iPSA Group Ia high = 10.3, low = 10.0 Median iPSA Group IIb high = 11.1, low = 8.4 Median T-stage and Gleason details given per group	1984–1997 retrospective, matched pair analysis Randomly matched by age and independent prognostic variables; 2 treatment arms, of low dose and high dose Group Ia matched on iPSA, T-stage and Gleason score Group IIb matched on T-stage and Gleason score Biochemical freedom from disease, freedom from distant metastasis, cause-specific survival, overall survival Kaplan–Meier method for estimation of rates for all end-points; comparisons between dose groups by log-rank tests	Univariate analysis showed that dose is a significant predictor of bNED, freedom from distant metastasis, and cause-specific survival for group I, and bNED, freedom from distant metastasis, cause-specific survival and overall survival for group II. Multivariate analysis showed that dose is a significant independent predictor for bNED and freedom from distant metastasis in group I, and for bNED, freedom from distant metastasis, cause-specific survival and overall survival in Group II. 3D-CRT group 1: 5 year survival rates for high dose = 88%, low dose = 84% (p = 0.211, ns)	This seems to be a robust study with good statistical tests and a clear presentation of data

continued

TABLE 41 *Three-dimensional conformal radiotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Evidence level 5					
Algan *et al*. (1999, USA)[84]	Conformal and conventional radiotherapy. No adjuvant/neoadjuvant ADT	*n* = 129 Conformal: *n* = 97 Conventional: *n* = 32 Median age = 70 years (51–89 years) Mean iPSA = 20 ng/ml, median = 35 ng/ml (20–191 ng/ml) T1,T2a/b Gleason < 7 12 with perineal invasion	1988–1994 retrospective case series Treatment volumes by T-stage/Gleason score and iPSA; median central axis dose 73 Gy. bNED failure definition of post-treatment PSA 1.5 ng/ml rising on 2 consecutive assays. Median follow-up = 50 months (mean 49, range 3–100 month). Univariate and multivariate analyses of covariates (e.g. dose, iPSA, perineal involvement, Gleason, T-stage, age) Estimates of bNED with Kaplan–Meier product-limit and compared with log-rank statistics. Patients stratified into two distinct subgroups, favourable (19) and unfavourable (110), by covariate analyses	Overall bNED control for group was 22% at 5 years bNED control significantly higher for group I patients (58%) than group II (23%) (p = 0.0027). There appears to be a favourable subgroup of patients with PSA 20 ng/ml where treating to doses > 73 Gy to the central axis is warranted (4-year bNED rate of 58%)	Relatively small numbers in study. 19 favourable and 110 unfavourable risk patients had conformal therapy; 32 unfavourable risk patients had the conventional EBRT intervention. It is not clear from this study how the 3D-CRT technique may have influenced outcome compared with conventional EBRT

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TABLE 41 *Three-dimensional conformal radiotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Anderson *et al*. (2000, USA)[85]	3D conformal EBRT	*n* = 163 T1/T2a: *n* = 113 T2b/T3: *n* = 50 Gleason 7 Median iPSA = 11.4 ng/ml Median dose = 76 Gy	1990–1997 case series Follow-up = 5 years (Median 50 months) bNED based on ASTRO definitions. Univariate and multivariate analyses to identify independent predictors for prognostic groups for bNED	5-year bNED was 66% for whole group. By iPSA 0–9.9 ng/ml bNED was 83%; 10–19.9 ng/ml = 65%; 20 ng/ml = 21%. Dose to the central axis found to be significant treatment factor, with patients receiving greater than or equal to 76 Gy experiencing 76% 5-year bNED control versus 54% when treated with <76 Gy to isocentre. Pretreatment PSA, dose and palpation stage were significant predictors for bNED control with multivariate analysis. Patients with iPSA < 10 ng/ml and 76 Gy had excellent 5-year bNED control = 100% (p = 0.002) compared with 50% bNED with > 10 ng/ml or radiation doses of < 76 Gy	See also Algan *et al*.[84] (both from Fox Chase Center, Philadelphia, USA)
Connell *et al*. (1999, USA)[90]	Conformal radiotherapy. No adjuvant/neoadjuvant ADT	*n* = 437 Subgroup 1: *n* = 191 Subgroup 2: *n* = 273 Median iPSA = 11.5 ng/ml (0.7–418 ng/ml) T1–T2 = 87.6% T3–T4 = 12.4% Gleason 2–7 = 95%; > 7 = 5%	1988–1997 case series Subgroup 1 monitored up to 2 years (median 1.1 years), subgroup 2 up to 3 years (median 1.5 years), original population up to 8 years (median 2.5 years) Biochemical failure defined by 3 consecutive PSA increases, or an increase large enough for androgen deprivation therapy Actuarial biochemical control and DFS, calculated by Kaplan–Meier method and compared by log-rank test	No significant differences were seen in pretreatment prognostic factors among the 3 groups. 2-year bNED of subgroups 1, 2 and original population was 86, 77 and 73%, respectively. Subgroup 1 had a superior bNED compared with the original population (p = 0.04); no differences in clinical recurrence rates were seen in any of the 3 groups. 4-year actuarial DFS rate for the original group was 88%. No significant differences were seen between subgroup 1 and subgroup 2 (p = 0.82), between subgroup 1 and the original population (p = 0.65) or between subgroup 2 and the original population (p = 0.15)	Although reviewing outcome (defined by bNED) of conformal RT, this study actually focuses on the influence of length of follow-up on the use of PSA for interpreting bNED. The length of follow-up reported here is only a maximum of 3 years

continued

TABLE 41 *Three-dimensional conformal radiotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Fiveash *et al*. (2000, USA)[86]	3D-CRT. Some adjuvant hormonal deprivation	$n = 180$ Median age = 72 years Gleason 8–10 T1–T2 = 56.7% T3–T4 = 41.7% Two subgroups of T1–T4 and T1–T2. iPSA details specified per group. 27% with adjuvant hormonal deprivation	Retrospective case series bNED at 5 years ASTRO definitions of biochemical (PSA) no failure (bNED) bNED and overall survival rates by Kaplan–Meier method; log-rank test to evaluate potential factors predictive of bNED control and overall survival Proportional hazards regression model to estimate risk ratios for overall survival and bNED	bNED control for entire cohort of T1–T4 was 62.5% at 5 years; overall survival for the entire cohort was 67% at 5 years. Radiation dose predictive of overall survival ($p = 0.04$); Gleason score 8 vs 9/10 approached significance ($p = 0.09$). Univariate analysis revealed that iPSA, radiation dose and T-stage predicted bNED Multivariate analysis showed only T-stage (T1–T2 vs T3–T4) to be statistically predictive of bNED. Statistically significant relationship between T-stage and radiation dose ($p = 0,0.01$). bNED percentage overall survival for 102 T1–T2 patients was 79.3 and 58.4% at 5 years. Lower radiation dose (< 70 Gy) and higher iPSA predicted for biochemical failure on multivariate analysis in T1–T2 patients. HT not associated with better bNED or overall survival	Selection of patients with more unfavourable tumours for AHT and higher radiation doses used may mask the influence of HT

continued

TABLE 41 *Three-dimensional conformal radiotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Fukunaga-Johnson *et al*. (1997, USA)[87]	3D-CRT	*n* = 707 Favourable group: *n* = 133 Unfavourable group: *n* = 465 Median age = 72 years (44–87 years) T1–T2 = 603 Median iPSA = 12.9 ng/ml (0.2–257.1 ng/ml) for 649 patients 209 with iPSA = > 20 ng/ml	1987–1994 retrospective case series Follow-up >8 years (median 36 months). bNED survival by PSA failure by 2 consecutive PSA rises > 2.0 ng/ml if nadir PSA 2.0 ng/ml; 2 consecutive rises over nadir if nadir PSA > 2.0 ng/ml; initiation of HT after RT 2 prognostic groups calculated: favourable: PSA 10 ng/ml, Gleason < 7, T1–T2; unfavourable: PSA 10 ng/ml, Gleason 7, T3–T4 Biochemical survival measured from date RT ended to date PSA failure, or last PSA measurement for censored patients Distribution of bNED survival estimated by Kaplan–Meier method and 95% CI at 5 years also provided. Log-rank test to compare length of bNED survival between patient groups. Multivariate analysis using a Cox regression model	bNED at 5 years was 75% for favourable group and 37% for unfavourable group. A subset of 'surgically suitable' patients < 70 years with T1–T2, PSA 10 ng/ml and Gleason 7 (*n* = 85) had an 84% 5-year bNED rate and 98% 5-year overall survival. 5-year overall survival for favourable group was 86% vs 79% for unfavourable. Surgical subset patients had an actuarial survival of 98% at 5 years vs 78% not suitable for surgery. Low rate of complications: 3% risk at 7 years of grade 3–4 complications and 1% risk at 7 years of grade 3 bladder complications (no grade 4)	Good use of statistical tests, although some data (iPSA, Gleason grade) not available for all patients in group

continued

TABLE 41 *Three-dimensional conformal radiotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Hanks *et al*. (1997, USA)[79]	Conformal RT with dose escalation	*n* = 233 Median age = ? T1/T2 and Gleason 2–7 = 209 T3 and Gleason 8–9 = 24	1989–1992 consecutive case series Follow-up = 3 years Dose escalated from 68 to 79 Gy. bNED survival by dose groups, defined as PSA > 1.5 ng/ml and rising on 2 consecutive measures. Dose response for bNED and late morbidity represented by logit response models. Kaplan–Meier methods, log-rank test and Cox regression models also used	No dose response is observed for bNED survival for patients with iPSA < 10 ng/ml compared with patients treated above or below 71.5 Gy or on multivariate analysis. Dose response observed for bNED survival for iPSA groups of 10–19.9 ng/ml and ≥ 20 ng/ml. 64 and 76 Gy associated with 50% bNED survival at 3 years. The slope of the dose responses is 13 and 9%, respectively, for cancer. Dose response demonstrated for grade 2 GI, grade 2 GU, and grade 3 and 4 combined GI and GU late morbidity. Slopes of morbidity responses steeper than for cancer control (19–21%)	Patients not stratified according to PSA prognostic grouping for treatment, only later during analyses of outcome by different variables

continued

TABLE 41 *Three-dimensional conformal radiotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Hanks *et al*. (2000, USA)[80]	3D-CRT	n = 618 Median age = ? For subgroups see Methods	1989–1997 consecutive case series Follow-up = 5 years (median 53 months) bNED outcomes as assessed by ASTRO definitions. Subjects divided into 3 groups by PSA and further into 6 groups by favourable (T1,2a; Gleason 6, no perineal involvement/unfavourable (T2b,T3; Gleason 7–10, perineal involvement) prognostic characteristics. Patients also divided at 75 Gy for all subgroups, except for favourable PSA <10 ng/ml, which was divided at 72.5 Gy. Dose comparisons made for each. 5 year bNED rates compared for median dose of each dose comparison subgroup Dose comparisons using Kaplan–Meier estimates and the fitted dose–response models. Cox proportional hazards regression to demonstrate the predictive utility of dose, independently of iPSA and prognostic group	Dose comparisons show a significant difference in 5-year bNED rates for 3/6 subgroups, but not favourable <10 ng/ml or favourable 10–19.9 ng/ml, or unfavourable 20 ng/ml. Significant differences ranged from 22 to 40% improvement in 5-year bNED with higher dose. Dose–response functions show significant differences in 5-year bNED rates comparing 73 and 78 Gy for 4/6 subgroups; no difference observable for the favourable < 10 ng/ml and unfavourable 20 ng/ml groups The significant differences observed in 5-year bNED ranged from 15 to 43% Dose was an independent predictor of bNED control (p = 0.0002) after adjusting for PSA and dichotomous prognostic groupings. Up to 80% 5-year bNED for patients with PSA < 10 ng/ml and 10–19.9 ng/ml with 76–80 Gy	See also study by Hanks *et al*. (1997),[79] above

continued

TABLE 41 *Three-dimensional conformal radiotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Hanlon *et al.* (2001, USA)[74]	3D-CRT No ADT	n = 195 **Group I**: n = 95 iPSA < 10 ng/ml; T1–T2a; Gleason 2–6; no perineal involvement **Group II**: n = 100 iPSA = 10 ng/ml; T2b–T3; Gleason 7–10; perineal involvement **Respondents**: Mean age = 67 years; median = 68 years see Results for other details	1992–1995 case series Mean and median follow-up 53 and 54 months for all respondents to 3 and 6 years QoL defined by bowel and bladder functioning Two health status surveys evaluating bowel and bladder functioning, with AUA Symptom Problem Index and BPH impact index mailed to 195 patients Group I treated to prostate only; group II to whole pelvis + boost to prostate 2-tailed Fisher's exact test for evaluation of percentage differences in 2 groups. Overall percentages compared with those for equivalent measures for a normal population of men with mean age 73 years	Response rate of 77%; group I = 66; group II = 73. Mean age = 67 years (49–82 years) Median ICRU dose levels were 73 for group I and 76 Gy for group II. Responses relating to bladder symptoms similar between the 2 groups. Observed differences in bowel functioning (rectal urgency) were 22% for group I and 40% for group II (p = 0.03); use of pads for incontinence 0% (I) vs 10% (II) (p = 0.01), and bowel satisfaction 88% (I) vs 72% (II) (p = 0.03). There was no significant difference in the degree of bother that bladder symptoms cause men treated with RT compared with men without cancer. Few patients reported bowel dysfunction bother as a big problem, but patients tend to have more very small to moderate bother from bowel dysfunction than the normal population (55 vs 33%; p = 0.0001). Radiation to the whole pelvis may result in decreased QoL, defined by rectal urgency and bowel function, but men were generally satisfied with their bowel and bladder functioning 3–6 years post-treatment	

continued

TABLE 41 *Three-dimensional conformal radiotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Hanks *et al*. (1997, USA)[88]	3D-CRT. No androgen deprivation	*n* = 202 Median age = 69 years (50–84 years) T1c PSA and Gleason details given	1989–1995 case series 5 year actuarial freedom from failure (bNED). Median 32 months (2–75 months) Kaplan–Meier for bNED rates, compared with log-rank test; stepwise Cox regression model for effect of clinical and treatment covariates (dose, iPSA, Gleason, perineal involvement age)	Actuarial bNED at 5 years for subjects with iPSA < 10ng/ml is 97%; with iPSA 10–19.9 ng/ml is 88%; with iPSA > 20 ng/ml is 32%. Younger age has no apparent independent prognostic effect. Late morbidity is favourable, with < 1% developing serious GI sequelae, < 1% experiencing incontinence and 61% maintaining sexual potency	This is an earlier study from the Fox Chase Center, reporting actuarial bNED; later studies summarised above focus on the different effects of radiation dose on outcome

continued

TABLE 41 *Three-dimensional conformal radiotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Perez *et al*. (2000, USA)[69]	3D-CRT and SRT. No androgen deprivation	$n = 277$ 3D-CRT: $n = 146$ SRT: $n = 131$ T1c–T2	1992–1997 non-randomised case series comparison Mean follow-up = 3 years (1–6 years). bNED by ASTRO consensus of PSA determinations. QoL indicators: urinary and rectal functioning. 11/146 3D-CRT and 29/131 with elective irradiation of pelvic lymph nodes because of higher risk: higher T grade (T2b,c), iPSA 10–17 ng/ml, Gleason 7–9. bNED by Cutler and Ederer actuarial life table Test differences between curves done using Mantel statistical method. All other comparisons with Yates-corrected χ^2-square test. Cox proportional hazards regression model for covariate survival analysis	For 3D-CRT, DVHs showed a two-thirds reduction in normal bladder/rectum with 70 Gy. Higher 5-year bNED observed with 3D-CRT (91% T1c and 96% T2) than with SRT (53 and 58%, respectively). For patients with Gleason 5–7, 5-year survival rates were 96% with 3D-CRT and 53% with SRT ($p = 0.01$). In 111 3D-CRT patients with iPSA = 10 ng/ml, bNED was 96% vs 65% for 94 SRT patients ($p = 0.01$). For iPSA 10.1–20 ng/ml, bNED for 26 3D-CRT patients was 88% vs 40% for 20 SRT patients; for iPSA > 20 ng/ml, 3D-CRT = 71 and SRT = 26% ($p = 0.30$). The most important prognostic factors for biochemical failure were iPSA ($p = 0.0223$), nadir PSA ($p = 0.001$) and 3D-CRT ($p = 0.033$). Moderate dysuria and difficulty in urinating for 2–5% of 3D-CRT patients, and 6–9% of SRT patients; moderate frequency and nocturia for 18–24% 3D-CRT patients and 18–27%, SRT. Loose stools/diarrhoea (4th week) 3–5% in 3D–CRT and 8–19% for SRT. Late intestinal morbidity (proctitis, rectal bleeding) 1.7% in 3D-CRT and 8% in SRT	A good study using robust statistical tests comparing both bNED and QoL outcomes between a new and a standard radiation intervention

continued

TABLE 41 *Three-dimensional conformal radiotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Pinover *et al.* (2000, USA)[76]	3D-CRT only	*n* = 488 Median age = 68 years (43–86 years) Median iPSA = 6.3 ng/ml (0.4–9.9 ng/ml) T1–T2a = 85% T2b–T3 = 15% Good prognosis: *n* = 310 Poor prognosis: *n* = 178	1989–1997 case series bNED control at 5 years by ASTRO consensus definitions (median follow-up = 36 months). Subjects stratified into 3 groups by dose: < 72.50, 72.50–75.99 Gy and 76.00 Gy, with median doses of 70.67, 72.78 and 77.34 Gy, respectively; then into good/poor prognosis: Good = T1–T2a, Gleason 2–6, no perineal involvement; poor = T2b–T3, Gleason 7–10 or perineal involvement. Univariate analysis to determine differences in bNED control by dose group	Dose response not demonstrated for entire group of patients with iPSA = 10 ng/ml. bNED at 5 years for < 72.50 Gy = 73%; 72.50–75.99 Gy = 86%; 76.00 Gy = 89% ($p = 0.12$) Multivariate analysis demonstrated prognosis group to be only independent predictor of bNED ($p = 0.038$). At 5 years bNED in good prognosis patients was 85% with no dose response seen, and 81% for the poor prognosis group with a dose response for 76.00, compared with 2 lower groups (95% vs 75% and 70%; $p = 0.0062$). For the poor prognosis group, dose was the only independent predictor for improved bNED control ($p = 0.01$)	This represents another subset of data on dose response from the Fox Chase Center, focusing on iPSA 10 ng/ml; see above for comparable studies

continued

TABLE 41 *Three-dimensional conformal radiotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Sandler *et al*. (2000, USA)[91]	Conformal RT	$n = 718$	Case series 5 years Biochemical relapse defined as 3 consecutive PSA rises Age at failure, iPSA, PSA at second rise, PSA nadir, time from RT to failure, time to nadir, Gleason score, T stage and rate of rise, both from nadir and from beginning of rise evaluated for associated with increased risk of death	Overall survival after conformal RT remains high 5 years after biochemical failure. 154 cases classified as biochemical failures, with 41 deaths in 23/41 due to prostate cancer. Overall survival after failure 58% at 5 years, while cause-specific failure was 73% at 5 years. Patients with biochemical failure have significantly worse prognostic factors than those without biochemical failure: median iPSA 15.9 vs 9.0 ($p < 0.001$), Gleason $\geq$ 7 for 48% of subjects vs 40% ($p = 0.1$). Relative PSA rise and slope in PSA vs time associated with cause-specific mortality ($p < 0.001$ and $p = 0.007$, respectively)	This study addresses the significance of biochemical failure after conformal RT. A good series with good use of statistical tests and adequate follow-up period
Schultheiss *et al*. (1997, USA)[83]	Conventional EBRT and 3D-CRT	$n = 712$ 3D-CRT: $n = 562$ EBRT: $n = 150$	1986–1994 case series comparison Late GI and GU complications Univariate and multivariate analyses with proportional hazards model and logistic regression. Also Kaplan–Meier and Greenwood's formulae	Grade 2 GI morbidity significantly related to central axis dose, use of increased rectal shielding and neoadjuvant androgen ablation therapy. Grade 2 or higher GU morbidity significant correlated with central axis dose and neoadjuvant ADT. Acute GU side-effects correlated significantly with late GU injury. Treatment with conformal fields was significantly negatively correlated with acute GU side-effects. Both late GI and GU morbidity demonstrate a dose dependence; a reduction in late grade 2–4 GI morbidity by increasing rectal shielding in lateral fields for final 10 Gy. Late GI and GU morbidity increased in patients with neoadjuvant HT	

continued

TABLE 41 *Three-dimensional conformal radiotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Slater *et al*. (1999, USA)[70]	Conformal proton therapy with CT. No adjuvant/neoadjuvant ADT	*n* = 319 Age = ? T1–T2b IPSA ≤ 15 ng/ml 74–75 Gy Gleason 2–10	1990–1995 case series 5-year (bNED), with 43-month mean and median follow-up Also QoL outcomes Kaplan–Meier product method for actuarial bNED and treatment-related morbidity; log-rank test for statistical inferences on actuarial curves; Cox regression models to evaluate covariables on bNED	Overall 5-year clinical and bNED survival rates were 97 and 88%, respectively. iPSA, stage and post-treatment PSA nadir were independent prognostic variables for bNED; a PSA nadir of 0.5 ng/ml was associated with a 5-year bNED rate of 98%, vs 88% for 0.51–1.0 ng/ml and 42% for > 1.0 ng/ml. No severe treatment-related morbidity was seen	Initial PSA is higher than for many studies, being ≤ 15 ng/ml, instead of ≤ 10
Slater *et al*. (1998, USA)[71]	3D conformal proton RP	*n* = 643 Protons *n* = 326 Photons and protons *n* =319	1991–1995 case series 5 years with a minimum 24 months before treatment follow-up (mean/median 43 months) bNED by 3 consecutive PSA rises of > 10%, or a single dramatic rise needing hormonal therapy (Zietman *et al*., 1996). Modified RTOG treatment-related toxicity grade 2 Actuarial clinical and bNED and treatment-related morbidity by Kaplan–Meier method. Log-rank test for statistical inferences on actuarial curves; Cox regression models to evaluate clinical variables on bNED and clinical DFS	Overall clinical DFS 89% at 5 years. Overall no significant survival difference between the 2 intervention arms, although there was an improvement in local control in the higher dose arm for poorly differentiated tumours. PSA-based bNED 100% at 4.5 years for patients with iPSA of < 4ng/ml; 89% for 4.1–10 ng/ml; 72% for 10.1–20 ng/ml and 53% for > 20 ng/ml. For patients with a post-treatment nadir of < 0.5 ng/ml, 5-year bNED = 91%, for 0.51–1.0 ng/ml = 79% and for > 1.0 ng/ml = 40% On multivariate analysis, T-stage and Gleason score were significant predictors of local failure, and together with iPSA predicted distant metastasis. Minimal radiation proctitis in 21% of patients and < 1% for greater severity	

continued

TABLE 41 *Three-dimensional conformal radiotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Skwarchuk *et al*. (2000, USA, France, Germany)[81]	3D-CRT (64.8–81.0 Gy)	*n* = 171 *n* = 52 at 70.2 Gy *n* =119 at 75.6 Gy Age = ? T1c–T3	1988–1995 case series 5-year actuarial rate of late rectal toxicity. Retrospective dosimetric analysis performed for patients treated to 70.2 Gy (*n* = 52) or 75.6 Gy (*n* = 119) for experience of late rectal bleeding (RTOG grade 2/3) within 30 months after treatment Assessment with Kaplan–Meier method. Univariate and multivariate analysis to correlate late rectal bleeding with several anatomical, dosimetric and clinical variables	For 70.2 Gy 13/52 subjects and for 75.6 Gy 36/119 subjects had grade 2/3 symptoms. A dose response for grade 2 late rectal toxicity was observed. Late rectal bleeding correlated with factors, that may indicate that a greater fractional volume of the rectal wall was exposed to high dose, such as smaller rectal wall volume, inclusion of rectum within the 50% isodose on the isocentre slice and higher rectal D_{max}	QoL outcomes rather than bNED by dose level only. Good statistical tests used. See study for detailed outcomes

continued

TABLE 41 *Three-dimensional conformal radiotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Zelefsky *et al*. (1998, USA)[89]	NAAD and 3D-CRT	$n = 213$ Median age = 68 years (52–83 years) T1c = 16% T2a = 5% T2b = 17% T2c = 21% T3 = 41% Median iPSA = 15.3 ng/ml (1–560 ng/ml) Median dose = 75.6 Gy (64.8–81 Gy) Subset NAAD + 3D-CRT: $n = 34$ 3D-CRT only: $n = 117$	1989–1995 retrospective case series Median follow-up 3 years (1–7 years) 3-month neoadjuvant androgen ablation of leuprolide acetate and flutamide before 3D-CRT. 5-year disease-free survival by PSA relapse-free survival and local control by freedom from anatomical disease progression (local recurrence/distant metastases) assessed with routine sextant biopsies every 2.5 or more years after 3D-CRT: $n = 34$ (subset). (Outcomes in this group later compared with $n = 117$ 3D-CRT-only group.) Distribution of times to relapse of disease by Kaplan–Meier method; patients classified into prognostic groups by iPSA 10 ng/ml, T-stage 1–2 and Gleason score. Differences between time-adjusted incidence rates evaluated with Mantel log-rank test for censored data. Relative impact of covariates affecting time-adjusted outcomes by stepwise Cox proportional hazards regression model	The significant predictors for improved outcome as identified in multivariate analysis included iPSA ≤ 10 ng/ml ($p < 0.001$), NAAD-induced preradiotherapy PSA nadir ≤ 0.5 ng/ml ($p < 0.001$) and clinical stage ≤ T2c ($p < 0.04$). The 5-year PSA relapse-free survival rates were 93, 60 and 40% for patients with pretreatment PSA levels ≤ 10, 10–20 and > 20 ng/ml, respectively ($p < 0.001$) Patients with preradiotherapy nadirs of ≤ 0.5 ng/ml after 3 months of NAAD had a 5-year PSA RFS rate of 74%, vs 40% with higher nadir levels ($p < 0.001$). Incidence of positive biopsy among 34 patients pretreated with NAAD was 12%, vs 39% for 3D-CRT only who underwent a biopsy ($p < 0.001$). 5-year PSA RFS for unfavourable risk patients treated with 3D-CRT alone was 38% compared with 32% for the 3D-CRT-only group ($p = 0.20$). No differences in the 5-year DFS (74 vs 68%, $p = 0.77$) and overall survival rates (87 vs 82%, $p = 0.76$) were observed for patients treated with or without NAAD. Incidence of distant metastases at 5 years was 22%	This study includes a subset of the original cohort of 213 patients later retrospectively compared with another 3D-CRT-only treatment group, although this was not clear from the summary information presented. These 2 groups do not seem matched in any way, but are compared simply for the influence of NAAD. Some statistical controlling for these differences has presumably been carried out

continued

TABLE 41 *Three-dimensional conformal radiotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Zelefsky *et al*. (1999, USA)[82]	High-dose, 3D-CRT. Some neoadjuvant ADT	*n* = 743 Median age = 69 years (51–84 years) T1c = 163 (22%) T2a = 239 (33%) T2b = 146 (20%) T3 = 195 (26%) Dose: 13% = 64.8 Gy; 36% = 70.2 Gy; 43% = 75.6 Gy; 8% = 81 Gy. 29% = 3 months neoadjuvant androgen deprivation	1988–1995 case series 5 years, median follow-up 42 months (18–109 months) of late toxicity graded by RTOG morbidity scoring scale Distribution of times to develop late toxicity by Kaplan–Meier method. Between-time adjusted incidence rates using Mantel log-rank test for censored data. Multivariate analysis with Cox proportional hazards regression model. Late complications determined as of the time of analysis in 1998	Late GI and GU toxicities absent or minimal in 90% of patients 11% likelihood of developing grade 2 and 0.75% grade 3 toxicity. Doses of 75.6 Gy ($p < 0.001$) and history of diabetes ($p = 0.01$) and presence of acute GU symptoms during treatment ($p = 0.02$) as independent predictors of grade 2 late GU toxicity. 39% of previously potent patients became impotent following treatment, with a 5-year actuarial risk of potency loss of 60%. Doses of 75.6 Gy ($p < 0.001$) and neoadjuvant androgen deprivation ($p = 0.01$) independent predictors of erectile dysfunction ($p = 0.01$)	Only 18% patients followed for 5 years. Includes 29% of patients with large prostate volume treated with neoadjuvant androgen deprivation through RT to reduce target size

continued

TABLE 41 *Three-dimensional conformal radiotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Zelefsky *et al*. (2001, USA)[72]	3D-CRT and IMRT	*n* = 1100 Median age = 69 years (46–86 years) T1c = 284 (26%) T2a = 354 (32%) T2b = 200 (18%)	1988–1998 case series Median follow-up = 60 months Local control by sextant biopsies; bNED based on ASTRO definitions of post-treatment sPSA. Late toxicity classified by RTOG morbidity scale. Patients classified into 3 prognostic risk groups (favourable, intermediate and unfavourable) by iPSA, Gleason score and clinical stage Distribution of PSA RFS by Kaplan–Meier product-limit method. Differences in time-adjusted incidence rates by Mantel log-rank test for censored data. Influence of covariates by stepwise Cox proportional hazards regression model. Results given with 95% CIs	At 5 years, bNED was 85, 58 and 38% for favourable, intermediate and unfavourable respectively (p = 0.001). Radiation dose was the most powerful variable influencing PSA RFS in each prognostic risk group. 5-year actuarial bNED for favourable group with 64.8–70.2 Gy was 77%; with 75.6–86.4 Gy was 90%; for intermediate risk group 50 vs 70% (p = 0.001); and 21% vs 47% in unfavourable group (p = 0.002). 10% receiving 81 Gy had a positive biopsy 2.5 years after treatment vs 23% after 75.6 Gy, 34% after 70.2 and 54% after 64.8 Gy. Incidence of toxicity after 3D-CRT was dose dependent, with a 5-year actuarial rate of grade 2 toxicity in patients receiving 75.6 Gy 14% vs 5% in those treated with lower doses (p < 0.001). Treatment with IMRT significantly decreased the incidence of late grade 2 rectal toxicity: 3-year actuarial incidence in 189 subjects receiving 81 Gy was 2%, vs 14% in 61 receiving the same dose by 3D-CRT (p = 0.005). 5-year actuarial rate of grade 2 GU toxicity with 75.6 3D-CRT was 13%, vs 4% in those treated up to lower doses (p = <0.001). IMRT did not affect the incidence of urinary toxicity	See earlier study by Zelefsky *et al*.,[182] which forms a precursor to this study, in that escalation to dose 81 Gy required enhanced conformality, such as that provided by IMRT, to decrease the risk of toxicity

continued

TABLE 41 *Three-dimensional conformal radiotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Zelefsky *et al*. (1999, USA)[73]	3D-CRT and transperineal I-125 brachytherapy with some neoadjuvant ADT	$n = 282$ 3D-CRT: $n = 137$ Median age = 68 years Median dose = 70.2 Gy iPSA = 6.6 **TPB**: $n = 145$ Median age = 64 years Median dose = 150 Gy iPSA = 6.1 All T1c–T2b; Gleason $\leq$ 6	1989–1996 retrospective comparison of outcomes between 2 case series. Biochemical relapse by PSA 5 year PSA RFS, median follow-up 3D-CRT = 36 months; TPB = 24 months Also QoL outcomes: rectal, urinary toxicity and sexual potency. Analyses with Kaplan–Meier method; Mantel log-rank test for censored data; covariates with stepwise Cox proportional hazards regression model	5-year bNED was 88% for 3D-CRT patients and 82% for TPB patients ($p = 0.09$). Protracted grade 2 urinary symptoms (> 1 year post-therapy) were more prevalent in TPB (31%), with median duration 23 months, than with 3D-CRT (8% 5 year actuarial figures) with acute grade 2 symptoms resolved within 4–6 weeks. Grade 2 late rectal toxicity at 5 years was 6% for 3D-CRT and 11% for TPB. No grade 3 or higher late rectal toxicity. Post-treatment erectile dysfunction at 5 years was 43% for 3D-CRT and 53% for the TPB group ($p = 0.52$). In multivariate analysis, neither mode of therapy, including NAAD, clinical stage age, nor dose had an impact on biochemical outcome in these patients	This study represents a comparison of outcomes of 2 unmatched separate series and compared retrospectively. The outcomes for these separate studies have also been published separately. Multivariate analyses show the limited value of a direct comparison between outcomes of these 2 series

NAAD: neoadjuvant androgen ablation; GI: gastrointestinal; GU: genitourinary; DVH: dose–volume histogram.

TABLE 42 *Intensity-modulated radiotherapy (primary studies)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Evidence level 5					
Kupelian *et al*. (2001, USA)[96]	SCIM-RT and 3D-CRT. Adjuvant ADT	*n* = 292 SCIM-RT: *n* = 191 3D-CRT: *n* = 101 Age = ?? T1–T2a = 79% T2b–T2c = 14% T3 = 7% PSA = 8.7 ng/ml (1.1–95.0 ng/ml) 50% with Gleason ≤ 6 69% high risk with T3, Gleason ≥ 7 or PSA > 10	1998–2000 parallel case series comparison Median follow-up = 9 months Acute and late urinary and rectal toxicity by RTOG toxicity scores 0–3. SCIM-RT delivered at 70.0 Gy at 2.5 per fraction; 3D-CRT delivered at 78.0 Gy at 2.0 per fraction 64% received adjuvant ADT (median duration 6 months). Multivariate factor analysis of age (continuous), race (black vs white) androgen (deprivation) and volume of rectum receiving prescription dose (VrPr of ≤ 15 ml vs > 15 ml)	**Rectal toxicity scores**: SCIM-RT: 0 = 30%, 1 = 55%, 2 = 14%, 3 = 0%; 3D-CRT: 0 = 14%, 1 = 67%, 2 = 19%, 3 = 0% **Urinary toxicity scores**: SCIM-RT: 0 = 17%, 1 = 62%, 2 = 20%, 3 = 1%; 3D-CRT: 0 = 22%, 1 = 58%, 2 = 20%, 3 = 0% No grade 3 urinary or rectal complications with SCIM-RT. Actuarial late rectal grade 2 toxicity at 18 months was 10% after SCIM-RT, vs 12% after 3D-CRT. Only VrPr was a significant independent predictor of grade 2–3 late rectal toxicity. 15 SCIM-RT (7%) and 20 3D-CRT (20%) subjects had VrPr > 15 ml. Grade 2–3 late rectal toxicity at 18 month for SCIM-RT with VrPr > 15 ml was 29%, vs 5% with VrPr ≤ 15 ml. With 3D-CRT, grade 2–3 late rectal toxicity at 18 month with a VrPr > 15 ml was 25%, vs 8% with a VrPr ≤ 15 ml SCIM-RT of 70.0 Gy at 2.5 per fraction had an acute and late toxicity profile at ≤ 18 months similar to that of 3D-CRT of 78.0 Gy at 2.0 per fraction. Grade 2 actuarial combined rectal toxicity rate was low (10%) at 18 months, but increased when rectal volumes > 15 ml received 70 Gy with SCIM-RT. Only 7% of SCIM-RT cases received 70 Gy to > 15 ml of the rectum	This is a study comparing QoL outcomes of acute and late urinary and rectal toxicity between 2 treatment modalities. There is no detailed description of statistical methodology, although this is clearly indicated by reports of multivariate factor analysis and reports of actuarial grade 2 toxicity rates

continued

TABLE 42 *Intensity-modulated radiotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Kupelian *et al.* (2001, USA)[95]	SCIM-RT (70 Gy at 2.5 Gy per fraction). Some adjuvant ADT	$n = 97$ SCIM-RT: $n = 51$ 3D-CRT: $n = 46$ Mean age = 69 years (53–84 years) T1c = 28 (55%) T2a = 17 (33%) T2b/c = 5 (10%) T3 = 1 (2%) Median iPSA = 8.3 ng/ml (1.1–90.0 ng/ml) Details provided Gleason $\leq$ 6 = 32 (63%); $\geq$ 7 = 19 (37%) 21 (41%) with adjuvant ADT	1998–1999 parallel case series comparison Follow-up = 18 months Late urinary and rectal toxicity and QoL. RTOG toxicity scores 0–3. SCIM-RT delivered at 70.0 Gy at 2.5 per fraction; 3D-CRT delivered at 78.0 Gy at 2.0 per fraction 41% received adjuvant ADT (median duration 6 months) Multivariate factor analysis of age, race, coverage of seminal vesicles, acute rectal toxicity and androgen deprivation, and volume of rectum receiving prescription dose of 70 Gy	Dose prescribed to an isodose line ranged from 82 to 90% (mean 87.2%). 73.5–78.5 Gy (average 75.3 Gy) mean doses to the individual prostate. Grade 1 late urinary toxicity = 1; grade 1 late rectal toxicity = 4; no grade 2/3 late urinary/rectal complications. Actuarial rectal bleeding at 18 months was 7%. No differences in scores from urinary, bowel, hormonal and overall QoL domains between SCIM-RT subjects and those treated with CRT. Only absolute volume of rectum receiving 70 Gy (ml) was independently predictive of late rectal bleeding ($p = 0.036$). Overall physical and mental QoL scores were also nearly identical to scores reported for general US population. At 24 months the actuarial biochemical failure rate for 51 SCIM-RT cases was 4% vs 7% for 73 CRT cases ($p = 0.47$)	Limited sample size. The controls for this study are not matched, and only 24 of the SCIM-RT group completed EPIC QoL questionnaires at 24 months post-therapy to be compared with scores from the 46 3D-CRT subjects; therefore, this cannot be seen as a proper matched control comparison, despite the report that the '2 groups were similar in all aspects, except for a higher proportion of CRT patients receiving androgen deprivation 76% vs 21%'. The RTOG outcomes for the 51 SCIM-RT subjects are probably the most valid outcome data. Complications outcomes also provided for 73 CRT patients, but 46 used for the comparison, with no further explanations, e.g. were these respondents from a larger cohort? Data could be presented more clearly

continued

TABLE 42 *Intensity-modulated radiotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Shu *et al*. (2001, USA)[94]	High-dose 3D-CRT or IMRT	$n = 44$ $D_{max} \leq 82$ Gy **3D-CRT**: $n = 26$ Median age = 69 years (53–76 years) iPSA = 9.8 ng/ml (2.9–62.8 ng/ml) T1 = 4 T2 = 17 T3 = 5 **IMRT**: $n = 18$ Median age = 70 years (50–79 years) iPSA = 12.0 ng/ml (4.4–39.5 ng/ml) T1 = 2 T2 = 10 T3 = 6 Gleason scores provided	1992–1998 case series Median follow-up (all patients) = 23.1 month (10.0–84.7 months) RTOG acute and late toxicity scales for late GI and GU morbidity Median Dose = 84.5 Gy (82.0–96.7 Gy) Subject age, iPSA and stage well matched for either treatment, with all receiving a D_{max} of $\geq$ 82 Gy Median follow-up: 3D-CRT = 30.1 months (14.6–84.7 months; IMRT = 18.7 months (10.0–31.2 months). IMRT subjects had higher Gleason scores Kaplan–Meier method for calculation of rates of complications. Univariate analyses of prognostic factors predictive for late GI and GU morbidity. 2-tailed Fisher's exact test for treatment-related toxicity	59.1% and 34.1% developed some level of acute GU and GI toxicity, respectively. One patient experienced grade 3 acute GI toxicity. No other grade 3 or greater acute toxicity was observed. The 2-year actuarial rates for freedom from late GI and GU morbidity were 77.1% (95% CI 60.4 to 87.5%) and 79.5% (95% CI 62.7 to 89.3%), respectively. Although no $\geq$ grade 3 late GU morbidity observed, 3 subjects had grade 3 GI morbidity Whole pelvis radiation correlated significantly with the incidence of both acute GI toxicity ($p = 0.001$) and acute GU toxicity ($p = 0.021$). No significant difference in acute GU toxicity noted between 3D-CRT and IMRT	A small sample series, matched except for IMRT with higher Gleason scores. Good range of statistical tests employed and outcomes reported for different levels of data analysis

continued

TABLE 42 *Intensity-modulated radiotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Zelefsky *et al*. (2001, USA)[72]	3D-CRT and IMRT	n = 1100 Mean age = 69 years (46–86 years) T1c = 284 (26%) T2a = 354 (32%) T2b = 200 (18%) 3D-CRT: n = 871 64.8–75.6 Gy: n = 810 81 Gy: n = 61 **IMRT**: 81–86.4 Gy: n = 229	1988–1998 case series Median follow-up = 60 months Local control by sextant biopsies; bNED based on ASTRO definitions of post-treatment sPSA. Late toxicity classified by RTOG morbidity scale Patients classified into 3 prognostic risk groups (favourable, intermediate and unfavourable) by iPSA, Gleason score and clinical stage Distribution of PSA RFS by Kaplan–Meier product-limit method. Differences in time-adjusted incidence rates by Mantel log-rank test for censored data. Influence of covariates by stepwise Cox proportional hazards regression model. Results given with 95% CIs	At 5 years, bNED was 85, 58 and 38% for favourable, intermediate and unfavourable, respectively (p =0.001). Radiation dose was the most powerful variable influencing PSA RFS in each prognostic risk group. 5-year actuarial bNED for favourable group with 64.8–70.2 Gy was 77 vs 90% with 75.6–86.4 Gy. For intermediate group 50 vs 70% (p = 0.001); and for unfavourable group 21% vs 47% (p = 0.002). 10% receiving 81 Gy had a positive biopsy 2.5 years after treatment vs 23% after 75.6 Gy, 34% after 70.2 and 54% after 64.8 Gy. Incidence of toxicity after 3D-CRT was dose dependent, with 5-year actuarial rate of grade 2 toxicity in patients receiving 75.6 Gy 14% vs 5% in those treated with lower doses (p < 0.001). Treatment with IMRT significantly decreased the incidence of late grade 2 rectal toxicity: 3-year actuarial incidence in 189 subjects receiving 81 Gy was 2%, vs 14% in 61 receiving the same dose by 3D-CRT (p = 0.005). 5-year actuarial rate of grade 2 GU toxicity with 75.6 3D CRT was 13% vs 4% in those treated with lower doses ($p \leq$ 0.001). IMRT did not affect the incidence of urinary toxicity	See earlier study by Zelefsky *et al*.,[82] which forms a precursor to this study, in that escalation to a dose of 81 Gy required enhanced conformality, such as that provided by IMRT, to decrease the risk of toxicity

TABLE 43 *Cryotherapy (primary studies)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Evidence level 5					
Bahn and Lee (2000, USA)[101]	Cryosurgical ablation therapy for prostate cancer Treatment includes temperature monitoring and uses 6–8 probes. 68 patients had failed radiotherapy and 20 patients failed initial cryosurgery	*n* = 643 Median age not reported Patients grouped according to pretreatment and grade Stage T1–T4 PSA and grade reported	Retrospective study of patients treated between 1993 and 1998 in one institution Outcome = 5-year actuarial BDF rates and complications Follow-up not reported	5-year actuarial BDF rates were 80% in T1–T2, 66% in T3–T4 with PSA < 1.0 as end-point. BDF was 68% and 47% when PSA < 0.5 was the end-point An earlier study[168] showed that out of 290 patients who were contacted 4.3% had stress incontinence, 85% impotence, 0.4% urethrorectal fistula and 9% outlet obstruction. 96% said that they would choose cryotherapy again	This study is an up-to-date summary of other studies: 2 on clinical effectiveness from 1995 and 1997, and 1 on complications from 1999, all from the same institution and the same authors[168–170]
Cohen *et al*. (1996, USA)[171]	Cryosurgical ablation of the prostate Includes patients who have had previous treatment and those who have not (virgin patients)	*n* = 383 Stage A–D Median age not reported iPSA and grade reported by treatment group	Retrospective study of patients treated between June 1990 and May 1994 in one institution Outcomes = PSA levels and negative biopsies at 21 months; also complications Mean follow-up = 32 months (21.5–57.4 months) Outcomes = PSA failure and positive biopsy rates	Of the virgin group 17/83 (21%) had a positive biopsy at 21 months. Of the androgen deprivation group 4–31 (13%) had a positive biopsy At 21 months the median PSA for the virgin group was 1.2 ng/ml. For the ADT group it was 1.85 Complications included urethral sloughing in 10% of patients, 4% were incontinent > 6 months, 1% had urinary retention and 4% had urethral stricture	No Kaplan–Meier methods used

continued

TABLE 43 *Cryotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Coogan *et al*. (1995, USA)[172]	Percutaneous cryoblation of the prostate	*n* = 87 Mean age = 65.4 years (50–80 years) Stage T1–T3 PSA and grade reported	Retrospective study of patients treated between Feb 1993 and Aug 1994 in one institution Median follow-up = 12 months, mean = 9.3 (1–24 months) Outcomes = PSA levels at 12 months and positive biopsy results; complications	Median PSA level at 12 months was 0.55 ng/ml with a 17% positive biopsy rate at 3 months. When the positive lymph node, radiation failure and postoperative HT groups were removed from analysis, the median PSA level was 0.8 with a 5% biopsy rate Complications included scrotal swelling 100%, impotence at 1 year 47%, urethral slough 9%, urinary retention 5%, urinary tract infection 4% and incontinence 3%. Other complications reported	No Kaplan–Meier methods used
Derakhshani *et al*. (1998, Germany)[104]	Cryoblation of localized prostate cancer Patients did not have prior radiation therapy or surgery. 30/48 received ADT before surgery Treatment was ultrasound guided and included urethral warming	*n* = 48 Mean age = 67.2 years (56–76 years) Stage T1–T3 T1 = 7 T2 = 18 T3 = 15 PSA and grade reported	Retrospective study of patients treated between Oct 1995 and Aug 1997 in one institution Follow-up = 4–27 months Outcomes = PSA failure PSA remaining above 1 ng/ml at 6 months post (operatively); complications and QoL	83% had a 6-month biopsy and PSA follow-up In T1 group 14.3% had PSA failure and negative biopsies. In T2 33.3% had PSA failure; of these, 3 patients had positive biopsies. In T3 40% had PSA failure and 4 had positive biopsies 68.6% had impotence after 6 months, 35.4% had dysuria, 2.9% had prolonged retention, 10.4 had 2nd TURP, 16.7% had scrotal haematoma and 10.4% had incontinence	No Kaplan–Meier methods used

continued

TABLE 43 *Cryotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Koppie *et al*. (1999, USA)[102]	Efficacy of cryosurgical ablation of clinically localised prostate cancer Urethral warming took place. Pelvic lymphaenectomy was performed before cryosurgery as indicated Patients split into low- and high-risk groups based on PSA, grade and stage	*n* = 176 Mean age = 68.6 years Stage T1–T4 Mean Gleason grade = 6.54 from biopsy iPSA = 0.7–235 ng/ml	Retrospective study of patients treated between June 1993 and Jan 1998 in one institution Outcomes = actuarial biochemical (PSA) RFS (Kaplan–Meier) at 1 and 3 years Mean follow-up = 30.8 months 60% followed for > 24 months and 36% for > 36 months	Actuarial biochemical RFS 1 and 3 years after cryosurgery, was 82 and 69%, respectively, for 22 low-risk patients, and 58 and 45% for high-risk patients (p = 0.048)	RFS is presented only for patients receiving initial cryotherapy. Neither patients having repeat treatment nor failed radiation therapy patients were included
Long *et al*. (1998, USA)[97]	Cryosurgical ablation of the prostate in patients with clinically localised prostate carcinoma 45 patients had NHT if gland volumes > 50 ml at time of entry to study Treatment included a urethral warming device	*n* = 145 Median age = 65.6 years (46–82 years) Stage T1c–T3c Mean iPSA = 10.1 ng/ml Gleason = 5–10	Prospective pilot study started in Jan 1993 in one institution Outcomes = time to treatment failure (Kaplan–Meier curves) = PSA > 0.3 ng/ml. Also Kaplan–Meier estimates of progression-free intervals. Progression = positive biopsy, a PSA rise > 1.0 (nadir < 1.0) or 3 successive rises (nadir > 1.0). Also complications Mean follow-up = 34 months (12–51 months)	Overall at 42 months the likelihood of maintaining a PSA of < 0.3 after treatment was 59% and a value < 1.0 was 66%. Overall, 56% of patients exhibited no evidence of disease progression. For early patients this was 42% and for more recent cases 58% At current follow-up 160 biopsies have been performed and 16% were positive 70% of patients had potency before treatment; after treatment it was 12%. 15% experienced clinical morbidity, mostly bladder outlet obstruction	Treatment results were more favourable for the 115 most recent cases than for the first 30 patients treated

continued

TABLE 43 *Cryotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Long *et al*. (2001, USA)[103]	Outcomes for cryosurgical ablation of the prostate in localised prostate cancer compared with outcomes from EBRT Patients separated into low-, moderate- and high-risk groups based on grade, stage and PSA ADT used for 3–8 months in 30% of patients	*n* = 975 Median age not reported Stage T1–T4 No metastases PSA and grade reported in detail	Retrospective study of database of patients treated between 1993 and 1998 in multiple institutions Outcome = BFS: 2 types, < 0.5 ng/ml and < 1.0 ng/ml (Kaplan–Meier method) Median follow-up = 24 ± 16.5 months	25% of patients were in the low-risk group, 34 in the moderate and 41 in one high-risk group For 5-year actuarial BFS < 0.5, the range was 36–61%. For BFS < 1.0, the range was 45–76%. Overall positive biopsy rate was 18% Complications included impotence 93%, incontinence 7.5%, rectourethral fistula 0.5% and TURP 13% EBRT BFS rates range from 29 to 64% in 2 studies that the authors chose to look at	BFS for other radiotherapy treatments are reported. The conclusion is that BFS rates for cryosurgery and radiotherapy are similar
Mack *et al*. (1997, Austria)[100]	Open perineal cryotherapy in patients with locally confined prostate cancer 3–4 months after cryosurgery all patients underwent an extensive transurethral resection of the prostate and/or perineal biopsy with at least 4 random biopsies	*n* = 66 Median age = 68.2 years (49–78 years) Stage T1c–T3c Grade of tumour reported No iPSA given	Retrospective review of patients treated between 1976 to 1989 in one institution Outcomes = positive biopsies and overall survival (Kaplan–Meier method); complications Mean follow-up = 8.5 years	For patients with stage T1c–T2b 66% had positive biopsies, and for patients with stage T2c–T3c 87% had positive biopsies To date, 28 patients have died. Mean overall survival in this group was 7.11 years for T1c–T2b and 7.29 years for T2c–T3c. Mean overall survival for 38 remaining patients is 8.5 years Complications occurred in 23% of patients. These included stress incontinence, impotence and urethrorectal fistula	

continued

TABLE 43 *Cryotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Robinson *et al*. (1999, Canada)[98]	QoL in men treated with cryosurgery for localised prostate cancer Questionnaires issued at 6 weeks, and 3, 6, and 12 months post-treatment	*n* = 70 Median age = 66 years (51–77 years) Stage T2–T3 Grade range = 5–9 PSA range = 1.5–30	Prospective, non-controlled, non-randomised study from one institution. Outcomes = all aspects of QoL from Functional Assessment of Cancer Treatment–Prostate (FACT-P). Follow-up = 12 months Wilcoxon tests were performed to assess differences between baseline scores and scores at 6 weeks and 12 months	By 12 months postoperation most of the FACT-P subscales had returned to pretreatment levels. Sexual function was most affected by cryosurgery and the score was still significantly below baseline at 12 months	
Saliken *et al*. (1999, Canada)[99]	Outcome and safety of TRUS-guided percutaneous cryotherapy for localised prostate cancer	*n* = 71 Median age = 66 years Stage T1–T3 PSA ≤ 30 ng/ml Grade reported in detail	Prospective, non-controlled, non-randomised study from one institution. Outcomes = clinical evidence of residual disease, PSA levels and complications Follow-up = 10–36 months	Overall, 68–69 patients had negative biopsy results (10 patients had repeat treatment for positive results). At 1 year 43/64 (67%) had an undetectable PSA level 4 patients had direct major complications. All patients suffered impotence and acute transient retention in the short term	No Kaplan–Meier methods used
Wake *et al*. (1996, USA)[173]	Cryosurgical ablation of the prostate for localised adenocarcinoma Ultrasound-guided cryosurgery. Does not report on temperature monitoring	*n* = 104 Median age = 69 years (52–83 years) Stage T1–T3 iPSA, stage and grade reported in detail	Retrospective study of patients treated since Aug 1993 in one institution Outcomes = postoperative biopsy results, stage and PSA Follow-up not reported in detail	Of the 63 patients who had a postoperative biopsy, 47 had a negative result Disease-free rate (as determined by negative biopsy and low PSA levels) was 95% at 3 months 64/100 patients experienced complications, mostly bladder outlet obstruction	No Kaplan–Meier methods used

continued

TABLE 43 *Cryotherapy (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Wong *et al*. (1997, USA)[174]	Cryosurgery as a treatment for prostate cancer 12 patients treated under ultrasound guidance. The remainder were also temperature monitored	*n* = 83 Median age = 69 years, (53–84 years) Stage T2–T3 PSA, grade and stage reported in detail 22 patients had previous treatments for prostate cancer	Retrospective study of patients treated between Apr 1993 and Sept 1995 in one institution Outcomes = postoperative biopsy results and complications Follow-up = 6–24 months	Of the 12 patients who did not have temperature monitoring, 10 (83%) had positive biopsies Of the 66 remaining patients who had biopsies, 6 (9%) had positive results The most common complication of cryosurgery, urethral sloughing, was experienced by 47% of patients	No Kaplan–Meier methods used

TABLE 44 *High-intensity focused ultrasound (primary studies)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Evidence level 5					
Beerlage *et al*. (1999, The Netherlands, Germany)[106]	Transrectal HIFU with and without RP	**HIFU**: *n* = 111 Age = >70 years T1–T3 iPSA < 25 ng/ml **HIFU+ RP**: *n* = 14 T2c–T4 Mean age = 62 years (55–69 years) Mean iPSA = 10.8 ng/ml (3.5–20 ng/ml)	2 parallel unmatched case series (HIFU + RP at Nijmegen; HIFU only at Munich) Histological and clinical outcome; no formal length of follow-up given	For HIFU + RP group, complete necrosis seen in treated region in all cases, but on dorsal border incomplete destruction of tissue observed, with small residual vital tumour focus in 4 cases. In the HIFU-only group, a negative biopsy was recorded for all in whom the entire prostate was treated; a negative biopsy and PSA < 4 ng/ml obtained in 60% and a PSA nadir < 0.5 ng/ml in 55%. Some QoL outcomes reported	These are the reports of outcomes of HIFU intervention, and neither group represents a serious study with a formal design as such; the patients are not particularly comparable in terms of age, disease stage, etc. In the larger series, the patients were those for whom surgery was not an option anyway. There are rather limited data provided on patient characteristics such as Gleason score and there is no report of statistical methodology used to analyse for patient subgroups based on covariates. In the HIFU + RP group, 6 of 14 patients were found to have a more advanced stage of disease upon biopsy, i.e. T3–T4 and the sample size is too small to make an adequate evaluation of outcome. In the second group, a rather limited inference on the efficacy of the intervention can be made based on patient outcomes, while 49 patients had unilateral or bilateral treatments and 62 had global (whole prostate treated), so these are not comparable. In neither is there a specified formal follow-up period defined for a given outcome, e.g. bNED at 5 years

continued

TABLE 44 *High-intensity focused ultrasound (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Chaussy and Thuroff (2000, Germany)[175]	HIFU (Ablatherm). Some neoadjuvant androgen (LH-RH) deprivation	*n* = 184 T1–2, NxMo Mean age = 72 years (59–81 years) 80% Gleason 5–7 Mean iPSA = 2.2 ng/ml	1996–1997 case series Patient criteria unsuitable for surgery. 3 year results Mean follow-up = 193 days (0–903 days) Biopsy and PSA. Also QoL outcomes 184 patients with total of 232 transrectal HIFU sessions	80% of patients cancer free by sextant biopsy, and of those with residual cancer, tumour mass reduced by > 90%. Nadir PSA < 4 ng/ml in 97%, including 61% with < 0.5 ng/ml. No severe side-effects (fistula, grades 2/3 incontinence, rectal mucosal burn) seen. Mild stress incontinence decreased to 4% with 'security margin' of 5 mm. Potency preserved in 33.3% of men with global treatment	Statistical methodology not reported. Cohort includes a group of patients (48%) with hormonal manipulation. Several had more than one HIFU session. Treatment methodology reported as not standardised until 1997, after the conclusion of this (trial?) series
Chaussy and Thuroff (2001, Germany)[175]	HIFU	Same as above	Same as above	Same as above	
Gelet *et al*. (1999, France)[109]	HIFU	*n* = 50 No. of sessions = 113 Mean age = 70.7 years (61–86 years) T1–T2 Mean iPSA = 9.61 ± 7.42 ng/ml Gleason 4–8	Case series; no dates specified Patient criteria unsuitable for surgery. Biochemical and clinical (local control) freedom from disease by PSA and random control sextant biopsies Median follow-up 24 months (3–46) Patients divided into 4 groups by response for evaluation of therapy	Overall local control achieved in 80%. Group 1 (complete response) included 28 (56%) with no residual cancer and PSA < 4 ng/ml (mean 0.93 ng/ml); group 2 (biochemical failure) 3 (6%) no residual cancer, PSA > 4 ng/ml (mean 6.22 ng/ml); group 3 (biochemical control) 9 patients with residual cancer (mean positive biopsies 1.1 of 6) and PSA < ng/ml (mean 0.90 ng/ml); group 4 (failures) 10 (20%) with residual cancer (mean positive biopsies 1.9 of 6), PSA > 4 ng/ml (mean 8.9 ng/ml). Group 4 required HT (*n* = 3) and RT (*n* = 5). Complication rate with first prototype device was 50%, decreasing to 17% with second prototype	Each patient treated for 1–4 sessions in total. Cohort includes 2 salvage procedures for local recurrence. Statistical methodology not reported. The study reports preliminary results only

continued

TABLE 44 *High-intensity focused ultrasound (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Gelet *et al*. (1996, France)[110]	Transrectal HIFU	*n* = 14 Mean age = 72.5 years T1, T2 iPSA = 12 ± 10 ng/ml	Case series (no dates recorded) Non-candidates for surgery. Biochemical and local control by PSA and sextant biopsy Mean follow-up = 380 days	Complications occurred in 9 of 14 patients (64%). Early complications in 6 (included rectal burns, urinary retention, transient incontinence); late complications in 5 (incontinence and bladder neck stenosis). Median PSA nadir (1.79 ± 2.35 ng/ml) achieved at 6 months; final PSA 2.94 ± 3.27. No residual cancer in 7 patients (50%) after several random sextant biopsies. Residual cancer in the other 7 (50%), 4 of whom required complementary therapy	This is an earlier report on treatment outcome of a pilot study for a small case series by Gelet *et al*. (1998).[109] The instrument used, Ablatherm 1.0™, is a prototype and this is still an investigational procedure. No statistical methodology reported. The number in this study is too small to draw any clear conclusions on efficacy
Gelet *et al*. (2001, France)[111]	HIFU. Some NHT	*n* = 102 Mean age = 70.8 ± 6.13 years T1b,c–T2c Mean iPSA = 8.38 ± 4.8 ng/ml, prostate vol. = 33.3 ± 16.71 cm^3	Case series (no dates recorded) Non-candidates for surgery. Disease progression (failure) defined by positive sample at control biopsy, biochemical control by PSA, or by 3 consecutive increases in PSA in case of negative biopsy Mean follow-up = 19 months (3–76 months)	Overall success rate was 66%. Statistically significant variations in overall success, with more favourable outcome by iPSA (≤ 10 ng/ml, 73 vs 50%, $p = 0.02$); Gleason score was ≤ 6 (81 vs 46%, $p < 0.001$); pretreatment biopsy evidenced 1–4 positive samples (68 vs 40%, $p = 0.01$)	A later study by Gelet *et al*. (see others above) includes 8 patients for salvage HIFU after failed primary treatment, and 8 with neoadjuvant androgen therapy. Some statistical analyses performed, methodology not reported

continued

TABLE 44 *High-intensity focused ultrasound (primary studies) (cont'd)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Gelet *et al*. (2000, France)[112]	HIFU. NHT	$n = 82$ Age = 71 ± 5.7 years T1–T2 iPSA = 8.11 ± 4.64 ng/ml, prostate vol. = 34.9 ± 17.4 cm^3	Consecutive case series Non-candidates for surgery. Disease progression (clinical control) as any positive biopsy by randomised sextant control biopsies, or bNED by 3 successive PSA increases. Treatment-related complications (continency and potency) by questionnaire Mean follow-up = 17.6 months (3–68.5 months) Actuarial survival rates by Kaplan–Meier method. Log-rank test for significance of difference in DFS with $p < 0.05$ as significant	Overall, 62% of patients exhibited no evidence of disease progression 60 months after therapy. The DFS rate was 68% for the moderate-risk group of 50 patients (iPSA < 15.0 ng/ml, Gleason < 8; prostate vol. < 40 cm^3, no. positive biopsies < 5). For the low-risk group of 32 patients (iPSA < 10 ng/ml, Gleason < 7), the DFS rate was 83%. Acute urinary symptoms were common 2 months after HIFU. 13% with stress incontinence. Potency preserved in 23% of previously potent patients	Another case series by Gelet *et al*. (see others above). Reports statistical methodology (unlike others) and generally seems more robust. Includes 4 patients with local recurrence after primary therap, 7 patients with NHT, and 2 with metastases who had also received HT
Kiel *et al*. (2000, Germany)[113]	Transrectal HIFU	$n = 62$ Mean age = 67.5 ± 7.8 years T1–T3 Mean iPSA = 7.64 ± 5.26 ng/ml, prostate vol. = 21.4 ± 7.9 cm^3	1997–2000 case series Local disease control by PSA, control sextant biopsies and transrectal, colour-coded duplex sonography at 1, 3, 6, 12 and 24 months Median follow-up = 15 months (5–29 months) Patients classified into 4 groups: 1: T1–T2, iPSA < 15 ng/ml; Gleason < 7, vol. < 30 cm^3, ≤ 4/6 positive random biopsies; 2: T1–T3, no PSA/Gleason limitations; 3: local recurrence after RP, radiation, etc.; 4: local debulking Therapy evaluated in 3 categories: 1: complete response and no residual cancer; 2: biochemical control + residual cancer; 3: failure	Group 1 = 33/48 (68.7%), no residual cancer, PSA < 4 ng/ml; 18 (55%) of these had a PSA < 0.5 ng/ml, 9 (27%) 0.5–1.0 and 6 (18%) 1.0–4.0 ng/ml. Group 2 = 8/48 (16.7%) with small residual cancer and PSA < 4 ng/ml, Group 3 = failure 7/7 (14.6%) with residual cancer and PSA > 4 ng/ml Potency was preserved in 55.6% of previously potent men. 11.5% previously impotent men regained potency. Some level of rectal and urinary complications consequent on earlier (failed) therapies (RP, EBRT, etc.). 20 patients (32.3%) required transurethral intervention to remove necrotic obstructive tissue	This study represents a mix of subjects, 11 of whom represent salvage interventions of previous failures of treatment, and others for whom surgery was not an option. Statistical methodology not reported. Few subjects and not a long follow-up period. bNED as < 4 ng/ml does not compare favourably with other studies as less than < 1.0 ng/ml. Overall not a particularly robust study

TABLE 45 *Interstitial microwave thermal therapy (primary study)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Evidence level 5					
Sherar *et al*. (2001, Canada)[114]	IMTT	$n = 25$ PSA ≤ 15 ng/ml Prostate volume were ≤ 50 cm^3 Localised recurrence	Case series Follow-up = 6 months Clinical and biochemical NED with DRE, urinalysis, sextant biopsy (24 weeks) and PSA. Complications by documentation of adverse sequelae at 4, 8, 12 and 24 weeks	3 patients lost to follow-up At 6 months, 13 (52%) had PSA nadir ≤ 0.5 ng/ml, 10 (40%) 0.51–4 ng/ml and 2 (8%) > 4 ng/ml. Biopsy results for 22/25 cases were negative in 16 and positive in 6. Including 3 lost to follow-up as though failures, results positive (failure) in 36% and negative (success) in 64%. No major complications observed, rate of complications decreased significantly in initial 3 months post-therapy; no patient had complete incontinence	This is a trial intervention carried out as a salvage procedure with subjects who previously failed EBRT. Number of subjects in series is too small and follow-up period of 24 weeks is too short to be able to evaluate the efficacy of the intervention

TABLE 46 *Transperineal radiofrequency interstitial tumour ablation (primary studies)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Evidence level 5					
Zlotta *et al*. (1998, Belgium, USA)[116]	Percutaneous transperineal RITA and RP	*n* = 15 RITA + RP = 14 RITA = 1 PSA for RITA *n* = 1 Only of 5.1 ng/ml, age 65 years	Case series For 8 subjects RITA immediately before RP; in 6, 1 week before RP by spinal anaesthesia. For 1 patient with RITA only, 3 months of neoadjuvant hormone ablation, followed by serial PSA which was undetectable at 3 months Outcomes for 14/15 by histology (macroscopic examination) after RP, to determine extent of lesions to tumour. No clinical or biochemical follow-up reported for 14/15	Macroscopic examination showed well-demarcated lesions including prostatic capsule. 1 patient (1/15) no residual cancer found in specimen. No complications of treatment reported	This is an appraisal of a new treatment modality still under early evaluation. Number of subjects in the series (10) too small and no follow-up of medium- to longer-term outcomes by established clinical or biochemical criteria make evaluation of the efficacy of the intervention impossible
Djavan *et al*. (1998, Belgium, USA)[115]	Transperineal RITA and RP	*n* = 10 Mean age = 70.4 years (66–74 years) Average IPSA = 11.5 ± 2.6 ng/ml (7–16 ng/ml) Gleason = 5.8 ± 2 (3–8)	Case series RITA with MRI performed 1–7 days before RP. Outcomes by histology after RP and postoperative MRI to determine extent of coagulative necrosis. No clinical or biochemical follow-up	No complications of treatment. MRI revealed no alterations of the rectum, NVB or region of the external urethral sphincter	This is an appraisal of a new treatment modality still under early evaluation. Number of subjects in series (10) too small and no follow-up of medium- to longer-term outcomes by established clinical or biochemical criteria make evaluation of the efficacy of the intervention impossible

TABLE 47 *Laser photocoagulation (primary study)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Evidence level 5					
Andersson *et al*. (1993, Sweden)[117]	TURP and neodymium-YAG laser photocoagulation	*n* = 20 Mean age = 71 years (64–84 years) T0–T2NxM0 T0 = 4 T2 = 16 No other details	1987–1990 case series Follow-up = 12 months Clinical outcome by DRE, TRUS, 'blood chemistry' (?PSA) and biopsies	Follow-up biopsies showed cancer in 16/20 patients (80%), 1 atypical malignancy suspect and only 3 subjects free from cancer. Repeat salvage therapy produced only 2 more cancer-free patients, with residual cancer in 6. Of a total of 20 patients, only 5 became biopsy negative for cancer. The side-effects of therapy were few and acceptable	This is an early study representing a simple report of treatment outcome of a limited case series. It lacks key patient characteristics such as PSA and Gleason score, and there is no statistical methodology given. The results are acknowledged to be poor, and the follow-up period is too brief to allow an adequate evaluation of the 3 cancer-free subjects (first operative procedure) after 12 months

TABLE 48 *Gene therapy (primary studies)*

Study	Treatment(s) evaluated	Subjects	Method	Results by outcome	Comments
Evidence level 5					
Shalev *et al*. (2000, USA)[119]	Suicide gene therapy. Toxicity after multiple and repeat injections Group 1 = patients who had rising PSA after first gene therapy Group 2 = patients who had persistent prostate cancer 1 year after radiation therapy Group 3 = patients with poor prognosis who had preradical prostatectomy gene therapy Group 4 = patients with newly diagnosed localised prostate cancer	*n* = 33 (7 in group 1, 10 in group 2, 8 in group 3, 8 in group 4) No details of median age, PSA, stage or grade reported. All subjects were selected from 4 different clinical trials for suicide gene therapy. No references given for the trials	Appears to be a prospective, non-randomised study, although very little information provided on how and why patients were selected for treatment Mean follow-up = 12.8 months (3–34 months) Outcomes = toxic events (e.g. fever, flu-like symptoms, thrombocytopenia, hypertension and anaemia)	After 3 cycles of treatment, in group 1 there was 1 toxic event, in group 2 there were 6, in group 3 there were 7 and in group 4 there were 19 toxic events No statistical tests performed	Only group 4 are of relevance to this report because patients had early localised cancer. However, this group of patients was treated with RT after diagnosis, in addition to receiving gene therapy
Teh *et al*. (2001, USA)[120]	Combined RT and *in situ* gene therapy with or without HT Group 1 = low-risk patients who received gene + RT Group 2 = high-risk patients who received gene + RT + HT Group 3 = stage D1 patients who received the same as group 2 Risk based on stage, Gleason score and pretreatment PSA	*n* = 30 (13 in group 1, 14 in group 2, 3 in group 3) Median age = 68 years (39–85 years) Details of stage and grade reported	Prospective, non-randomised study (Phase I/II clinical trial) Median follow-up = 5.5 months Outcome = treatment-related toxicity	11 patients (37%) had flu-like symptoms that resolved within 24 h. 4 patients (13%) and 2 patients (7%) developed grade 1 and grade 2 fever, respectively. 1 patient developed grade 3 elevation in liver enzymes. 11 and 2 patients developed grade 1 and grade 2 abnormal liver function tests, respectively	

Appendix 6

Incidences of chronic adverse effects of treatments used in the model

The incidences of particular toxicities for a particular treatment can vary considerably. As discussed in the text, there are several possible reasons for this: different toxicity definitions, different measurement methods and different times from treatment. Where possible, meta-analysis data have been used, or patient number weighted means calculated either from data included in other reviews, or from this review. As far as possible, extreme values for high and low estimates have been avoided by taking the highest or lowest value from a reasonably large trial (at least 200 patients), or calculating the mean of several small trials at the high or low end of the spectrum. For some of the newer treatments this was not always possible, as noted in the data sources.

TABLE 49 *Incidences of chronic (> 12 months) adverse effects of treatments*

Treatment	Impotence			Urinary symptoms			Bowel injury		
	Central	Low	High	Central	Low	High	Central	Low	High
Active monitoring	0	0	0	0	0	0	0	0	0
RP	0.58[a]	0.44[b]	0.6[c]	0.15[d]	0.05[e]	0.25[f]	0	0	0
Radical radiotherapy	0.31[a]	0.29[g]	0.36[h]	0.2[i]	0.09[j]	0.23[k]	0.15[l]	0.08[m]	0.26[n]
3D-CRT	0.36[o]	0.32[p]	0.39[q]	0.2[i]	0.09[j]	0.23[k]	0.05[l]	0.02[m]	0.12[n]
Brachytherapy	0.18[r]	0.04[s]	0.51[t]	0.14[u]	0.14[u]	0.3[v]	0.03[w]	0.01[x]	0.05[y]
Cryotherapy	0.86[z]	0.67[aa]	0.93[bb]	0.18[cc]	0.14[dd]	0.46[ee]	0.004[ff]	0.004[ff]	0.005[ff]

[a] Mean, meta-analysis of primary data from 9403 patients 1970–1994 by Robinson *et al*., reported in 'Improving outcomes in urological cancers'.[124]
[b] Mean, analysis of 1291 patients 1994–1995 by Stanford *et al*., reported in 'Improving outcomes in urological cancers'.[124]
[c] As note *a*, but upper 95% confidence limit.
[d] Selley *et al*.[4] patient number weighted mean.
[e] Selley *et al*.[4] low value, five trials altogether including several hundred patients with results of this order.
[f] Selley *et al*.[4] highest value from large trial.
[g] As note *a*, but lower 95% confidence limit.
[h] Nguyen *et al*[75] study comparing RT with 3D-CRT. Note Stanford (as in note *b*) upper confidence limit 34%.
[i] Mean of recent RCTs[67,68] comparing RT with 3D-CRT, not significantly different from each other.[67,68,75,83] Selley *et al*.[4] patient number weighted mean RT = 17%.
[j] Rates for 3D-CRT (see note *i*). Hanks *et al*.[79] (n = 233) and Zelefsky *et al*.[72] (n = 1100, 5-year actuarial, 10%).
[k] Dearnaley *et al*.[67] rate for RT, same for 3D-CRT (see note *i*).
[l] Dearnaley *et al*.[67] Use Dearnaley as central rate in preference to other RCTs,[68,75] as rate for RT (15%) similar to Selley *et al*.[4] patient number weighted mean (14%).
[m] Perez *et al*.[69] comparison of RT with 3D-CRT.
[n] Means of three RCTs[67,68,75] comparing RT with 3D-CRT.
[o] Mid-point low/high (see notes *p* and *q*). Note both large trials at high, so patient number weighted mean =38%.
[p] Zelefsky *et al*.[73]
[q] Hanks *et al*.[88] Zelefsky *et al*.[82]
[r] Patient number weighted mean of studies included in clinical review. Note Crook *et al*.[42] range 4–14%.
[s] Crook *et al*.[42] low.
[t] Joly *et al*.[64] but small study (n = 71) and patients also had RT.
[u] Crook *et al*.[42] at 24 months.
[v] Ragde *et al*.[51] large study (n = 769), also Crook *et al*.[42] at 12 months.
[w] Crook *et al*.[42] high.
[x] Crook *et al*.[42] low.
[y] Wills and Hailey.[41]
[z] Patient number weighted mean of studies included in clinical review.
[aa] Mean of three small trials.[97,104,170]
[bb] Long *et al*.[103] large trial (n = 975).
[cc] Cohen *et al*.[171] large study (n = 383). Figures include urethral sloughing, incontinence and stricture.
[dd] Bahn and Lee[101] large study (n = 643). Figures include outlet obstruction and incontinence.
[ee] Derakshani *et al*.[104] small study only (n = 48). Figures include dysuria and incontinence.
[ff] Data only available from two studies: Bahn and Lee[101] and Long *et al*.[103]

Appendix 7

Summary of utility values for prostate cancer states

TABLE 50 *Study characteristics*

Main author (year)	Method	Subjects	*n*	1.0 =	Comments
Albertsen (1998)	TTO	Prostate cancer patients	50	Not having that problem	Also used other methods to establish utilities. Patients had completed treatment at least 1 year before
Cantor (1995)	TTO	Men aged ~50 years in good health	10	No treatment-related problems	Assumption that without side-effect utility = 1
Cowen (1998)	TTO	Men aged 55–57 years in a general medicine practice, no prostate cancer	63	Perfect health	Pilot study in 1996, similar results. Investigated difference between mean and individual QALYs: very different. Results shown in table combined validation and derivation groups
Krahn (1994)	TTO	Physicians (urologists, oncologists and interns)	10	No treatment or disease related problems	
Saigal (2001)	TTO	Patients scheduled for prostate biopsy	401	Ideal health for age	Looked at effect on morbidity and sociodemographic characteristics on utilities
Bennett (1996, 1997)	TTO	Physicians	43	Perfect health	May be biased by relatively well patients able to attend clinics
	TTO	Patients with localised disease	27		
	TTO	Patients with metastatic disease	17		
Rosendahl (1999)	Q-tility (TTO)	Patients to describe states, Q-tility to assign utility	113	Perfect health?	
Souchek (2000)	TTO (shown), SG, rating scale	Patients with metastatic cancer	61	Perfect health	Compares TTO, SG and rating scale. Differences between states similar for each scale, but TTO results 0.1–0.2 higher than other two methods

TABLE 51 *Study results*

Main author (year)	No prostate problems	Asymptomatic localised cancer	Symptoms				Hormonally metastatic cancer		
			Impotence	Incontinence	Bowel injury	Bladder outlet obstruction	Responsive	Responsive with toxicity	Refractory
Albertsen (1998)	–	–	0.898	0.892	0.978	See incontinence	–		–
Cantor (1998)	–	–	0.75	0.68	0.45	0.6	–		–
Cowen (1998)		0.73	0.70	0.60	Small impact		0.44		0.15
Krahn (1994)			0.92, 0.85[a]	0.61, 0.81[a]			0.58	See responsive	See responsive
Saigal (2001)	0.91		0.71	0.79	0.6				
Bennett (1996, 1997)	–	–	–	–	–	–	0.92	0.84	0.83, 0.42[b]
	–	–	–	–	–	–	0.88		0.53, 0.05[b]
	–	–	–	–	–	–	0.78		0.58, 0.05[b]
Rosendahl (1999)							0.91	0.89	0.85, 0.76[c]
Souchek (2000)							0.72, 0.83[d]	0.71, 0.81[d]	0.44, 0.55[d]

[a] Complete, partial (impotence/incontinence).
[b] Early, late progressive disease.
[c] Objective, subjective (pain) progression.
[d] Surgical, medical castration.

Appendix 8

Costs of brachytherapy treatment

TABLE 52 *Costs of brachytherapy treatment*

Annual staff costs to treat 50 patients		
	Sessions	**Costs (including on costs)**
Consultant radiologist	2	£11,610
Clinical oncologist	1	£5,805
Medical physicists	2	£8,495
Consultant anaesthetist	1	£5,805
Programme coordinator	0.5 WTE	£11,000
Total		£42,715
Cost per patient		£854.30
Equipment		
TRUS machine	£25,000	
Silicone sheath stand-off for ultrasound	£350	
Fixation and control system for probe	£12,000	
Dosimetry planning system	£22,000	
Total capital cost	£59,350	
Cost depreciated over 5 years	Interest rate	6.00%
Year	**Capital on which interest paid**	**Interest**
1	£59,350	£3,561
2	£47,480	£2,849
3	£35,610	£2,137
4	£23,740	£1,424
5	£11,870	£712
Total interest		£10,683
Total equipment cost (including interest)		£70,033
Patients per year	50	
Equipment cost per patient	£280	
Miscellaneous cost items	**Inpatient**	**Day-case**
Outpatient ultrasound scan	£174	£174
Theatre costs	£112	£112
Overnight stay/day-care	£162	£110
CT scan	£174	£174
Iodine seeds	£3,500	£3,500
Needles	£300	£300
Total	£4,422	£4,370
Total brachytherapy costs per patient	**Inpatient**	**Day-case**
	£5,556.43	£5,504

Appendix 9

Hormone therapy costs

TABLE 53 *Costs of neoadjuvant hormone therapy*

Trial	Drug	Dose (mg)	Administration	Frequency (week)	Frequency (months)	Duration (week)	Duration (months)	Pack size (vial vol. of tablets)	Cost per pack (£)	No. of packs required	Total drug cost (£)	No. of outpatient attendances[a]	Total treatment cost (£)
Aus (1998)	Triptorelin	3.75	Injection		1		3	4.2 mg vial	105	3	315	3	
Hugosson (1996)	Gyproterone acetate	50	Oral	14		3		56 × 50 mg	32	1	32 347		512
Dalkin (1996)	Coserelin acetate	3.6	Injection		1		3	3.6 mg vial	122	3	367	3	531
Debruyne (2000) &	Goserelin acetate	4.6	Injection		1		3	3.6 mg vial	123	3	370	3	
Fair (1999)	Flutamide	250	Oral		90		3	84 × 250 mg	65	4	260 630		794[c]
Laverdiere (1997)	Leuprolide	7.5	Injection		1		3	3.75 mg vial	125	6	752	3	
Gleave (2001)	Flutamide	250	Oral		90		3	84 × 250 mg	65	4	260		
Soloway											1,012		1,177[d]
Klotz (1999)	Cyproterone acetate	300	Oral		90			84 × 100 mg	97	4	387		387[b]

[a] Outpatient attendances for drug administration, costed at £55 per attendance.[153]
[b] Low, [c] central and [d] high costs used in the model.

TABLE 54 *Costs of adjuvant hormone therapy*

Trial	Drug	Dose (mg)	Administration	Frequency (month)	Pack size (vial vol. of tablets)	Cost per pack (£)	Cost per month (£)	Treatment duration (months)	Measure of duration	Total drug cost (£)	Outpatient costs[a] (£)	Total treatment cost (£)
Regimen	Leuprolide	7.5	Injection	1	3.75 mg vial	125	125					
	Flutamide	250	Oral	90	84 × 250 mg	65	70					
							195					
Trials:												
Laverdiere (1997)[e]								11	Regimen	2,145	603	2,748
Horwitz (1999)								3	Median	585	164	750
Anderson (1997)								10	Mean	1,950	548	2,499
								3	Median			
Regimen	Goserelin acetate	4.6	Injection	1	3.6 mg vial	123	123					
	Flutamide	250	Oral	90	84 × 250 mg	65	70					
							193					
Trials:												
Horwitz (1999)								3	Median	579	164	743[b]
Anderson (1997)								10	Mean	1,929	548	2,477[c]
								3	Median			
D'Amico	LHRH + antiandrogen (both unspecified, assume goserelin and flutamide)							6	Regimen	1,157	329	1,486
Regimen	Leuprolide or goserelin (costed as goserelin; see above)						123					
	Flutamide or biclutamide (costed as flutamide; see above)						70					
	Finasteride	5	Oral	30	28 × 5 mg	25	27					
							220					
Trials:												
Leibowitz (2001)								13	Median	2,855	713	3,567[d]

[a] Outpatient attendances for drug administration, costed at £55 per attendance,[153] one per injection.
[b] Low, [c] central and [d] high costs used in the model.
[e] Includes 3 months of NHT.

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Feedback

The HTA Programme and the authors would like to know your views about this report.

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We look forward to hearing from you.

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