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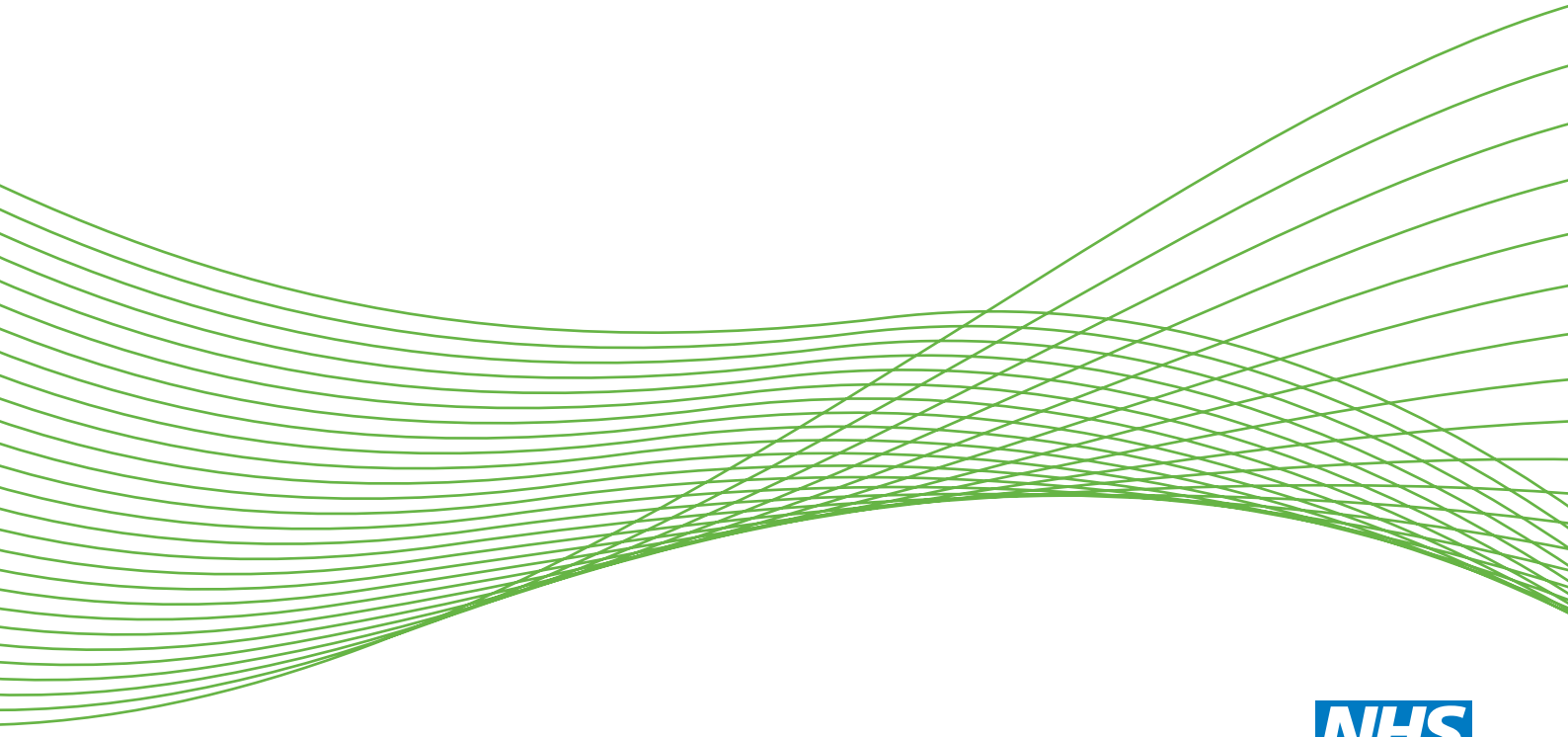

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Abstract

Ablative therapy for people with localised prostate cancer: a systematic review and economic evaluation

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Background: For people with localised prostate cancer, active treatments are effective but have significant side effects. Minimally invasive treatments that destroy (or ablate) either the entire gland or the part of the prostate with cancer may be as effective and cause less side effects at an acceptable cost. Such therapies include cryotherapy, high-intensity focused ultrasound (HIFU) and brachytherapy, among others.

Objectives: This study aimed to determine the relative clinical effectiveness and cost-effectiveness of ablative therapies compared with radical prostatectomy (RP), external beam radiotherapy (EBRT) and active surveillance (AS) for primary treatment of localised prostate cancer, and compared with RP for salvage treatment of localised prostate cancer which has recurred after initial treatment with EBRT.

Data sources: MEDLINE (1946 to March week 3, 2013), MEDLINE In-Process & Other Non-Indexed Citations (29 March 2013), EMBASE (1974 to week 13, 2013), Bioscience Information Service (BIOSIS) (1956 to 1 April 2013), Science Citation Index (1970 to 1 April 2013), Cochrane Central Register of Controlled Trials (CENTRAL) (issue 3, 2013), Cochrane Database of Systematic Reviews (CDSR) (issue 3, 2013), Database of Abstracts of Reviews of Effects (DARE) (inception to March 2013) and Health Technology Assessment (HTA) (inception to March 2013) databases were searched. Costs were obtained from NHS sources.

Review methods: Evidence was drawn from randomised controlled trials (RCTs) and non-RCTs, and from case series for the ablative procedures only, in people with localised prostate cancer. For primary therapy, the ablative therapies were cryotherapy, HIFU, brachytherapy and other ablative therapies. The comparators were AS, RP and EBRT. For salvage therapy, the ablative therapies were cryotherapy and HIFU. The comparator was RP. Outcomes were cancer related, adverse effects (functional and procedural) and quality of life. Two reviewers extracted data and carried out quality assessment. Meta-analysis used a Bayesian indirect mixed-treatment comparison. Data were incorporated into an individual simulation Markov model to estimate cost-effectiveness.

Results: The searches identified 121 studies for inclusion in the review of patients undergoing primary treatment and nine studies for the review of salvage treatment. Cryotherapy [3995 patients; 14 case series, 1 RCT and 4 non-randomised comparative studies (NRCSs)], HIFU (4000 patients; 20 case series, 1 NRCS) and brachytherapy (26,129 patients; 2 RCTs, 38 NRCSs) studies provided limited data for meta-analyses. All studies were considered at high risk of bias. There was no robust evidence that mortality (4-year survival 93% for cryotherapy, 99% for HIFU, 91% for EBRT) or other cancer-specific outcomes differed between treatments. For functional and quality-of-life outcomes, the paucity of data prevented any definitive conclusions from being made, although data on incontinence rates and erectile dysfunction for all ablative procedures were generally numerically lower than for non-ablative procedures. The safety profiles were comparable with existing treatments. Studies reporting the use of focal cryotherapy suggested that incontinence rates may be better than for whole-gland treatment. Data on AS, salvage treatment and other ablative therapies were too limited. The cost-effectiveness analysis confirmed the uncertainty from the clinical review and that there is no technology which appears superior, on the basis of current evidence, in terms of average cost-effectiveness. The probabilistic sensitivity analyses suggest that a number of ablative techniques are worthy of further research.

Limitations: The main limitations were the quantity and quality of the data available on cancer-related outcomes and dysfunction.

Conclusions: The findings indicate that there is insufficient evidence to form any clear recommendations on the use of ablative therapies in order to influence current clinical practice. Research efforts in the use of ablative therapies in the management of prostate cancer should now be concentrated on the performance of RCTs and the generation of standardised outcomes.

Study registration: This study is registered as PROSPERO CRD42012002461.

Funding: The National Institute for Health Research Health Technology Assessment programme.

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3D-CRT	three-dimensional conformal radiotherapy
AS	active surveillance
AUS	artificial urinary sphincter
BAUS	British Association of Urological Surgeons
BD	bowel dysfunction
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
COMET	Core Outcome Measures in Effectiveness Trials
COSMIN	Consensus-based Standards for the Selection of Health Measurement Instruments
CrI	credible interval
DARE	Database of Abstracts of Reviews of Effects
DRE	digital rectal examination
EAU	European Association of Urology
EBRT	external beam radiotherapy
ED	erectile dysfunction
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30
EQ-5D	European Quality of Life-5 Dimensions
ERSPC	European Randomised Study of Screening for Prostate Cancer
HIFU	high-intensity focused ultrasound
HRQoL	health-related quality of life
HTA	Health Technology Assessment
I-125	iodine-125
IIEF-5	International Index of Erectile Function-5
IMRT	intensity-modulated radiotherapy
I-PSS	International Prostate Symptom Score
Ir-192	iridium-192
LHRH	luteinising hormone-releasing hormone
MDT	multidisciplinary team
MR	magnetic resonance
MRI	magnetic resonance imaging
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NRCS	non-randomised comparative study
ONS	Office for National Statistics
OR	odds ratio
PBT	proton beam radiation therapy
Pd-103	palladium-103
PDT	photodynamic therapy
PSA	prostate-specific antigen
pT	pathological tumour
QALY	quality-adjusted life-year
RCT	randomised controlled trial
ReBIP	Review Body for Interventional Procedures
RITA	radiofrequency interstitial tumour ablation
RP	radical prostatectomy
RTOG	Radiation Therapy Oncology Group
SF-36	Short Form questionnaire-36 items
TNM	tumour node metastasis

TRUS	transrectal ultrasound	UI	urinary incontinence
UCAN	Urological Cancer Charity	UICC	Union for International Cancer Control
UCLA-PCI	University of California at Los Angeles – Prostate Cancer Index	WHO	World Health Organization

Plain English summary

Ablative therapies are relatively new procedures for the treatment of localised prostate cancer. These therapies are promising because they may be as effective as either surgery or radiotherapy (i.e. standard treatments), while causing fewer side effects (e.g. incontinence or erection difficulties). They may also be better than active surveillance (whereby patients are monitored and only treated if there is cancer progression) because they actively treat cancer at diagnosis. They involve the application of different types of energy to either the entire prostate or specific areas with cancer, to achieve tissue destruction. Examples include cryotherapy (using rapid freezing and thawing), high-intensity focused ultrasound (HIFU, using heat generated from sound waves) and brachytherapy (using radioactive seeds implanted into the prostate). These procedures are generally carried out on a day-patient basis with patients allowed home the following day. The results from our study suggested that cryotherapy, HIFU and brachytherapy may have potential clinical benefits for many patients in terms of reduced incontinence and erection difficulties, while possessing similar benefits in terms of cancer control compared with either surgery or radiotherapy. However, the overall quality of the available evidence was very poor owing to the low quality of identified studies, and it remained impossible to determine if the benefits were real. In terms of balancing the cost of the ablative treatments against the benefits and harms produced, no technology appears better.

Scientific summary

Background

People diagnosed with cancer of the prostate, a sex gland in the pelvis, have a choice of treatment options depending on the severity of disease. For people whose cancer is at medium and low risk of spread, the main options are surgical removal of the prostate, radical prostatectomy (RP), use of external beam radiotherapy (EBRT) to destroy the cancer or delaying treatment until there are signs that the cancer is getting worse [active surveillance (AS)]. RP and radiotherapy are effective at curing the cancer but may also cause long-term urinary incontinence and sexual problems. AS, on the other hand, may be quite difficult for people to cope with as they know that the cancer is still present. Newer treatments aim to target the disease more precisely so that surrounding normal tissues can be preserved, reducing the risk of side effects but still effectively destroying the cancer. These more targeted ablative therapies include cryotherapy, high-intensity focused ultrasound (HIFU), brachytherapy, photodynamic therapy (PDT), radiofrequency interstitial tumour ablation (RITA) and laser therapy, among others.

Aims

This study aimed to

- develop clinical care pathways relevant to a UK NHS context
- review systematically the evidence of the clinical effectiveness and safety of each newer ablative therapy concerning primary and salvage treatment of localised prostate cancer
- determine which therapies are most likely to be cost-effective for implementation in the UK NHS
- identify and prioritise future research needs.

Methods

Clinical effectiveness review

We conducted two discrete systematic reviews:

(a) primary ablative treatment of localised prostate cancer compared with AS, RP or EBRT
(b) salvage ablative treatment for local prostate cancer relapse after primary EBRT compared with salvage RP.

MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Bioscience Information Service (BIOSIS), Science Citation Index, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) databases were searched to the end of March 2013. Reference lists of all included studies were scanned and experts on our advisory panel were contacted for details of additional reports. Evidence came from randomised controlled trials (RCTs), non-randomised comparative studies (NRCSs) (if no RCT evidence was identified) and single-arm cohort studies (case series) with greater than 10 participants for the ablative procedures only. Conference abstracts or non-English-language reports were excluded. For the primary therapy systematic review, the ablative therapies considered were cryotherapy, HIFU, PDT, RITA, laser ablation and brachytherapy. The comparators were AS, RP and EBRT. For the salvage therapy systematic review, the ablative therapies considered were cryotherapy and HIFU. The comparator was RP. Outcomes were cancer related, adverse effects (functional and procedural) and quality of life. Two reviewers extracted data and carried out quality assessment. For meta-analysis, a Bayesian indirect mixed-treatment comparison was used.

Cost-effectiveness

The cost-effectiveness of the different treatments and their subsequent care pathways was assessed using a modified Markov individual simulation model, applied to a UK NHS setting. The perspective for the model was a health services perspective. Parameter estimates were derived from the systematic review of clinical effectiveness, a micro-costing exercise, other literature, the expert advisory group and other UK sources. The outputs of the model were costs and quality-adjusted life-years (QALYs) for each procedure, incremental costs and QALYs and incremental cost per QALY over the remaining lifetime. Both costs and QALYs were discounted at 3.5%. An elasticity analysis, together with probabilistic and deterministic sensitivity analyses, were performed to explore the uncertainty surrounding parameter estimates.

Results

Clinical effectiveness

Cryotherapy

Data from 3995 patients who received cryotherapy across 19 studies (1 RCT, 4 NRCSs and 14 case series) were included, with most studies considered to be at high risk of bias. In the short term, there was conflicting evidence relating to cancer-specific outcomes when cryotherapy was compared with either EBRT or surgery. The only finding that reached statistical significance was 1-year disease-free survival, which was worse for cryotherapy than for either EBRT or RP. However, none of the other cancer-specific outcomes, such as biochemical failure or overall survival, showed any significant differences between them. The findings in relation to cancer-specific outcomes are best regarded as inconclusive.

There was evidence that the rate of urinary incontinence at 1 year was lower for people undergoing cryotherapy than for those undergoing RP [3% vs. 66%; odds ratio (OR) 0.02, 95% credible interval (CrI) < 0.01 to 0.34], but the size of the difference decreased with longer follow-up. There was a general trend for cryotherapy to have fewer procedural complications, apart from urinary retention. The only difference that reached statistical significance was for urethral stricture, which was less frequent after cryotherapy than after RP (1% vs. 8%; OR 0.24, 95% CrI 0.09 to 0.54).

High-intensity focused ultrasound

Data from 4000 patients who received HIFU across 21 studies (1 NRCS and 20 case series) were included, with all studies considered to be at high risk of bias.

There was some evidence that biochemical failure rates were higher at 1 year when using HIFU than when using EBRT, and this was statistically significant. However, the difference was no longer statistically significant at 5 years. Similar findings were observed with regard to disease-free survival at 1 year, with worse outcomes for HIFU than for EBRT, which were statistically significant. The differences were no longer significant at 3 years. The biochemical result was in contrast to overall survival at 4 years, which was higher when using HIFU.

There were insufficient data on any urinary incontinence, erectile dysfunction or bowel problems to draw any robust conclusions, although at 1 year HIFU had lower incontinence rates than RP (10% vs. 66%; OR 0.06, 95% CrI 0.01 to 0.48). The safety profile for HIFU was generally good, apart from a potential numerical increase in rates of urinary retention and dysuria. However, HIFU appeared to have a slightly higher incidence of urethral stricture than EBRT, and the difference was statistically significant (8% vs. 1%; OR 5.8, 95% CrI 1.2 to 24.5).

Brachytherapy

This review considered data from 26,129 patients who received brachytherapy across 40 studies (2 RCTs and 38 NRCSs), with most studies considered to be at high risk of bias. The data for brachytherapy were generally more robust than for other ablative therapies.

In the short term, there was some evidence at 5-year follow-up that the rate of biochemical failure was lower for brachytherapy (7%) than for EBRT (13%; OR 0.46, 95% CrI 0.32 to 0.67) or RP (11%; OR 0.35, 95% CrI 0.21 to 0.56). There was also some evidence that disease-free survival was better for brachytherapy at 3-year follow-up.

There was evidence that the rate of urinary incontinence up to 5 years after treatment was lower for people undergoing brachytherapy than for RP, but the size of the difference decreased with longer follow-up. There was also a trend towards lower erectile dysfunction rates for brachytherapy than for EBRT or RP and this reached statistical significance at 3 years after treatment (60% vs. 81% for EBRT and 88% for RP). There were insufficient data to draw any conclusions on bowel problems.

The findings regarding procedural complications were mixed. Dysuria rates were higher for brachytherapy and this reached statistical significance when compared with RP. Urinary retention was also statistically significantly higher for brachytherapy than for EBRT. Stricture rates for brachytherapy were higher than those for EBRT, but lower than those for RP. The differences for stricture reached statistical significance when compared with RP. For rectal pain, there was evidence that rates were significantly lower for brachytherapy than for EBRT. Acute genitourinary toxicity, though rare, had statistically higher rates for brachytherapy than for EBRT, but acute gastrointestinal toxicity was lower for brachytherapy.

Other ablative therapies

Only two other ablative therapies were identified in the review: focal laser ablative therapy and PDT. Data were too scarce (a total of 35 participants for these two procedures) for any conclusions.

Salvage therapy

Data from 400 participants who were treated with salvage therapy following primary EBRT across nine case series were included. Six studies involved salvage RP, two involved salvage cryotherapy and one involved salvage HIFU. In six studies, data were not collected prospectively, and only short-term outcomes were reported. As such, all of the studies were considered as having a high risk of bias. There was no robust evidence that mortality or other cancer-specific outcomes differed between salvage cryotherapy and salvage RP in the short term. There were no data on cancer-specific outcomes for salvage HIFU. In regard to functional and quality of life outcomes, lack of data prevented any conclusions. In terms of adverse event outcomes, salvage cryotherapy had numerically fewer periprocedural complications (especially for bladder neck stenosis) than salvage HIFU or salvage RP, but there was a high level of uncertainty with this observation.

Focal ablation

Descriptive subgroup assessment within studies reporting the use of focal ablation was limited, but suggested that cancer-specific outcomes were at least comparable with those seen in full-gland therapy studies. Urinary incontinence rates may be lower following focal ablation, but the evidence is weak in light of the poor quality and quantity of the data.

Active surveillance

Lack of outcome data prevented comparison of the efficacy of ablative therapies with a programme of AS, apart from the rate of erectile dysfunction at 12 months, where there was no statistically significant difference.

Cost-effectiveness

Assuming equal recurrence in line with the lack of statistical differences from the effectiveness review, EBRT was the least costly (£19,363 per patient) and least effective (3.63 QALYs), whereas HIFU was more costly (£19,860 per patient) and more effective (3.86 QALYs). HIFU was more effective and less costly than the other newer ablative interventions. The lifetime incremental cost per QALY for HIFU compared with EBRT was £2915. There was a 75% chance that HIFU would be considered cost-effective at a £30,000-per-QALY threshold. In a plausible best-and-worst-case analysis, the probability that HIFU would be considered cost-effective varied between 60% and 70%.

Strengths and limitations

The main strength of the study was the systematic approach taken to review the literature and the inclusion of a relatively large quantity of studies, giving a high total number of participants. The main limitations were the low quantity and poor quality of the data available on cancer-related outcomes and long-term adverse events of urinary incontinence, sexual and bowel dysfunction, and the changing technology over the review period. Many published studies were poorly reported or lacked sufficient detail. Inconsistency in outcome definition, measurement and reporting was also a significant problem, and much of the information available was unsuitable for meta-analysis. Another major limitation resulted from the majority of comparisons being made using case series, with few head-to-head comparisons of ablative therapies against current practice. The estimates were therefore generated using indirect comparisons. Like all analyses, they require assumptions to be made that may or may not be reasonable. Accordingly, the results should be interpreted with a large degree of caution. Despite the considerable efforts to construct a model and seek the best data available, the lack of effectiveness data had implications for the economic evaluation. The limited data meant that there was insufficient evidence to assume that there was any difference between interventions for a number of parameters, a particular issue for biochemical recurrence, which was a key parameter in the evaluation. The impact of these assumptions was explored in sensitivity analyses.

Conclusions

Implications for health care

For primary ablative therapy, neither cryotherapy nor HIFU had sufficiently robust data to enable any definitive conclusions to be made. The effectiveness data on brachytherapy were more robust and there was some evidence that cancer-specific outcomes in the short term were either better or equivalent to either EBRT or RP, with comparable adverse effect profiles apart from a possible increased risk of dysuria and urinary retention. The findings on focal ablative therapy were mostly derived from data on focal cryotherapy, which suggested that cancer-specific outcomes were at least comparable with those of full-gland cryotherapy, and there was a suggestion that the urinary incontinence outcome may be better following focal cryotherapy than whole-gland cryotherapy. The cost-effectiveness analysis confirmed the uncertainty from the clinical review and that there is no technology which appears superior, on the basis of current evidence, in terms of average cost-effectiveness. The probabilistic sensitivity analyses suggest that a number of ablative techniques are worthy of further research.

For salvage ablative therapy following primary EBRT, a lack of reliable and robust data prevented any meaningful conclusions from being made, in comparison with salvage RP.

The findings from the review indicate that there is insufficient evidence to help inform recommendations on the use of ablative therapies in the UK NHS.

Need for further research

The main gaps in the evidence base are the lack of direct comparative studies of ablative therapies; the consequent lack of robust data to inform calculations of cost-effectiveness and the role of focal ablative therapies; and the lack of longer-term data on cancer control, such as overall and cancer-specific mortality. The key research recommendations, in order of importance, are as follows:

1. HIFU and brachytherapy seem the most promising newer interventions but they lack high-quality evaluation. Such evaluation should ideally be by multicentre RCT with long-term follow-up, and would include predefined assessment of cancer-specific, dysfunction and health-related quality-of-life measures. Such studies should incorporate economic evaluations and also inform economic modelling.

2. The role of focal therapies in the management of people with localised prostate cancer should be investigated. It may be desirable to incorporate the focal approach into the design described above. It is noted, however, that the use of focal therapies is dependent on prior precise localisation of the cancer, for which the technology remains developmental.
3. AS is an increasingly used strategy for people with localised prostate cancer that is deemed to be at low initial risk of spread. The results of ongoing studies are required to assess its safety, acceptability to people with prostate cancer and cost-effectiveness.
4. Agreed definitions of outcomes in urology and agreed measures for recording them are urgently needed. Partnership between governing bodies and international initiatives such as Core Outcome Measures in Effectiveness Trials (COMET) may be desirable.

Study registration

This study is registered as PROSPERO CRD42012002461.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Background

Description of the underlying health problem

The management of an individual diagnosed with prostate cancer is highly complex and fraught with difficulties, especially in relation to localised prostate cancer. This is due to many factors which influence decision-making: the array of available interventions, each with different treatment characteristics and associated adverse effects; uncertainties regarding the most accurate ways of determining the grade and stage of the disease and making predictions regarding prognosis; and controversies regarding the natural history of the disease. The relative clinical effectiveness of standard and widely accepted interventions for localised prostate cancer, such as radical prostatectomy (RP) and external beam radiotherapy (EBRT), have been the subject of various health technology assessments (HTAs) around the world. The present assessment is tasked with determining the relative clinical effectiveness and cost-effectiveness of ablative therapy, which is a relatively new intervention, for the treatment of people diagnosed with localised prostate cancer, in comparison with other standard interventions from the perspective of the UK NHS.

Importance of prostate cancer as a health problem

Prostate cancer is the commonest cancer diagnosed in people in the UK and is the second commonest cause of cancer deaths.[1] In 2011, 41,736 people in the UK were diagnosed with prostate cancer (*Figure 1*).[2] It accounts for approximately 7% of cancer-related deaths in people in the UK, with an age-standardised mortality rate of 35 in 100,000, amounting to 10,837 people in 2012.[2] In 2006, the 10-year prevalence in the UK was estimated to be 181,463.[3] The disease also incurs significant economic costs to health-care providers. In 1997 the annual cost to the NHS was estimated at £55M.[4] An economic analysis published in 2012 reported that the total cost of prostate cancer in the UK in 2009 – encompassing treatment costs for surgery, radiotherapy, hospital and community care, premature deaths, time off work and unpaid care

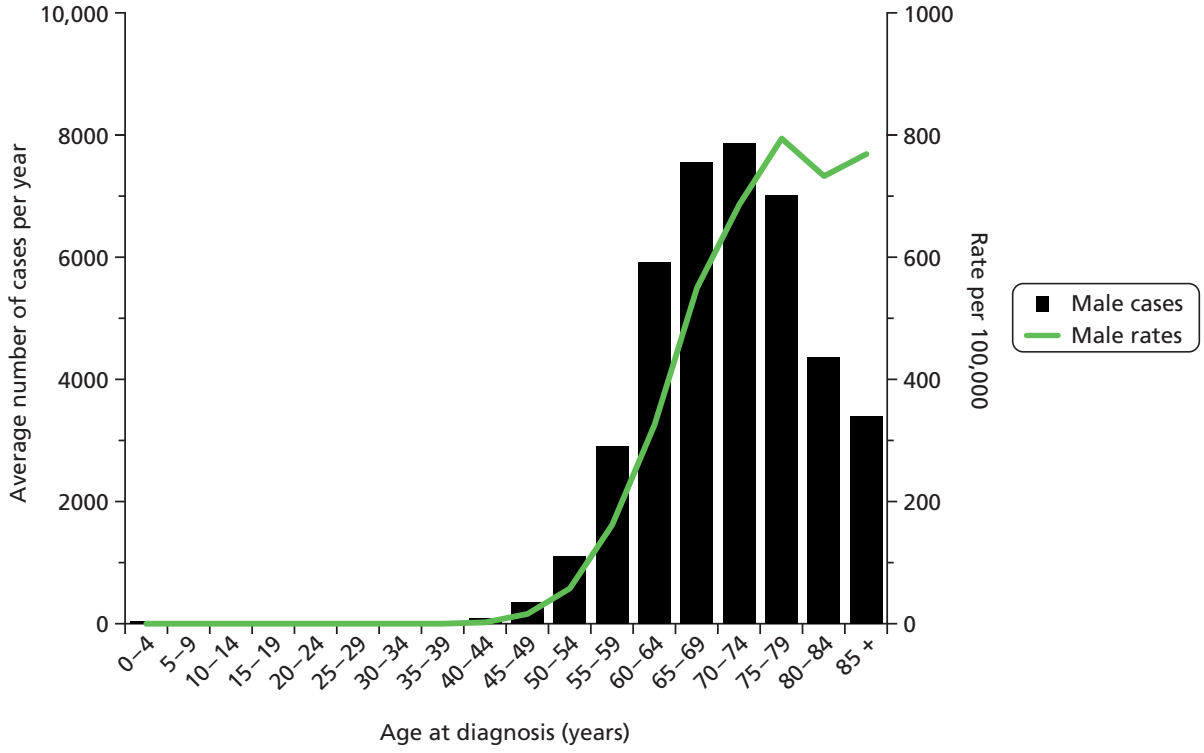

FIGURE 1 Age-specific incidence rates for prostate cancer in the UK, 2009–11.[3]

given to patients by family and friends – was estimated at around £800M per annum.[5] This ties in with a recent estimate from the USA that a diagnosis of prostate cancer incurs an average health-care and personal cost of US$20,000 (£13,000) over the individual's remaining lifetime.[6,7]

Since the advent in the mid-1980s of testing for prostate-specific antigen (PSA), an organ-specific serum marker of prostate cancer, there has been a substantial increase in the number of people diagnosed with prostate cancer.[8] The largest rise in incidence is among relatively younger people as a consequence of case-finding and screening for asymptomatic disease using serum PSA and multiple transrectal ultrasound (TRUS)-guided needle biopsies of the prostate.[9,10] By the same token, the use of PSA testing has resulted in a gradual stage migration towards the earlier stages of the disease in terms of diagnosis. Indeed, presently the majority of people (i.e. up to 80%) with prostate cancer are diagnosed in the localised stages of the disease,[11,12] and a large proportion of them often have favourable pathological characteristics.[13,14]

Standard curative treatment options for localised prostate cancer

The decision to treat and the choice of treatment are influenced heavily by four major factors:

i. the patient's life expectancy, as determined by his chronological age, comorbidities and fitness in terms of activities of daily living (called performance status)
ii. tumour characteristics, determined by the PSA level at diagnosis; the aggressiveness of the tumour, as determined by histological examination using a microscope [or tumour grade, categorised by Gleason sum score (2–10)]; other histological parameters, including volume of the cancer and length of involvement of the biopsy strands of tissue with cancer; and the stage (or extent of spread) of the disease on clinical examination and imaging, all of which can be used for risk stratification to predict behaviour or outcomes using nomograms[15,16]
iii. clinician or patient preference linked to risk of adverse effects
iv. availability of resources underpinning each treatment option.

A standard clinical treatment care pathway for people with localised prostate cancer is given in MacLennan and colleagues,[17] and this is further described in *Chapter 2*. As the majority of people present with asymptomatic, early and localised disease, most of them can be cured by way of radical (or curative) treatment options, which include either RP or radical EBRT. However, it is also clear that prostate cancer has a wide spectrum in terms of the risk and time course of disease progression,[18] and in spite of the use of nomograms, the disease course for some patients can be unpredictable.

Radical prostatectomy

Radical prostatectomy involves removing the prostate and seminal vesicles, with or without removal of adjacent lymph nodes depending on tumour grade and PSA level.[19,20] The aims of the operation are to achieve cancer cure, to minimise perioperative morbidity and to preserve continence and sexual function. This can be achieved by the traditional open technique through a lower abdominal incision, by laparoscopic (keyhole) surgery through several small incisions and, most recently, by robotic-assisted laparoscopic prostatectomy, where the surgeon controls the instruments remotely, giving a more comfortable and precise surgical technique.[21] Contemporary high-volume units record very low perioperative morbidity, whichever technique is used. The main concerns are to minimise the risk of recurrence by maintaining a low positive margin rate and maximise recovery of continence and erectile function by preserving the pelvic neurovascular bundles. Recent literature reviews suggest a median positive margin rate of 22% with RP.[22]

Radical external beam radiotherapy

Radical EBRT typically involves delivery of a minimum dose of 74 Gy of radiation to the prostate at no more than 2 Gy per fraction.[9] There are, however, variations in terms of radiation dose, treatment schedules and whether or not the treatment is combined with a 3- to 6-month course of chemical androgen ablation, as neo-adjuvant or adjuvant therapy. Recent developments in radiation and imaging technology have facilitated the emergence of newer techniques including three-dimensional conformal radiotherapy

(3D-CRT), whereby the delivery of the radiation beam conforms to the three-dimensional structure of the prostate gland, and intensity-modulated radiotherapy (IMRT), which is a further development of 3D-CRT but with more precise control of the radiation beam and improved optimisation of treatment planning.[23] Another relatively new form of radiotherapy is proton beam radiation therapy (PBT),[24] in which protons rather than photons are delivered in a conformal manner to the prostate. PBT has the potential to improve the therapeutic ratio of prostate radiation by allowing for an increase in dose without a substantial increase in side effects. There are variations in each EBRT treatment modality, in terms of radiation dose, treatment schedules and whether the treatment is combined with hormonal therapy or otherwise, in either a neo-adjuvant or adjuvant fashion, or combined with other EBRT modalities (e.g. PBT may be combined with 3D-CRT). EBRT is also increasingly being used in combination with high-dose-rate brachytherapy boost.[25,26] The main complications from radiotherapy include bowel disturbance, urethral stricture formation, lower urinary tract symptoms, erectile and ejaculatory dysfunction and skin irritation.

Radical interstitial brachytherapy, which is often considered as a form of radical radiotherapy technique, will be considered under ablative therapies for the purposes of this review, in accordance with the HTA commissioning brief for this review.

In summary, both RP and radical EBRT are widely accepted as the current standard curative treatment options for the treatment of localised prostate cancer. Both are associated with a relatively high cure rate.[27] However, both procedures are associated with a significant risk of adverse effects which impair function, including erectile dysfunction in between 24% and 90% of patients, urinary incontinence in 2–72% and bowel-related problems in 2–15%.[27–30] These adverse events can significantly impair quality of life.[27,31] There is increasing recognition that a large proportion of people with early, localised disease will neither develop progressive disease nor die from it.[32,33] As such, it is possible that the harms of radical interventions, which are highly invasive, may outweigh the benefits for some people. In spite of this, there is evidence to indicate that the use of radical treatment for early, localised prostate cancer is increasing.[34] In this regard, there is a risk of overtreatment. It has been estimated that more than 40% of people with early localised prostate cancer have been overtreated,[35] and this has important repercussions for the people concerned and for the NHS.

Active surveillance

The strategy of active surveillance (AS) for low- and intermediate-risk localised prostate cancer[36] is based on the premise that such cancers are unlikely to cause ill health during an individual's lifespan and will not contribute to early death. It involves an active decision not to begin treatment immediately but to monitor the cancer by regular PSA checks, digital rectal examination (DRE) and planned rebiopsy to detect disease advancement. If subsequent disease changes pass defined thresholds, then appropriate interventions such as radical or newer ablative treatment options are suggested. Trends in population-based cohort studies on the incidence and mortality rates of prostate cancer detected by PSA screening,[13] and in retrospective cohort studies of people with clinically localised prostate cancer identified in both the pre-PSA[32] and the post-PSA[37] eras, appear to support such a strategy. However, there is no consensus on the definition of disease progression, such as thresholds for absolute or time-dependent PSA rise, and degree of change in microscopic disease appearance on biopsy (Gleason sum score or other histological parameters such as volume of cancer) or on imaging, such as multiparametric magnetic resonance imaging (MRI). The disadvantages of AS as a cancer management strategy include patient and clinician anxiety in leaving a deliberately detected cancer untreated, uncertainty regarding when to initiate treatment and risk of more rapid disease progression precluding cure.

In summary, deciding between treatment options is complex for both clinicians and patients because of a lack of reliable predictors of disease progression and of risk of suffering cancer-related morbidity during an individual's natural lifespan. The basic problem is differentiating between indolent tumours that are not a threat to health and aggressive cancers that are likely to cause symptomatic disease or early death.[38] As a result of this uncertainty, most otherwise healthy people younger than 70 years diagnosed with localised prostate cancer currently choose to undergo immediate curative treatment rather than AS,[39]

although there is little high-quality evidence to guide this choice.[27] In addition to this uncertainty for the population at risk, any potential oncological benefit of curative treatment (e.g. cancer-specific survival) may take at least 10 years to accrue.[40] The recent decrease in disease-specific mortality from prostate cancer seen in communities with high rates of radical treatment, such as the USA, is seen by some as evidence of success for the strategy of early intervention,[41] whereas others consider it more likely to be due to a combination of lead-time and length-time bias resulting from earlier detection of less aggressive disease.[42]

It is against the backdrop of the apparent tension between extremely invasive radical treatment options on one hand, versus a conservative approach inherent in a policy of AS on the other, that alternative, minimally invasive ablative therapies were developed.

Description of the interventions

Evolution of ablative therapies for localised prostate cancer

Ablative therapies refers to a group of interventions which aim for either total, subtotal or focal ablation (or destruction) of the prostate gland in order to treat localised prostate cancer. These therapies have some common characteristics, including (i) a minimally invasive nature, that is they are performed percutaneously through the perineum, transurethrally or transrectally; (ii) being technically simple and easy to master; (iii) allowing repeat treatments; and (iv) allowing salvage radical treatment for treatment failure (i.e. failure to eradicate disease) or disease recurrence following initial cure. These therapies destroy the cancer in the prostate gland in a minimally invasive manner using a range of energy sources, while simultaneously minimising damage to adjacent structures such as the urinary sphincter, urethra, bladder, rectum and nerves for erectile function, hence potentially reducing the risk of adverse effects.

The technology was first described in the mid-1990s, with cryotherapy, high-intensity focused ultrasound (HIFU) and interstitial brachytherapy being used to treat localised and locally advanced prostate cancer in a non-focused manner, whereby the entire prostate gland was subjected to treatment. Over the past two decades, advances in imaging by ultrasound (US) or MRI, together with template biopsy protocols and improvement to the treatment technologies, have all driven the possibility that these therapies can be used in a more precise way, whereby the part of the prostate harbouring the most aggressive cancer can be preferentially targeted for destruction.[43,44] This is achieved in several ways, including lesion-targeted therapy, hemi-ablative therapy (where one half of the gland is targeted) and subtotal ablative therapy. This approach enables preservation of areas of the gland without cancer, together with surrounding structures such as the nerves and blood vessels for erectile function, and the urinary sphincter muscle, bowel and bladder, hence potentially reducing the risk of adverse effects. The approach is also potentially applicable to the common finding of multifocal disease, where the dominant foci with less favourable pathological characteristics are treated, while other, smaller, low-risk foci are left and AS continued.[44] Although primarily undertaken using general anaesthetic, ablative therapies may also be performed under local anaesthetic or sedation in the outpatient setting. Other advantages include the ability to repeat the ablative procedure if required, and if the procedure fails to achieve cancer control, then salvage treatment by way of surgery or radiotherapy can be undertaken.

In addition, ablative therapies have also been used in treating people with local relapse after radical EBRT. Although radical EBRT is considered a curative treatment option for localised prostate cancer, a relatively high proportion of people, estimated at approximately 30%,[45] will develop recurrent disease signalled by a rising PSA and a positive rebiopsy. This recurrence rate is, to some extent, inflated by the higher proportion of people being treated for more advanced disease compared with RP. If left untreated, at least 75% of these people will develop localised prostate cancer recurrence within 5 years[46] and hence require further treatment, although the timing of second-line treatment remains controversial. Subsequent treatment options include palliative hormonal therapy and potentially curative salvage procedures. The currently recommended option, salvage prostatectomy, carries a high risk of morbidity including urinary incontinence and rectal injury.

The ablative technologies considered in this review are (1) brachytherapy; (2) cryotherapy; (3) HIFU; (4) vascular-targeted photodynamic therapy (PDT); (5) transperineal radiofrequency interstitial tumour ablation (RITA) therapy; and (6) laser ablation therapy (encompassing procedures such as photothermal therapy, laser interstitial tumour therapy and laser photocoagulation).

Technical description of the interventions

Brachytherapy

Interstitial brachytherapy involves the ultrasound and template-guided insertion of radioactive seeds into the prostate gland. It is an established curative treatment option for low-risk, early-stage prostate cancer.[9,47] Owing to its more localised effects of radiation, the procedure offers the potential advantage of delivering a higher radiation dose to the prostate than would be possible with conventional EBRT. Brachytherapy is thought to be at least equivalent to the other curative treatment options for localised prostate cancer in terms of cancer control.[47–49] There are various brachytherapy protocols, each with subtle differences in technique, including variations in radiation dosages and scheduling. It can be used either singly or in combination with EBRT (especially IMRT). Two types of radioactive implants are available: permanent seeds [with either iodine (I)-125 or palladium (Pd)-103] or temporary implants [iridium (Ir)-192]. The recommended prescription doses for permanent seed brachytherapy (as monotherapy) are 145 Gy for ^{125}I and 120–125 Gy for ^{103}Pd.[48] For temporary brachytherapy, the radiation dose is delivered at a higher dose rate than for a permanent implant, because the implant can be removed after the treatment session. As such, temporary brachytherapy is termed high-dose-rate brachytherapy. High-dose-rate brachytherapy is commonly delivered in two or more fractions of 810 Gy or more. The commonest adverse effects associated with brachytherapy include urinary, bowel and sexual dysfunction. Since it was first introduced, brachytherapy has been used to treat the entire prostate gland. However, the ability to target discrete lesions within the prostate, by virtue of improved imaging techniques, has made it possible to use brachytherapy as an intraprostatic targeted treatment option for early, localised prostate cancer.[44]

Cryotherapy

Cryotherapy is the ablation of tissue using localised application of extreme cold. It achieves tissue destruction by three processes: (i) direct cell damage from the freeze–thaw cycle; (ii) coagulative necrosis within a few days after treatment; and (iii) apoptosis. The efficiency of tissue ablation is influenced by various factors, including velocity of cooling and thawing, nadir temperature, duration of freezing, number of freeze–thaw cycles and the presence of large blood vessels, which can act as heat sinks. A minimum freezing cycle of –40 °C for 3 minutes is required for tumour eradication.[50] The procedure involves the placement of needle probes transperineally using a template under TRUS guidance. The probes are then cooled to generate an ice ball within the prostate. Cryotherapy has been in use for prostate cancer whole-gland treatment for more than 20 years but the technology has evolved considerably recently. TRUS guidance and urethral warmers were introduced, resulting in more accurate probe placement and enabling monitoring of the ice ball in real time, while the urethral warmers decreased the risk of urethral sloughing.[51] Current third-generation devices utilise probes in which pressurised gas is used to freeze (argon gas) and thaw (helium gas). This enables the use of finer-calibre probes, which further enhance the precision of probe placement and improve the efficiency of tumour cell killing while reducing damage to surrounding structures.[52] The main adverse effects of cryotherapy are erectile dysfunction, urinary incontinence, urethral sloughing, rectal injury and rectourethral fistula formation.[53]

High-intensity focused ultrasound

High-intensity focused ultrasound uses high-energy ultrasound waves (0.8–3.5 MHz) focused to a specific point within the target organ in order to ablate tissue. Cellular damage occurs by two mechanisms: (i) conversion of mechanical energy into heat and (ii) a process termed inertial cavitation. Once tissue temperature exceeds 56 °C, irreversible cell death occurs from coagulative necrosis. Inertial cavitation results from the alternating cycles of compression and rarefaction of the sound waves. At the time of rarefaction, gas can be drawn out of solution to form bubbles, which then collapse rapidly, causing acoustic shock waves which induce mechanical stress. The procedure involves the placement of an ultrasound probe

transrectally. HIFU is also able to deliver its ablative energy more precisely than cryotherapy, with minimal effect on surrounding tissues outside the target zone. However, unlike cryotherapy, there is no 'ice ball' equivalent, and hence it can be difficult to monitor the ablative effects of HIFU during treatment, although the process is guided by ultrasound. To minimise the thermal effects on the rectal wall, the rectum is irrigated with degassed, cooled water, which also eliminates acoustic interference between the transducer and the rectal mucosa. HIFU has been widely used in Europe for whole-gland therapy, and two systems are currently marketed. Both work by generating and focusing high-energy ultrasound waves at the target to generate temperatures above 60 °C. The major adverse effects of HIFU include acute urinary retention, erectile dysfunction, urethral stricture, rectourethral fistula and pelvic pain.[54] Disadvantages of HIFU include difficulty in achieving complete ablation of the prostate, especially in glands larger than 40 ml, and in targeting cancers in the anterior zone of the prostate.[55]

Vascular-targeted photodynamic therapy

Photodynamic therapy is a technology which achieves destruction of targeted tissues using a light-sensitive agent (photosensitiser) and laser light of a specific wavelength in the presence of oxygen. The photosensitiser absorbs light of specific wavelength and transfers the energy to adjacent oxygen molecules, to create reactive oxygen species that trigger cell destruction.[56] To treat prostate cancer, the photosensitiser [Tookad® WST09 and WST11 (STEBA Biotech S.A., Luxembourg City, Luxembourg)] is administered intravenously and accumulates preferentially in the tumour blood vessels. The photosensitiser is activated by laser light of specific wavelength, which is delivered transperineally using optical fibres. Alternative photosensitisers are also under investigation. Complications of vascular-targeted PDT include phototoxicity, skin photosensitisation, erectile dysfunction, urethral damage and rectourethral fistula formation.[55]

Radiofrequency interstitial tumour ablation

Radiofrequency interstitial tumour ablation is a procedure that utilises low-level radiofrequency energy (approximately 460 kHz) to heat and ablate tissue in a focused manner. Tissue destruction is achieved by coagulative necrosis resulting from heating tissues to 100 °C for 5 minutes. The procedure has been shown to be effective and safe in the treatment of primary and secondary liver tumours[57] and in renal cancer as an alternative to nephron-sparing surgery.[58] For the treatment of localised prostate cancer, the radiofrequency energy is delivered through needle probes which are inserted transperineally into the prostate, and treatment is conducted under TRUS guidance. Temperature in the rectal wall is monitored and both the urethra and rectum are irrigated with cooling solutions to avoid heat damage. The procedure is conducted under sedation on an outpatient basis. Patients are usually catheterised urethrally for a day. Adverse effects include frank haematuria, bladder spasms and dysuria, all of which appear to be transient.[59]

Laser ablation therapy

Laser ablation is a generic term implying thermal destruction of tissue by laser energy. It encompasses a number of technologies that have been used to treat prostate cancer and are therefore relevant to this review, including photothermal therapy, laser interstitial tumour therapy and laser interstitial photocoagulation. Tissue destruction occurs by local coagulative necrosis, with temperatures ranging from 42 °C to more than 60 °C. However, laser energy has a localised effect, resulting in minimal damage outside the targeted ablation zone. Experience with laser ablation for solid tumours comes from the focal treatment of liver metastases from colorectal cancer.[60] The Nd-YAG laser, with a wavelength of 1064 nm, was initially used for prostate cancer ablation but it is being superseded by more compact and less expensive infrared diode lasers (wavelength 800–980 nm). The laser is delivered transperineally through flexible quartz fibres within a flexible fibre-optic device which also allows the use of water-cooled laser application sheaths, which prevent overheating close to the fibre tip.[61] Targeting of the lesion and real-time monitoring of the ablation can be performed using either magnetic resonance (MR) thermometry or contrast-enhanced ultrasound. The use of MR thermometry is particularly advantageous as it allows for individually adjusted heat dosing application, thereby ensuring adequate tumour ablation while simultaneously avoiding damage to adjacent normal tissues. Reported adverse effects include transient perineal discomfort and haematuria.[62] Laser ablation therapy has the theoretical advantages of accurate, predictable and reproducible delivery of energy. Real-time monitoring by either MR or contrast-enhanced ultrasound is also more easily performed.

Current use of ablative therapies in the UK NHS

The ablative technologies described in the previous section are currently not recommended for routine use in people with localised prostate cancer in UK NHS hospitals. The last National Institute for Health and Care Excellence (NICE) clinical guideline[9] suggested that HIFU and cryotherapy should only be used within controlled clinical trials comparing their use with standard interventions. Since the publication of this guideline, ablative technology has evolved, such that focal ablative therapies are increasingly being considered as a feasible and valid minimally invasive option in the treatment of people with localised prostate cancer.[43,44] Apart from cryotherapy and HIFU, which are currently being investigated within the context of clinical trials, none of the other techniques are available in the UK. However, newer ablative techniques such as vascular-targeted PDT and transperineal RITA are being assessed elsewhere around the world. Further options currently being tested in early-phase clinical studies include interstitial hyperthermia using magnetic nanoparticles, and electroporation.[43,63]

Although promising, newer ablative therapies for localised prostate cancer are still relatively untested in comparison with other, established treatment modalities such as surgery or radiotherapy, and are likely to evolve as new technologies emerge. The most important challenges for the effectiveness of minimally invasive ablative therapy include the need for accurate imaging modalities to target treatment; identification and localisation of areas of higher-risk aggressive cancer using precise biopsy templates with reproducible pathological categorisation; defining disease persistence and disease recurrence; and finally determining the most appropriate salvage treatment options for treatment failure.

Projected rise in the number of people in the UK requiring treatment for localised prostate cancer

At present in the UK, localised prostate cancer is detected by case finding among asymptomatic people who request a PSA test and during the assessment of people complaining of unrelated urinary symptoms. In 2010, almost 41,000 people were diagnosed with prostate cancer in the UK,[1] with 18,408 (45%) aged younger than 70 years.[3] The majority of these people will have localised-stage disease, and are hence suitable for curative treatment.[1] Previous annual estimates of treatment suggest that over a 12-month period, 3922 people underwent RP,[64] while approximately 4000 underwent EBRT and 1455 underwent brachytherapy.[64] The corresponding figure for AS was approximately 800.[65] There is evidence from the USA to suggest that the use of RP as a primary treatment option for localised prostate cancer is increasing.[34] The results from a PSA screening trial, the European Randomised Study of Screening for Prostate Cancer (ERSPC), showed a doubling of cancer detection rate among people in the target age group (55–69 years) accompanied by a similar increase in the number of people going on to have potentially curative treatment.[66] Overall, 3% of people screened and 1% of controls underwent RP during the 9 years of follow-up. Findings from the US-based Prostate, Lung, Colon and Ovarian Cancer Screening Study (PLCO) were similar, with 3% of people screened and 2% of controls having RP during the 10-year study duration.[67] Translating these figures to the UK 2011 population of 5.05 million people aged 55–69 years, the annual number of RPs would rise to approximately 7000 with increased case finding and to 11,000 if a screening programme was instituted.

Recent evidence from the HTA-funded UK trial of treatment for localised prostate cancer, Prostate Testing for Cancer and Treatment (ProtecT), suggests that the incidence of disease in younger people aged under 55 years is also significant, further increasing the population potentially requiring consideration towards treatment.[68] Evidence from the USA suggests that increasing incidence of low-risk cancer is accompanied by increased use of AS and newer ablative therapies such as cryotherapy, with AS being selected by 10.2% and newer ablative therapies by 4.4% of affected people between 2004 and 2006.[34] In NHS hospitals in England, the numbers of people with prostate cancer treated with newer ablative options remains small, with 66 recorded as undergoing cryotherapy and 168 HIFU,[64] although discussion with relevant clinicians suggests that the numbers are increasing.

Summary

In summary, increasing incidence of low- and medium-risk localised prostate cancer makes it likely that demand for alternative, non-radical treatment options for prostate cancer in the UK will increase substantially over the next decade, requiring appropriate service provision and the need for policy decisions regarding the cost-effectiveness of available treatment options. As such, policy-makers within the NHS are faced with the need to plan service provision for such alternative treatment options, in particular ablative therapies. This assessment has therefore been designed to help inform decisions regarding the commissioning and use of ablative therapy for people with localised prostate cancer in the NHS.

Aims of the assessment

This assessment aims to systematically review and meta-analyse evidence on the clinical effectiveness and harms of ablative therapies, including those recently developed for localised prostate cancer within the UK NHS, and to model the cost-effectiveness of these therapies. The specific objectives of this assessment are to:

1. develop clinical care pathways for the treatment of localised prostate cancer in a UK NHS context (objective 1)
2. review systematically the evidence of the clinical effectiveness and safety of each ablative therapy (objective 2), concerning:

    i. primary treatment of localised low-/intermediate-risk prostate cancer compared with AS, RP and EBRT
    ii. primary treatment of localised high-risk prostate cancer compared with RP and EBRT
    iii. salvage treatment for local prostate cancer relapse after EBRT compared with salvage RP

3. determine which therapies are most likely to be cost-effective for implementation in the UK NHS (objective 3)
4. identify and prioritise future research needs (objective 4).

Chapter 2 Description of care pathways

Patient group

Introduction

The population of patients considered for this review are people with localised prostate cancer who are considered suitable for active treatment or AS and are managed within the UK NHS. The patient characteristics that define this population include age and comorbidity that collectively determine an estimated life expectancy of at least 10 years.

Disease factors provide the estimated risk of developing recurrent disease, either from distant metastases not identified at pre-operative assessment, or because of failure to completely remove localised disease. The approximate magnitude of this risk for an individual diagnosed with prostate cancer can be calculated using a nomogram. The most commonly used version is hosted by the Memorial Sloan Kettering (MSK) Cancer Institute in web-based form.[69] These models use the pre-operative disease variables of age, PSA, clinical tumour stage, Gleason grade and number of needle biopsy cores positive for cancer.

The described care pathway was constructed using available evidence, previous care pathways (*Figure 2*) developed by the Aberdeen Academic Urology group in conjunction with a national and international panel of experts, and consensus-building through several meetings of the expert panel convened for this review. Although it is primarily constructed as the basis of the modelling of cost-effectiveness reported in *Chapters 9* and *10*, the pathway is consistent with previously published clinical pathways of care.[9,70–73] The complete care pathway developed for the review is shown in *Chapter 9* (see *Figure 16*, with *Figures 17–20* illustrating how the care pathway varies for alternative interventions under investigation).

Pretreatment level of prostate-specific antigen

The pretreatment PSA level is an independent statistically significant predictor of future recurrence, but on its own is limited in reliability and predictive value. For prognostic purposes the value is defined in risk groupings corresponding to low (< 10 ng/ml), intermediate (10–20 ng/ml) and high (> 20 ng/ml) risk of disease progression following radical treatment.[36]

Staging of prostate cancer

The stage of an individual's cancer is categorised according to the Union for International Cancer Control (UICC) 2009 tumour node metastasis (TNM) classification.[74] Pre-operatively, this is determined by clinical assessment using DRE and imaging and is given the prefix 'c'. Following removal and pathological examination of the prostate and, in some cases, adjacent lymph nodes, the staging is adjusted accordingly and given the prefix 'p'.

Gleason grading

The qualitative low-magnification microscopic histological description of prostate cancer first suggested by Gleason in 1966[75] remains an essential aspect of prognostic categorisation, although there have been substantial modifications over the years.[76] Standard practice consists of identifying the first and second most prevalent patterns within a set of biopsy cores which give the primary and secondary Gleason grades (each rated 1–5). These are then added together to give the overall Gleason sum score (2–10). Recent consensus tends to limit the use of grades 1 and 2 and therefore scores generally range between 6 and 10.[77] Higher individual grade and total score indicate more aggressive disease, with primary grade being more predictive. An individual whose tumour is categorised as Gleason score $4 + 3 = 7$ will therefore tend to have a worse prognosis than if the Gleason score was $3 + 4 = 7$, for example.[78]

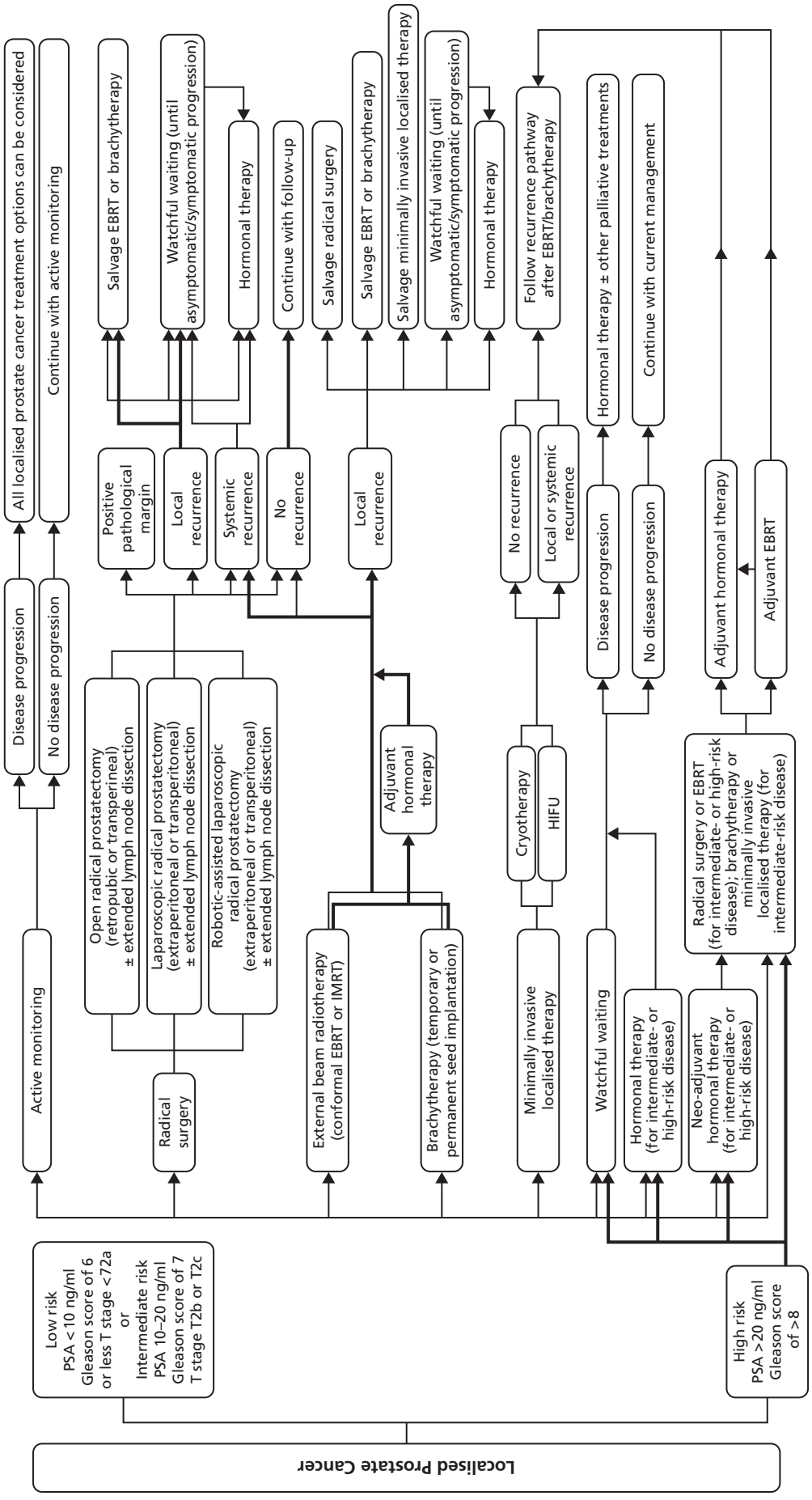

FIGURE 2 Localised prostate cancer care pathway.[17]

Cancer volume

There is some evidence that cancer volume is also an independent prognostic factor for progression of the cancer following initial management. For this reason, pathologists examining biopsy cores will estimate cancer volume by stating the number of cores that contain cancer and estimating the proportion of each core that is affected by the cancer.[79]

Summary

Pretreatment information including age, serum PSA, tumour stage, Gleason sum score and tumour volume predicts the risk of disease recurrence. It is therefore important that studies comparing treatments, such as this current assessment, include an evaluation of whether or not the patient groups undergoing each procedure are balanced for these variables. For the purposes of the current assessment, people with localised prostate cancer will be stratified into three groups according to D'Amico risk of recurrence following curative treatment[36] (*Table 1*): low, intermediate and high risk. The system utilises pretreatment variables of serum PSA level, Gleason sum score and T stage of the TNM staging system.

Treatment characteristics

Introduction

This study includes a cost-effectiveness analysis of ablative therapies compared with other standard interventions (see *Chapters 9* and *10* for more details). For the economic modelling, it is assumed that the procedures being considered will be carried out in hospitals that have the necessary resources in terms of staff, facilities and NHS cancer plan approval to carry out the various interventions on a routine basis. For surgical procedures (i.e. RP, HIFU or cryotherapy), this will comprise operating theatre and recovery facilities, including critical care and standard urology wards; the required clinical and technical expertise, including surgeons, anaesthetists, theatre nursing team, pathologists and technicians; and continued care, including outpatient review, repeat imaging and facilities for further treatment for adverse events or cancer progression. For EBRT, the resource estimates were modelled after IMRT, because in most cancer units around the UK, IMRT has superseded 3D-CRT as the standard for EBRT. The resource estimation includes costs associated with radiotherapy planning visits, treatment sessions, staff time, consumables, etc. For brachytherapy, the resource estimates were modelled after low-dose brachytherapy (i.e. involving permanent seed implantation), and resource estimation includes costs for seed implantation under general anaesthetic, incorporating costs for a radiologist, urologist, oncologist, anaesthetist, theatre staff, consumables, etc.

A detailed description of the various interventions are provided in *Chapter 1*, and a more detailed description of the treatment care pathways for each intervention in terms of resource use is provided in *Chapter 9*.

TABLE 1 D'Amico risk of biochemical recurrence after radical treatment stratified according to tumour characteristics[36]

Group	PSA (ng/ml)		Gleason score (0–10)		Clinical stage
Low risk	< 10	and	≤ 6	and	T1–T2a
Intermediate risk	10–20	or	7	or	T2b–T2c
High risk	> 20	or	8–10	or	T3–T4

Learning curve of procedures

For safe conduct of all interventions, it is essential that all members of staff involved in delivering the therapy have had specific training and are competent to undertake the procedure. In the UK, all of the surgical procedures (including RP, cryotherapy and HIFU) are normally performed by consultants who have received specific training. As such, for the economic modelling, it is assumed that such procedures are undertaken by a trained consultant. Non-surgical procedures such as EBRT and brachytherapy are less susceptible to learning curve effects of individuals. The review assumes that such procedures are undertaken by experienced teams led by a consultant oncologist.

Hospital stay

For surgical procedures, people are generally admitted to hospital either on the day of surgery or the evening before. For RP, a rectal enema is administered to clear the lower bowel. Immediately prior to the procedure, prophylactic antibiotics are given according to local policy and venous thrombosis/embolism prophylaxis is commenced as required. After surgery, the patient is routinely nursed on a standard ward although specific comorbidities or intraoperative complications may require a period in a critical care bed. For RP performed laparoscopically, people are typically discharged home after 3 days with an indwelling catheter, although this may be variable (e.g. hospitalisation time can be reduced by managed care programmes). They then return to the ward as a day patient after a further 7–14 days, according to local protocol, for urinary catheter removal and voiding check. For cryotherapy, people stay up to 2 nights in hospital after their procedure, whereas for HIFU they stay for 0–1 night. In both instances, they return to the ward after a further 7–14 days as a day patient for urinary catheter removal and voiding check.

Perioperative complications

Although people undergoing surgery for localised prostate cancer (including RP, cryotherapy and HIFU) generally do not have concurrent comorbidity that is a persistent threat to their health, a proportion will be expected to suffer adverse events associated with surgery, and anaesthetic-related problems such as cardiac ischaemia and pulmonary embolism. In addition, specific complications include urinary and blood stream infection, inadvertent injury to adjacent organs (e.g. rectal injury), excessive blood loss requiring transfusion, prolonged urinary or lymphatic leakage from abdominal drains, development of urethral stricture or fistula, etc. The adverse effect of these complications in terms of their severity and requirement for additional interventions and hospital stay can be summarised according to the Clavien system (*Table 2*).[80,81]

TABLE 2 Abbreviated Clavien–Dindo classification of surgical complications[80]

Grade	Definition	Exclusions
0	No deviation from planned postoperative course considering procedure and pre-existing comorbidity	
I	Any deviation from the normal postoperative course without the need for specific pharmacological treatment or surgical, endoscopic and radiological interventions	
II	Requiring pharmacological treatment with drugs other than those allowed for grade I complications. Includes blood transfusions and total parenteral nutrition	Treatments listed under grade I
IIIa	Requiring surgical, endoscopic or radiological intervention *not under* general anaesthesia	
IIIb	Requiring surgical, endoscopic or radiological intervention *under* general anaesthesia	
IVa	Life-threatening complication affecting *single* organ system requiring IC/ICU management	TIAs
IVb	Life-threatening complication affecting *more than one* organ system requiring IC/ICU management	TIAs
V	Death of a patient	

IC, intensive care; ICU, intensive care unit; TIA, transient ischaemic attack.

For RP, an additional specific short-term complication is narrowing (bladder neck stenosis) of the sutured join between the top of the urethra and bladder outlet (vesicourethral anastomosis). This will become noticeable after removal of the draining catheter and will result in voiding problems reported by the patient at the 6-week outpatient review. It is treated with endoscopic incision of the narrowed area, which requires an additional short hospital stay and a 7-day period of catheterisation. For most people the problem is cured by a single incision, although for some this may need to be repeated once or twice.[82]

For non-surgical interventions (e.g. EBRT and brachytherapy), the management of adverse events depends on the severity, graded according to common acute and late toxicity grading systems [e.g. Radiation Therapy Oncology Group (RTOG) Common Toxicity Criteria].[83] In this assessment, for the estimation of resource use, expected duration of hospital stay based on the severity of adverse events was graded based on clinical judgement from members of the study team.

Histopathological examination of prostate biopsies and radical prostatectomy specimen

For RP, careful and thorough microscopic examination of the removed prostate by an experienced pathologist is required to determine the true extent of the disease, to decide whether or not the surgery may have been unable to remove all the contained cancer (positive margin) and whether or not the cancer had spread outside the prostate (extracapsular extension), and, if lymphadenectomy has been performed, to detect the presence of lymph node metastatic disease. In addition, a more comprehensive description of the distribution of Gleason patterns within the cancer is possible. This examination will recategorise the disease according to stage [pathological tumour (pT) and pathological node (pN)] and postoperative Gleason score, which will allow more accurate estimation of prognosis according to available post-RP prognostic nomogram[69] and inform whether or not early additional (adjuvant) treatment should be advised. The crucial nature of this examination has led to consensus meetings of expert pathologists who have set out a specified protocol of specimen collection, processing, examination and analysis.[77,84]

For interventions whereby repeat prostate biopsies are necessary as part of the follow-up protocol (e.g. AS, cryotherapy and HIFU), or triggered by a suspicion of biochemical recurrence, the economic model assumes that the biopsies are performed using the TRUS approach, and where appropriate, this may be augmented by MRI-directed or guided strategies. The biopsy specimens are reviewed and reported by an experienced pathologist within a urological cancer multidisciplinary team setting.

Surveillance following initial treatment

Follow-up schedule

People who have undergone RP are generally seen by the operating team as outpatients 6 weeks after their surgery, then 3-monthly for the first year and 6-monthly for the next 4 years. At each follow-up, serum PSA is checked for tumour recurrence and a qualitative assessment made for continence and desired sexual function. If further assessment or treatment is required for any of these aspects, then the pathway of care will be changed accordingly.

For EBRT and brachytherapy, patients were assumed to have follow-up as part of post-treatment surveillance for up to 5 years, assuming that there were no changes in the patient's condition, nor any evidence of biochemical recurrence such that they had to leave the surveillance state. In the first year of surveillance, patients would attend four nurse-led urology outpatient appointments, with PSA tests conducted in each of these. For the second year through to the fifth it was assumed that patients would attend two nurse-led urology outpatient appointments with PSA testing at each. After the first 5 years, it was assumed that patients would receive an annual PSA test conducted by a practice nurse in a primary care setting. Patients would also have an annual DRE each year for the first 5 years.

For cryotherapy and HIFU, similar assumptions were made. Where repeat prostate biopsies were mandatory within the first year of treatment, this was regarded as a part of the 'package of treatment' rather than as a part of follow-up. The economic model also made allowance for imaging of the prostate using multiparametric MRI during the follow-up period.

For AS, the following assumptions were made based on a standard protocol. In the first year of follow-up, patients would attend four nurse-led urology outpatient appointments with PSA tests conducted at each appointment. At 12 months, a multidisciplinary team cancer meeting would take place to review each patient. Patients in year 2 would attend two nurse-led urology outpatient appointments, again with PSA tests performed at each appointment. In addition, patients would undergo a standard 12-core TRUS-guided biopsy. Year 4 of AS was assumed to be identical to this, and years 3 and 5 were assumed to be the same with the exception of the TRUS-guided biopsy. Patients would also have an annual DRE in years 1–5. After the first 5 years, it was assumed that patients would receive an annual PSA test conducted by a practice nurse in a general practice setting.

Detection of persistent or recurrent disease

The risk of disease recurrence is higher if one or more of the disease factors, including pre-operative PSA > 20 ng/ml, Gleason score of > 7, extracapsular disease (T3/T4), positive margin or positive lymph nodes (N stages N1/N2 of the TNM staging system), are present as determined by lymphadenectomy. If the likelihood of disease persistence or recurrence is deemed to be very high, then immediate adjunctive treatment may be offered. For the majority of people, PSA surveillance is started according to the above schedule. There are multiple definitions of the threshold of PSA rise that signifies biochemical recurrence between interventions, and within an intervention. For RP, because the prostate gland and prostate cancer (which are the only sources of PSA in the blood) have been removed, if cure has been achieved, the expectation is a complete absence of serum PSA 3 weeks after treatment. However, laboratories have different sensitivity and specificity thresholds. The commonest baseline is 0.2 ng/ml. As such, for a definition of cure, the patient should have reached a nadir (i.e. lowest PSA reading) which is below 0.2 ng/ml after 3 weeks following treatment. The most common definition for biochemical recurrence is two successive serum PSA readings > 0.2 ng/ml.[85]

For EBRT and brachytherapy, several definitions are in existence, the commonest of which is the Phoenix definition.[86] This defines recurrence as 'a rise by 2 ng/ml or more above the nadir PSA'.

For cryotherapy and HIFU, there is no consensus regarding what should constitute biochemical recurrence. Although the Phoenix criterion is often reported, it has not been validated for either intervention.

For AS, because the cancer remains untreated but merely monitored, definitions for biochemical recurrence do not apply. The main immediate cancer-related outcome of relevance for AS is disease progression or upgrading of cancer grade (often collectively termed 'reclassification of disease'). However, there is controversy regarding what constitutes progression or reclassification, with AS protocols adopting different definitions.[87]

For all interventions except AS, the occurrence of biochemical recurrence does not automatically trigger salvage treatment; in some instances, the patient may continue to be monitored until a point where salvage treatment is deemed necessary. However, most patients will undergo salvage treatment once biochemical recurrence occurs. The decision whether to institute immediate salvage treatment or further monitoring will be informed by tests such as MRI and/or a radionuclide bone scan designed to demonstrate the site of recurrence as being in the prostatic bed (i.e. localised recurrence), or as lymph node or bone metastases (i.e. systemic recurrence).

Salvage treatment

Following localised recurrence, the salvage treatment options are salvage RP, salvage EBRT, savage brachytherapy and salvage ablative therapy (HIFU or cryotherapy) (see *Figure 16* in *Chapter 9*). The assumption for the model is that salvage treatment should differ from the primary treatment (i.e. patients who have had primary RP would be ineligible for salvage RP). With the exception of salvage RP, the model allows for the addition of androgen deprivation therapy for a duration of up to 2 years following salvage treatment.

For people with likely systemic recurrence, long-term androgen deprivation therapy (medical castration), most commonly achieved with a luteinising hormone-releasing hormone (LHRH) agonist, is recommended. This consists of 3-monthly injections of a depot preparation of the chosen drug. For people whose disease progresses despite local and systemic adjuvant treatment, palliative symptom control will be instituted.

Urinary incontinence

Urinary incontinence is one of the most important long-term adverse effects of treatment for localised prostate cancer. Recovery of continence following some interventions, such as RP, can take up to 12 months, although most people will regain continence by 6 months. Therefore, people suffering urinary incontinence will be advised to use containment devices such as absorbent pads or penile sheath drainage for the initial 12 months. For the majority of interventions, the expectation is for urinary incontinence to improve within the first year, beyond which further improvement is unlikely. As such, if bothersome leakage persists beyond this time, then the main treatment options will be surgical implantation of an artificial urinary sphincter (AUS) or continued use of containment devices.

Erectile dysfunction

Of people who were sexually active prior to treatment, a large proportion will experience worsening of their sexual function, and in particular difficulty initiating and sustaining penile erection sufficient for intercourse. This is particularly dependent on preservation of one or both neurovascular bundles during treatment. For these people, treatment options will include drug treatment taken as required, vacuum constriction device or penile implant surgery. Most people will first trial the oral phosphodiesterase inhibitors sildenafil, tadalafil (Cialis®, Lilly) or vardenafil (Levitra®, Bayer) which, under NHS prescribing rules, are limited to one tablet weekly. The next option will be alprostadil given as an intraurethral pellet or an intracavernosal injection with NHS supply, again limited to once-weekly doses. For people who achieve satisfactory restoration of sexual activity with these drugs, it is assumed that their use will continue long term. If drug treatments are unsuccessful, people may trial a vacuum constriction device, or consider surgical implantation of a penile prosthesis. The proportion of people pursuing the last two options is small, as most will accept their loss of sexual function in the longer term.

Chapter 3 Methods of, and studies included in, the systematic reviews of clinical effectiveness

Search methods

Comprehensive electronic searches were conducted to identify reports of published studies. Highly sensitive search strategies were designed, including appropriate subject headings and text word terms, interventions under consideration and included study designs. Given the anticipated large number of studies requiring full-paper assessment, only English-language reports were included, with the exception of randomised controlled trial (RCT) evidence that involved an ablative procedure, where no language restriction was applied. Searches were not restricted by year of publication. MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Bioscience Information Service (BIOSIS), Science Citation Index, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and the HTA databases were searched. All databases were searched up to March 2013. Reference lists of all included studies were scanned and we asked our expert panel for details of additional reports. All database search strategies and details of dates of searches for clinical effectiveness are detailed in *Appendix 1*.

Identification of other relevant information, including unpublished data

The World Health Organization (WHO) International Clinical Trials Registry, EU Clinical Trials Register, Current Controlled Trials, ClinicalTrials.gov and National Institute for Health Research (NIHR) Portfolio were searched for ongoing studies. Websites of manufacturers, professional organisations, HTA organisations and regulatory bodies were also checked for additional reports (see *Appendix 1*, *Websites consulted*).

Inclusion and exclusion criteria

Types of study

For all three reviews, we considered evidence from RCTs and non-randomised comparative studies (NRCSs) (if no RCT evidence was identified), and from single-arm cohort studies (case series) (greater than 10 participants) for the ablative procedures only. Had comparative studies of the ablative procedures been identified, consideration would have been given to removing single-arm cohort studies from the reviews.

Studies comparing only multiple treatments of the same non-ablative therapy within the same comparative study (e.g. comparing different dosages of radiotherapy, or open vs. laparoscopic prostatectomy) were excluded. Conference abstracts were excluded, as were non-English-language reports with the exception of RCTs incorporating an ablative procedure comparison, for which no language restriction was applied.

Types of participants

The types of participant considered were people with localised prostate cancer, defined as cancer confined to the prostate gland. Eligible patients had clinical stage T1 or T2 disease at presentation (not pathological staging).

We planned to stratify people into localised low/intermediate risk and localised high risk of progression, based on the criteria shown in *Table 3* (adapted from D'Amico risk stratification).[69]

TABLE 3 Risk stratification for people with localised prostate cancer[69]

Group	PSA (ng/ml)		Gleason score (0–10)		Clinical stage
Low risk	< 10	and	≤ 6	and	T1–T2a
Intermediate risk	10–20	or	7	or	T2b–T2c
High risk	> 20	or	8–10	and	T2c or lower

The criteria for assessing the patient's risk of recurrent disease were the same for primary or salvage treatment. For studies with patients of mixed clinical stages (i.e. T1 to T4), studies were included if greater than 80% of the patients were stage T1 or T2. Additionally, for the salvage therapy review the patients must have received EBRT prior to salvage therapy being considered. Studies of people with locally advanced prostate cancer (considered as stage T3/T4) were excluded.

Although the systematic reviews of primary treatment of localised low-/intermediate-/high-risk prostate cancer and salvage therapy relate to subsets of T1 and T2 disease, we included any studies that reported comparative data on T1 and/or T2 disease. This reflects the observation during scoping (and our experience of conducting such reviews in prostate cancer) that many studies do not report outcomes by the substages of T1 or T2 disease. Given the difficulty in attributing studies to subsets of T1 and T2 disease, it was not possible to undertake analyses of subsets on risk.

For the primary review, studies were included if patients were fit for surgery. Where studies enrolled patients for both primary and salvage procedures and reported combined results, the study was eligible if 5% or less of the study population were salvage patients.

For the salvage review, studies were included if at least 80% of all salvage patients had received prior treatment with EBRT.

Types of interventions and comparators

For the primary therapy systematic review on low-/intermediate-risk localised prostate cancer, the ablative therapies considered were cryotherapy, HIFU, PDT, RITA, laser ablation and brachytherapy. The comparators were AS, RP and EBRT.

For the primary therapy systematic review on high-risk localised prostate cancer, the ablative therapies considered were cryotherapy, HIFU, PDT, RITA, laser ablation and brachytherapy. The comparators were RP and EBRT.

For the salvage therapy systematic review, the ablative therapies considered were cryotherapy and HIFU. The comparator was RP.

Types of outcome measures

In addition to contacting content experts to identify outcomes of importance, we also elicited the views of a group of people living with prostate cancer. The group consisted of seven male participants who had undergone ablative therapy (HIFU), robotic, laparoscopic and open RP, and radiotherapy. The participants were invited to join a group discussion and express their own opinions on the choice of relevant outcomes following treatment for localised prostate cancer. They were recruited through a local Urological Cancer Charity (UCAN) and were not aware of the views of the content experts.

On the whole, the participants were in agreement with the content experts as to the key outcomes of importance. For example, clear primary importance was placed on survival and recurrence (cancer-specific outcomes). Several people commented that other outcomes were irrelevant in the event of death. Survival

was deemed the most important outcome, but some noted that, in the context of localised disease, they assume that they will survive the cancer and so other outcomes then take on more importance. The interaction between survival, recurrence, progression and treatment success was also considered important in treatment decision-making.

Other outcomes that were highlighted as being meaningful to all of the participants were urinary incontinence and erectile dysfunction, followed by quality of life. Outcomes that were mentioned by some of the participants were catheterisation, urethral stricture, Peyronie's disease, length of hospital stay, faecal incontinence, rectal itching and bleeding, emptying the bladder when ejaculating, having to travel for treatment, getting 'back to normal' and recovery times. Financial cost to the NHS was not deemed to be of high importance.

The outcomes considered in this assessment were categorised as follows:

- cancer related
    - biochemical (PSA) recurrence (primary cancer-related outcome)[43]
    - disease-free survival, defined as the absence of clinically detectable disease in a surviving patient
    - overall survival
    - further prostate cancer treatment
- adverse effects: functional outcomes
    - sexual (penile erection) function, defined by validated score [such as the International Index of Erectile Function-5 (IIEF-5)], or as defined by the triallists
    - urinary continence, defined, for example, as ≤ 1 thin pad per day and/or by validated symptom score [such as the International Consultation on Incontinence Modular Questionnaire – Urinary Incontinence (ICIQ-UI)], or as defined by the triallists
- quality of life
    - generic and disease-specific quality of life [validated quality of life score such as the Short Form questionnaire-36 items (SF-36)][88]
- procedural
    - length of hospital stay (if applicable)
    - abandonment of the procedure
- adverse events: procedural complications and early death
    - including, but not restricted to, urethral sloughing, rectourethral fistula formation, urethral stricture formation, acute urinary retention, dysuria, pelvic pain, rectal injury, perioperative death, and periprocedural death and Clavien score (if applicable).

Exclusion criteria

The following types of report were excluded:

- reports focusing on people with metastatic disease
- non-English-language reports of non-randomised studies
- conference abstracts
- reports of retrospective studies of AS.

Data extraction strategy

Two reviewers independently screened titles and abstracts of all citations identified by the search strategies. Full-text copies of all potentially relevant reports were obtained and independently assessed by two reviewers to determine whether or not they met the predefined inclusion criteria. Any disagreements were resolved by consensus or arbitration by a third person. A data extraction form was developed specifically for the purpose of this assessment to collect information on study design, characteristics of participants, characteristics of interventions and outcome measures. For studies reporting adverse events, surgeons categorised each complication using the Clavien–Dindo Classification of Surgical Complications,[80] with a third surgeon acting as arbiter in cases of disagreement about classification.

Quality assessment strategy

Risk of bias

Experience has demonstrated that multiple quality assessment tools are required for systematic reviews where multiple study designs are considered. One reviewer assessed the quality of included studies using one of three prespecified checklists, depending on study design. The standard Cochrane risk-of-bias tool[89] was used to assess the risk of bias in randomised trials, and the risk-of-bias tool recommended by the Cochrane Non-Randomised Studies Methods Group was used for NRCSs.[89] For NRCSs, the main confounders were identified a priori by the expert panel (by outcome). A study was considered to be at high risk of bias if any of the confounders were imbalanced (e.g. age or D'Amico risk). We developed a case series tool for assessing risk of bias through our partnership in the Review Body for Interventional Procedures for NICE.[90–93] The case series tool rates bias and generalisability, sample definition and selection, description of the intervention, outcome assessment, adequacy of follow-up and performance of the analysis. Discrepancies were resolved by discussion or referred to a third party. Copies of the risk-of-bias tools are given in *Appendices 3–5*.

Data analysis

Data from each study were tabulated and summarised for each procedure in a form appropriate for the data and the meta-analysis. If data were only available from Kaplan–Meier graphs, they were extracted from the graphs using Engauge Digitizer version 4.1 (http://digitizer.sourceforge.net/) and transformed into outcomes using methods proposed by Tierney and colleagues.[94] The lack of RCT evidence precluded undertaking any standard two-group meta-analyses; therefore, an indirect comparison (cross-design) approach allowing inclusion of non-randomised comparative data and case series was adopted.[95] The main parameters in the models for dichotomous outcomes are the logarithm of the odds ratios (log-ORs) of each ablative procedure compared with the reference comparative procedures. Models were run in a pairwise fashion for each ablative procedure against each comparative procedure; this was repeated for each outcome where studies had reported data that facilitated meta-analysis. Odds ratios (ORs) and associated 95% central credible intervals (CrIs) were estimated between each ablative comparative procedure where possible. An estimate of the probability of each outcome was also modelled within each ablative and comparative procedure using a single-arm meta-analysis. This is summarised as the probability of the outcome and 95% CrI. The CrIs reflect the degree of uncertainty around these estimated model parameters. In the tables, for a positive outcome (i.e. overall survival), an OR of > 1 favours the ablative procedure; for a negative outcome (i.e. biochemical failure), an OR of < 1 favours the ablative procedure. We calculated, for each comparison made, the probability that the ablative procedure was better, denoted by 'p (ablative > comparator)' in the results tables.

Vague prior distributions were used on the log-ORs of ablative procedures compared with comparative procedures. Owing to a paucity of data, models would often not converge with a vague prior on the between-study (random-effects) standard deviation. To ameliorate this we used an informative prior

for the between-study standard deviation that reflected moderate between-study heterogeneity [a uniform (0, 2) distribution]. For most outcomes, a burn-in period of 10,000 iterations was adequate to achieve convergence and a further 10,000 samples were taken. The model parameters were estimated with Bayesian methodology with the use of WinBUGS software version 1.4.3[96] (MRC Biostatistics Unit, Cambridge, UK), using the winbugs from stata package[97] in Stata 13 (StataCorp LP, College Station, TX, USA).

Pre-planned subgroup analyses

After discussion at the first expert advisory group meeting for this assessment, three subgroup analyses were identified to be undertaken. The subgroups were:

- low risk of bias studies only
- focal ablative therapy versus EBRT or RP
- low-risk disease treated with ablative therapy versus AS.

Clinical effectiveness: overview of included studies

Number of studies identified

Title and abstract searches identified 7134 potentially relevant citations, from which 548 reports were retrieved for full-text screening. Of these, 121 were included and 427 were excluded, with reasons given in *Figure 3*. Of the 121 included reports, 113 reports (88 studies) were eligible for inclusion in the review of patients undergoing primary treatment for localised prostate cancer,[36,49,52,98–207] and eight additional reports (nine studies) were included in the review of patients undergoing salvage treatment for recurrence of local prostate cancer following EBRT failure.[208–215] In one report,[120] two studies were reported, each eligible for primary and salvage reviews; another[121] reported data separately for a subset of participants who were

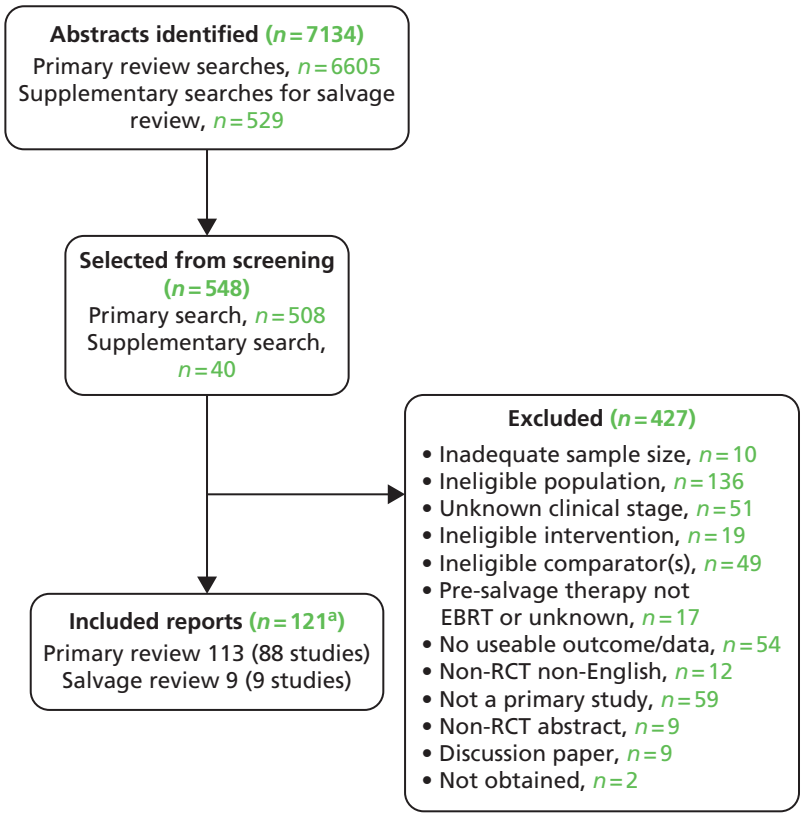

FIGURE 3 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of potentially relevant reports of identified studies and the numbers subsequently included and excluded from the clinical effectiveness review. a, one included in both reviews.

randomised and also for all randomised and non-randomised participants. These reports were treated as contributing two studies each to this review. Uchida and colleagues[195] was found to be related to five other reports;[183,190,192–194] Ferrer and colleagues[130] was related to two reports;[137,167] Shah and colleagues[182] was related to Mohammed and colleagues[164] and Vicini and colleagues;[201] Bul and colleagues[111] was related to van den Bergh and colleagues;[197] Klotz 2010[146] was related to three reports;[147,148,157] Selvadurai and colleagues[181] was related to van As and colleagues;[196] Caso and colleagues[114] was related to a secondary report with the same lead author[115] and to Polascik and colleagues;[175] Truesdale and colleagues[188] was related to Lambert and colleagues;[152] Donnelly and colleagues[125] was related to Robinson and colleagues;[179] another study by Donnelly and colleagues[124] was related to three reports;[177,178,180] and Paulson and colleagues[168] also published their report in German.[169] *Appendix 6* details the references of the included reports and shows the linked reports, and *Appendix 7* details the excluded reports.

Primary review (quantity and quality of included studies)

Number and types of studies included

Of the 88 studies, four RCTs were included in the primary review, one each comparing cryotherapy with EBRT[125] and EBRT with RP,[168] and two comparing brachytherapy with RP.[49,121] Forty NRCSs,[36,100,101,103,105,108–110,113,117,119,121,123,126,128,130,131,135,136,144,145,149,151,153,156,160,163,170–172,176,182,184,186,189,198,203,205–207] including 25 prospective studies,[100,101,103,108–110,113,117,121,123,128,130,144,145,149,153,156,160,163,172,176,182,184,186,198] were included in the primary review. The method of data collection could not be determined for the study by Beyer and colleagues.[105] Thirteen studies compared brachytherapy versus EBRT,[105,119,126,135,136,170–172,182,189,205–207] one brachytherapy versus cryotherapy,[203] nine brachytherapy versus RP,[101,108–110,113,121,123,145,149] one AS versus EBRT versus RP,[198] one brachytherapy versus cryotherapy versus RP,[160] one brachytherapy versus cryotherapy versus EBRT versus RP,[128] 13 brachytherapy versus EBRT versus RP[36,100,117,130,131,144,151,153,156,163,176,184,186] and one brachytherapy versus cryotherapy versus HIFU versus PDT.[103] Forty-four case series,[52,98,99,102,104,106,107,111,114,116,120,122,124,127,129,132–134,138–143,146,150,154,155,158,159,161,162,166,173,174,181,185,187,188,191,195,199,202,204] including 20 prospective[52,98,99,104,111,114,124,134,139–141,143,146,150,155,161,181,187,199,202] and 13 retrospective studies,[102,106,107,127,132,133,138,154,162,166,173,185,188] were included in the primary review. Fourteen studies were case series of cryotherapy,[52,102,114,122,124,129,138,139,154,158,166,188,202,204] 20 of HIFU,[98,99,106,107,116,120,127,132,133,142,143,150,159,161,162,173,174,185,191,195] one of laser therapy[155] and nine of AS.[104,111,134,140,141,146,181,187,199] *Table 4* summarises the number and types of included studies.

To further summarise the network of studies in the primary review, *Table 5* is a matrix of the number of studies in the primary review by comparison/intervention.

Two studies were considered to include potential patient overlap: Ganzer and colleagues[133] derived data from the multicentre-based @-Registry for 804 participants who were recruited between February 1993 and July 2009 and treated with HIFU in Lyon (France), Regensburg (Germany), Como (Italy) and Montpellier (France), while Blana and colleagues[107] reported 356 HIFU participants recruited between February 1993 and October 2010 from the same registry, from nine centres. These studies were treated separately because Blana and colleagues, in addition to similar inclusion criteria reported by Ganzer and colleagues, also selected participants with anteroposterior prostate height of ≤ 24 mm and a treated volume of $> 120\%$ of the prostate volume, while Ganzer and colleagues also selected participants with a minimum follow-up of 3 years. Similarly, Uchida and colleagues[191] reported the results of 72 consecutive participants treated with HIFU in different centres within an unspecified period of time. The same authors also reported data related to 517 participants recruited between January 1999 and December 2007 from a single clinical centre.[195] These data sets were treated as two separate studies because if any patient overlap existed it was likely to have a minor impact on meta-analyses, as the study sample sizes were significantly different.

Malcolm and colleagues[160] and Hubosky and colleagues[52] were, respectively, a NRCS and a case series conducted in the same centre around the same time period. The same number of participants enrolled by Hubosky and colleagues[52] was enrolled into the cryotherapy arm of the study by Malcolm and colleagues.[160]

TABLE 4 Number and types of included studies

AS	EBRT	RP	BT	CRYO	HIFU	Laser therapy	PDT	RCT	Prospective NRCS	Retrospective NRCS	NRCS: unknown data collection	Prospective CS	Retrospective CS	CS: unknown data collection	Total
				✗								5	5	4	14
					✗							5	8	7	20
						✗						1			1
✗												9			9
		✗	✗					2	9						11
			✗	✗						1					1
	✗	✗						1							1
	✗		✗						2	10	1				13
	✗			✗				1							1
		✗	✗	✗					1						1
	✗	✗	✗						10	3					13
✗	✗	✗							1						1
			✗	✗	✗		✗		1						1
	✗	✗	✗	✗					1						1
															88

BT, brachytherapy; CRYO, cryotherapy; CS, case series.

TABLE 5 Matrix of studies included in the primary review by comparison/intervention

	CRYO	BT	HIFU	Laser therapy	PDT	AS	EBRT	RP
CRYO	14 CS	1 NRCS (RP*)			1 NRCS (BT, HIFU*)		1 RCT	
		1 NRCS (RP, EBRT*)						
		1 NRCS						
BT	1 NRCS (RP*)	✗					13 NRCSs	9 NRCSs
	1 NRCS (RP, EBRT*)						13 NRCSs (RP*)	2 RCTs
	1 NRCS							
HIFU			20 CS					
Laser therapy				1 CS				
PDT	1 NRCS (BT, HIFU*)				0 CS			
AS						9 CS	1 NRCS (RP*)	
EBRT	1 RCT	13 NRCSs				1 NRCS (RP[b])	✗	1 RCT
		13 NRCSs (RP*)						
RP		9 NRCSs					1 RCT	✗
		2 RCTs						

BT, brachytherapy; CRYO, cryotherapy; CS, case series.
1 NRCS (RP*) = 1 NRCS of BT vs. CRYO vs. RP.
1 NRCS (RP, EBRT*) = 1 NRCS of BT vs. CRYO vs. EBRT vs. RP.
1 NRCS (RP*) = 1 NRCS of AS vs. EBRT vs. RP.
13 NRCSs (RP*) = 13 NRCSs of BT vs. EBRT vs. RP.
1 NRCS (BT, HIFU*) = 1 NRCS of BT vs. CRYO vs. PDT vs. HIFU.
Total number of studies = 88 (4 RCTs, 40 NRCSs, 44 CS).

However, the baseline characteristics of the patient groups were different and therefore the data sets were considered as separate studies.

The RCTs of brachytherapy versus RP by Giberti and colleagues[49] and Crook and colleagues[121] were conducted in Italy and Canada respectively; Donnelly and colleagues[125] conducted a study of cryotherapy versus EBRT in Canada, and Paulson and colleagues[168] conducted a study of EBRT versus RP in the USA. The NRCS of brachytherapy versus cryotherapy conducted by Williams and colleagues[203] was set in the USA. About two-thirds of the NRCSs of brachytherapy versus EBRT were set in the USA, while one[172] was conducted in Germany, two in Canada[171,189] and two in both the Netherlands and Austria.[135,136] Of nine non-randomised studies of brachytherapy versus RP, there were three each from the USA[101,110,123] and Germany,[108,109,145] and one each from France,[113] Canada[121] and Japan.[149] The non-randomised study of AS versus EBRT versus RP[198] was conducted in the Netherlands. Both non-randomised studies of brachytherapy versus cryotherapy versus RP were from the USA.[128,160] Of 13 studies of brachytherapy versus EBRT versus RP, 11 were conducted in the USA[36,100,117,131,144,151,153,156,163,176,186] and one each in Spain and Australia.[130,184]

Characteristics of study participants

A total of 72,259 study participants from 88 studies were enrolled; 26,129 had brachytherapy, 3995 had cryotherapy, 4000 had HIFU, 12 had laser therapy, 23 had PDT, 12,547 had EBRT, 19,961 had RP and 5592 had AS. Of these, 70,804 (99%), including 25,805 brachytherapy, 3964 cryotherapy, 3997 HIFU, 12 laser therapy, 23 PDT, 5437 AS, 12,426 EBRT and 19,140 RP participants, were included in the analyses. *Table 6* shows the demographic and disease characteristics of the study participants.

Most studies reported either the mean or median age; 12 studies did not report this information.[36,100,103,128,133,150,163,168,182,203,205,207] The average age was similar across interventions.

At least half of the participants in all interventions were clinical stage T1, except in cryotherapy, where T1 participants constituted one-fifth. T2 participants made up about one- to two-fifths across all intervention groups.

About 20–25% of brachytherapy, cryotherapy, EBRT, RP and HIFU participants were Gleason 6, as were the majority of AS, laser therapy and PDT participants. The proportion of participants with a Gleason score of 7 ranged from 2.1% in AS to 22.1% in cryotherapy.

The average PSA ranged from 5.55 ng/ml in AS to 8.43 ng/ml in cryotherapy. Of those reporting PSA, 18 studies did not report it as a mean or median.[36,102,103,105,108,117,123,126,129,138–140,146,187,202,203,205,206]

Thirty studies reported prostate size;[49,99,106,107,111,113,116,120,122,123,125–127,130,132,133,139,142,143,155,159,161,162,172–174,185,188,191,195] most studies on HIFU and laser therapy and almost half the studies on AS reported the prostate size, whereas most of the studies on other interventions did not. The average prostate size reported ranged from 26.5 ml in HIFU to 45.0 ml in RP.

Categorising studies into low-, medium- and high-risk localised disease

As the results in *Table 6* illustrate, the variety of differences in reporting of clinical stage, Gleason score and PSA made it impossible to categorise the studies according to the criteria described in *Table 3*. Although the inability to categorise studies according to the risk strata had no significant effect on comparisons including EBRT and RP, the inability to identify studies of people with low-risk localised disease meant that no comparison with AS would have been possible. After discussion with the expert advisory group, a pragmatic decision was made to categorise as studies of low-risk localised disease all those in which the Gleason scores of two-thirds of the patients were Gleason 6 or less in the ablative studies.

TABLE 6 Summary of the characteristics of the study participants included in the primary review, where data were combinable, from the information reported by the study authors

Variable	BT	CRYO	HIFU	Laser therapy	PDT	EBRT	RP	AS
Number of studies	41	19	21	1	1	34	30	10
Number of participants	26,129	3995	4000	12	23	12,547	19,961	5592
Mean age, years (SD/IQR)	66.05 (2.97)	68.56 (2.45)	67.58 (3.53)	56.5[a] (51–62)		69.17 (2.03)	62.09 (2.68)	66.09 (2.52)
n (%)	13,397 (51.3)	2773 (69.4)	3155 (78.9)	12 (100.0)		7394 (58.9)	15,046 (75.4)	5511 (98.6)
Missing/unknown, *n* (%)	12,732 (48.7)	1222 (30.6)	845 (21.1)		23 (100.0)	5153 (42.0)	4915 (24.6)	81 (1.4)
Clinical stage, *n* (%)								
T1	14,399 (55.1)	802 (20.1)	1994 (49.9)	12 (100.0)		3959 (31.6)	10,709 (53.6)	4304 (77.0)
T2	9313 (35.6)	1493 (37.4)	1554 (38.9)			4619 (36.8)	4653 (23.3)	761 (13.6)
≤T2a[b]	12 (0.1)	50 (1.3)	21 (0.5)		23 (100.0)			
T3–T4	219 (0.8)	223 (5.6)	86 (2.2)			232 (1.8)	83 (0.4)	4 (0.1)
Missing/unknown	2186 (8.4)	1427 (35.7)	345 (8.6)			3737 (29.8)	4516 (22.6)	523 (9.4)
PSA								
Mean, ng/ml (SD)	7.19 (1.60)	8.43 (2.63)	7.77 (1.13)	5.7 (1.1)		8.49 (2.39)	6.68 (1.46)	5.55 (0.5)
n (%)	9771 (37.4)	695 (17.4)	3713 (92.8)	12 (100.0)		5056 (40.3)	9822 (49.2)	3773 (67.5)
Missing/unknown, *n* (%)	16,358 (62.6)	3300 (82.6)	287 (7.2)		23 (100.0)	7491 (59.7)	10,139 (50.8)	2009 (32.5)

Variable	BT	CRYO	HIFU	Laser therapy	PDT	EBRT	RP	AS
Gleason score, *n* (%)								
≤ 6	9538 (36.5)	1695 (42.4)	1116 (27.9)	12 (100.0)	23 (100.0)	5686 (45.3)	7515 (37.6)	4920 (88.0)
7	2091 (8.0)	883 (22.1)	541 (13.5)			1931 (15.4)	2719 (13.6)	116 (2.1)
8–10	101 (0.4)	187 (4.7)	165 (4.1)			691 (5.5)	637 (3.2)	29 (0.5)
Missing/unknown	14,399 (55.1)	1230 (30.8)	2178 (54.5)			4239 (33.8)	9090 (45.5)	527 (9.4)
Prostate size								
Mean, ml (SD/IQR)	37.48 (2.51)	36.6 (8.16)	26.5 (6.87)	37 (16–85)		42.67 (6.77)	45.03 (0.93)	44 (35–57)
n (%)	893 (3.4)	221 (5.5)	3875 (96.9)	12 (100.0)		456 (3.6)	361 (1.8)	2494 (44.6)
Missing/unknown, *n* (%)	25,236 (96.6)	3774 (94.5)	125 (3.1)		23 (100.0)	12,091 (96.4)	19,600 (98.2)	3098 (55.4)

BT, brachytherapy; CRYO, cryotherapy; IQR, interquartile range; SD, standard deviation.
a Median.
b Clinical stage for all patients as reported by Barret 2013.[103] This group could not be included in any other category.

Thirty-four studies[36,49,101,103,105,107,109,110,116,117,119,123,126,129,135,138,151,153,155,156,160,162,170–172,174,184,186,189,198,202,205–207] met this criterion and were compared with the AS participants in a subgroup analysis. This subset of participants included 9069 brachytherapy, 1377 cryotherapy, 5628 EBRT, 994 HIFU, 12 laser therapy, 23 PDT and 7840 RP participants at enrolment.

Focal ablative therapies

Each included ablative study was categorised depending on whether or not a focal approach was the primary intervention.

Focal cryotherapy

Of the 19 studies on primary cryotherapy,[52,102,103,114,122,124,125,128,129,138,139,154,158,160,188,202–204,216] six used a focal ablative approach.[103,129,138,166,188,202] These studies included 1394 participants at enrolment.

Focal high-intensity focused ultrasound

Of the 21 studies on primary HIFU,[98,99,103,106,107,116,120,127,132,133,142,143,150,159,161,162,173,174,185,191,195] four, comprising two studies by Ahmed and colleagues,[98,99] Barret and colleagues[103] and El Fegoun and colleagues,[127] used a focal ablative approach. These studies included 94 participants at enrolment.

Focal photodynamic therapy

The only study identified for PDT, Barret and colleagues,[103] reported using a focal technique and included 23 participants at enrolment.

Focal brachytherapy

Of the 41 studies on brachytherapy,[36,49,100,101,103,105,108–110,113,117,119,121,123,126,128,130,131,135,136,144,145,149,151,153,156,160,163,170–172,176,182,184,186,189,203,205–207] only Barret and colleagues[103] reported a focal technique and included 12 participants at enrolment.

Overview of type of outcomes reported

Efficacy

Fifty-four studies (61%) reported the rate of biochemical failure[49,106,114,119,125,127,135,138,143,149,154,159,162,168,173,184,188] or control[36,52,102,105,107,109,116,120,122–124,126,129,132,133,136,139,144,149–151,155,158,161,166,170,171,174,182,185,189,191,195,202,205–207] using varying definitions and time points.

Twelve studies (14%) reported data on both overall survival and prostate cancer-specific mortality,[111,125,134,140,143,144,146,158,162,173,181,187] while an additional 10 (11%) reported either overall survival[103,105,124,127,154,182] or prostate cancer-specific mortality.[101,123,171,195]

Functional outcomes

Thirty-seven studies (42%) reported data on postoperative urinary incontinence status.[49,52,99,102,109,110,113,114,116,117,120,121,124,125,127,129–131,138,139,145,154,158,159,166,172,174,176,182,184–186,188,191,202–204] Twenty-seven studies (31%) provided data on the status of urinary function or dysfunction[49,52,99,103,108,114,116,121,125,127,130,131,149,150,153,155,159–161,163,172,184–186,189,195,199] and six (7%) on unspecified urinary symptoms,[49,98,145,161,189,191] while some reported specific urinary symptoms such as frequency,[114,189] nocturia,[189] urgency,[108,113,114,143,145,159,174,189] weak stream and incomplete emptying,[121,189] and splayed stream.[114] Ten studies (11%) provided data on the status of postoperative bowel function,[52,121,125,130,131,149,153,156,160,172] four studies (5%) reported faecal incontinence[109,113,182,191] and four (5%) reported bowel symptoms/problems.[49,110,186,189]

Thirty-three studies (38%) provided data on erectile dysfunction or the status of sexual potency.[49,98–100,110,113,114,116,117,120,121,124,125,129,138,139,141,143,154,158,159,166,174,184,185,189,191,195,198,202,203,206,207] Of these, nine studies in eight reports also reported the status of sexual function,[98,99,114,121,141,159,184,195] with an additional 14 (16%) also providing this information.[52,103,121,130,131,149,155,160,161,163,172,186,188,199]

Adverse events

Forty-three studies (49%) reported one or more adverse events as a result of the intervention.[49,52,98,99,102,103,113,114,116,120,121,124–129,138,139,142,143,150,154,155,158,159,161,166,171,172,174,182,185,188,189,191,195,202–207] The main adverse outcomes reported were dysuria, urinary retention, urethral sloughing, infection, urethral stricture, bladder neck stenosis, bladder contracture, bladder spasm, rectal pain, rectal bleeding and acute radiation toxicities.

Quality of life

Twenty-two studies reported quality-of-life outcomes using one or more validated tools.[49,98,99,104,109,110,116,121,124,125,130,145,149,153,159,172,176,184,191,195,198,199]

Risk-of-bias/quality assessment

Forty-three studies, comprising 39 NRCSs[36,100,101,103,105,108–110,113,117,119,121,123,126,130,131,135,136,144,145,149,151,153,156,160,163,170–172,176,182,184,186,189,198,203,205–207] and 4 RCTs,[49,121,125,168] were assessed for risk of bias for the primary outcomes of this review using the Cochrane risk-of-bias tool.[89] Forty-four case series were assessed for methodological quality using the Review Body for Interventional Procedures (ReBIP) checklist.[52,98,99,102,104,106,107,111,114,116,120,122,124,127,129,132–134,138–143,146,150,154,155,158,159,161,162,166,173,174,181,185,187,188,191,195,199,202,204] One study which reported exclusively adverse events, but not other relevant outcomes, was not assessed for risk of bias.[128]

Randomised controlled studies

The results of the risk-of-bias assessments for individual studies are shown in *Appendix 9*. The assessments are summarised in *Figures 4–8*.

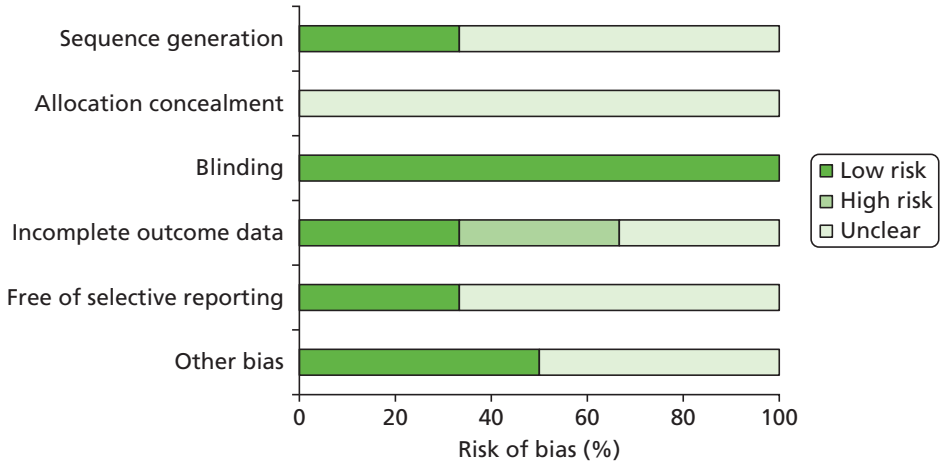

FIGURE 4 Summary of risk-of-bias assessments for RCTs reporting efficacy ($n = 3$).

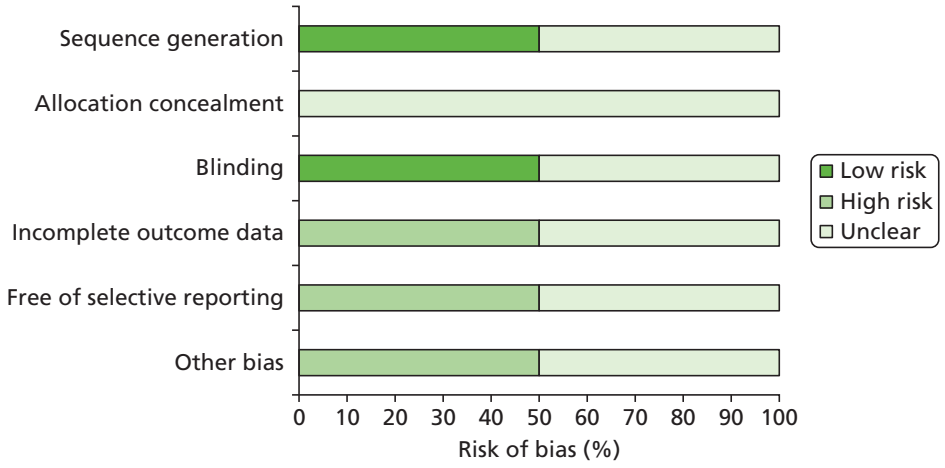

FIGURE 5 Summary of risk-of-bias assessments for RCTs reporting urinary function ($n = 2$).

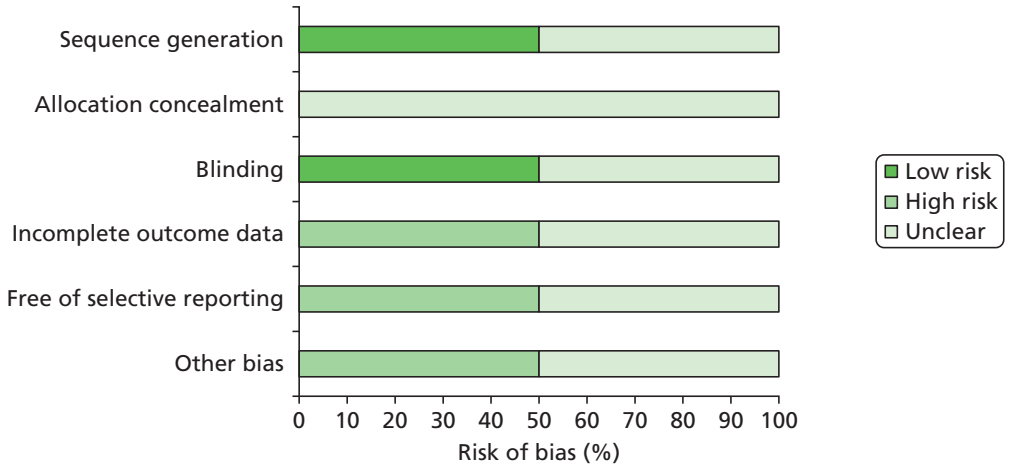

FIGURE 6 Summary of risk-of-bias assessments for RCTs reporting sexual function ($n = 2$).

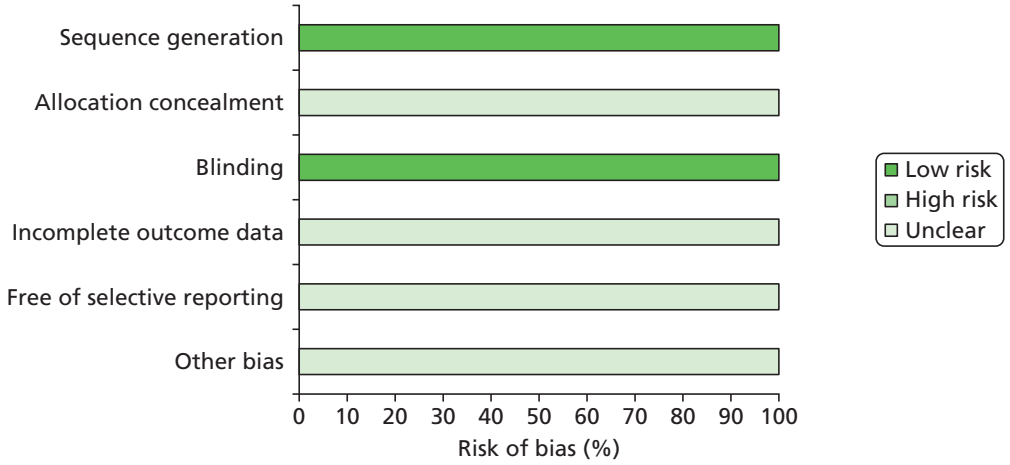

FIGURE 7 Summary of risk-of-bias assessments for RCTs reporting bowel function ($n = 1$).

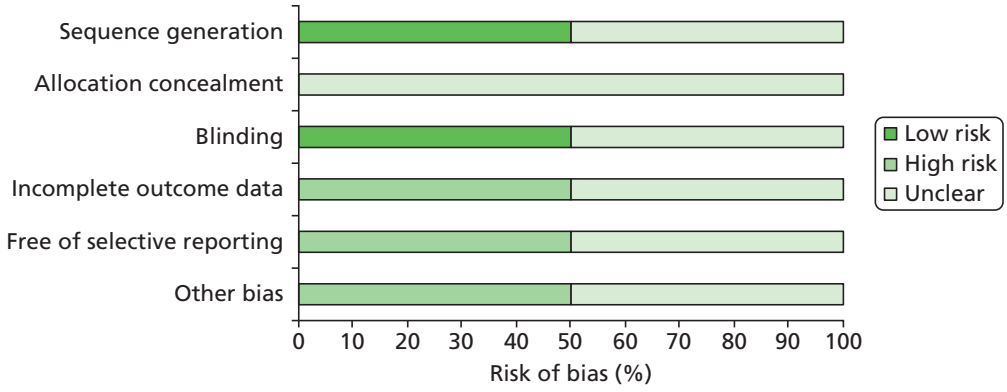

FIGURE 8 Summary of risk-of-bias assessments for RCTs reporting quality of life ($n = 2$).

Efficacy

Three studies were assessed for risk of bias of efficacy outcomes.[49,125,168] Of these, only the study by Giberti and colleagues[49] was considered to be at low risk for sequence generation and others were unclear. None provided adequate information for the assessment of allocation concealment.

Urinary function

Two studies were assessed for risk of bias of urinary function outcomes.[49,121] The study by Giberti and colleagues[49] was considered low risk of bias for sequence generation whereas this was unclear in the study by Crook and colleagues,[121] and both were judged as unclear risk of bias for allocation concealment.

Sexual function

Two studies were assessed for risk of bias of sexual function outcomes.[49,121] The study by Giberti and colleagues[49] was considered to be at low risk for sequence generation, whereas there was insufficient information to assess sequence generation in that by Crook and colleagues[121] or allocation concealment in either study.[49,121]

Bowel function

Only one study[49] was assessed for risk of bias of bowel function outcomes; it was considered to be at low risk of bias for sequence generation and unclear for allocation concealment.

Quality of life

Two studies were assessed for risk of bias of quality of life outcomes.[49,121] The study by Giberti and colleagues[49] was considered to be at low risk for sequence generation whereas that by Crook and colleagues[121] was unclear. Both studies were judged as unclear for allocation concealment.[49,121]

Non-randomised controlled studies

The results of the risk-of-bias assessments for individual studies are shown in *Appendix 9*. The assessments are summarised in *Figures 9–13*.

Efficacy

Twenty-one studies were assessed for risk of bias of efficacy outcomes.[36,101,103,105,109,119,123,126,135,136,144,149,151,170,171,182,184,189,205–207] Of these, nine[103,105,109,119,135,144,184,205,206] were considered to be at low risk of bias for confounding and one[182] was unclear.

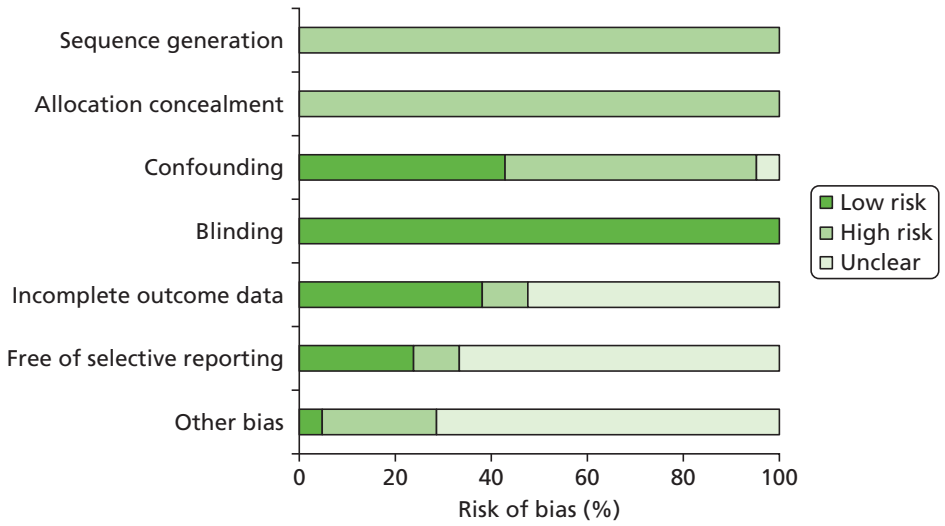

FIGURE 9 Summary of risk-of-bias assessments for NRCSs reporting efficacy ($n = 21$).

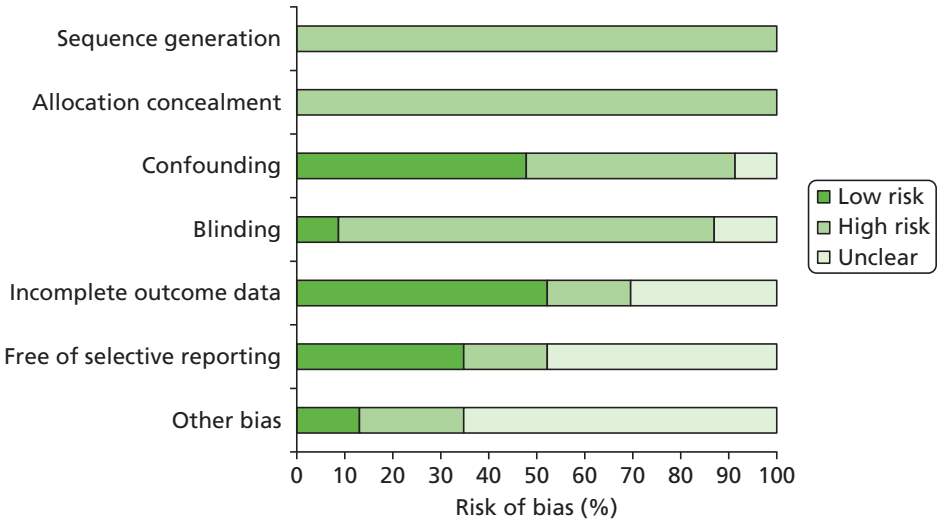

FIGURE 10 Summary of risk-of-bias assessments for NRCSs reporting urinary function ($n = 23$).

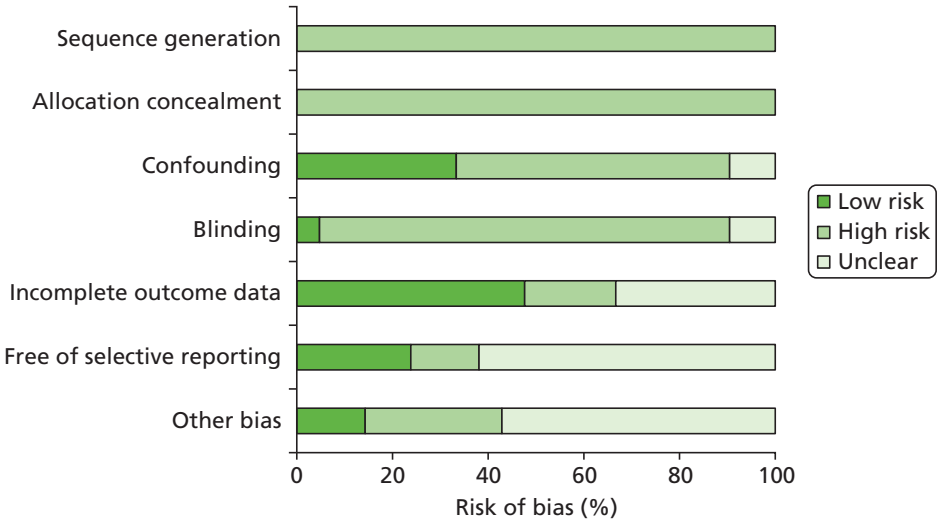

FIGURE 11 Summary of risk-of-bias assessments for NRCSs reporting sexual function ($n = 21$).

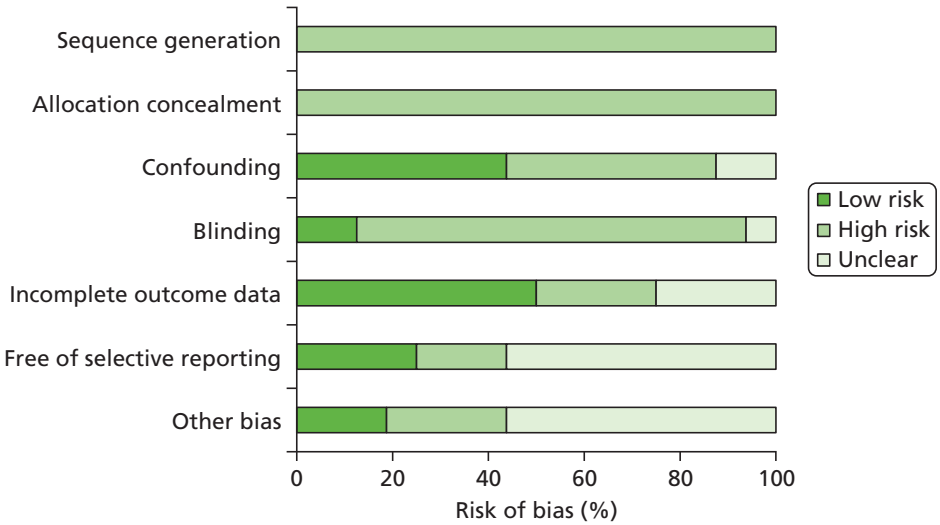

FIGURE 12 Summary of risk-of-bias assessments for NRCSs reporting bowel function ($n = 16$).

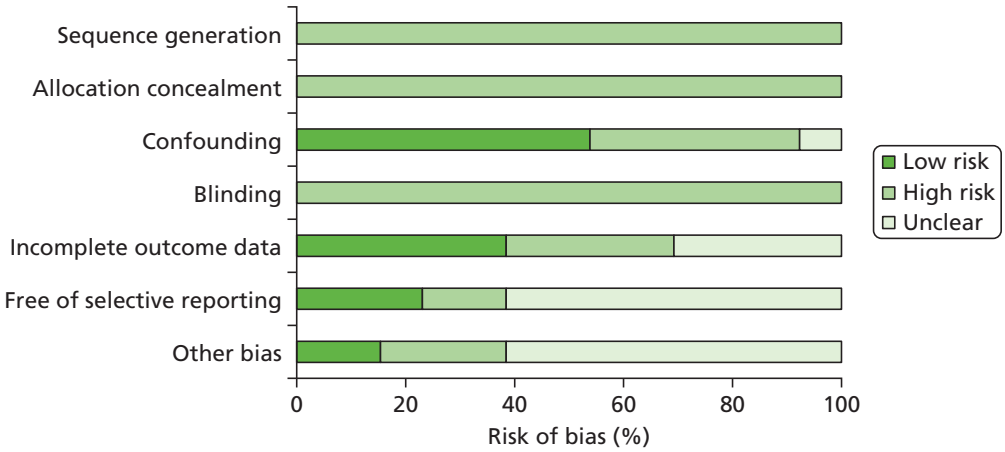

FIGURE 13 Summary of risk-of-bias assessments for NRCSs reporting quality of life ($n = 13$).

Urinary function

Twenty-three studies were assessed for risk of bias of urinary function outcomes.[103,108–110,113,117,121,126,130,131,145,149,153,160,163,172,176,182,184,186,189,203,206] Of these, 11[109,121,130,149,153,172,176,184,186,203,206] were considered to be at low risk of bias for confounding. The studies by Frank and colleagues[131] and Shah and colleagues[182] were unclear.

Sexual function

Twenty-one studies were assessed for risk of bias of sexual function outcomes.[100,103,109,110,113,117,121,126,130,131,149,160,163,172,182,186,189,198,203,206,207] Of these, seven[109,130,172,184,186,189,203] were considered to be at low risk of bias for confounding. The studies by Barret and colleagues[103] and Frank and colleagues[131] were unclear.

Bowel function

Sixteen studies were assessed for risk of bias of bowel function outcomes.[109,110,113,117,126,130,131,149,156,160,172,184,186,189,203,206] Of these, seven[109,130,156,184,186,189,206] were considered to be at low risk of bias for confounding. The studies by Williams and colleagues[203] and Frank and colleagues[131] were unclear.

Quality of life

Thirteen studies were assessed for risk of bias of quality of life outcomes.[109,110,121,130,131,145,149,153,160,172,176,184,198] Of these, seven were considered to be at low risk of bias for confounding.[109,121,131,149,153,172,184] The study by Reeve[176] was unclear.

Case series

The ReBIP checklist was used to assess the methodological quality of the case series. Studies with all items scored as 'no' or 'unclear' were considered at high risk of bias. All case series included in this review were judged as having a high risk of bias. The results of the quality assessment are summarised in *Figure 14* and further details are provided in *Appendix 9.*

Summary of risk-of-bias assessment in the primary review

The risk-of-bias assessment and the quality of the case series in the primary review suggested that the included studies were generally at a high or very high risk of bias. No subgroup analysis of studies at low risk of bias was therefore undertaken.

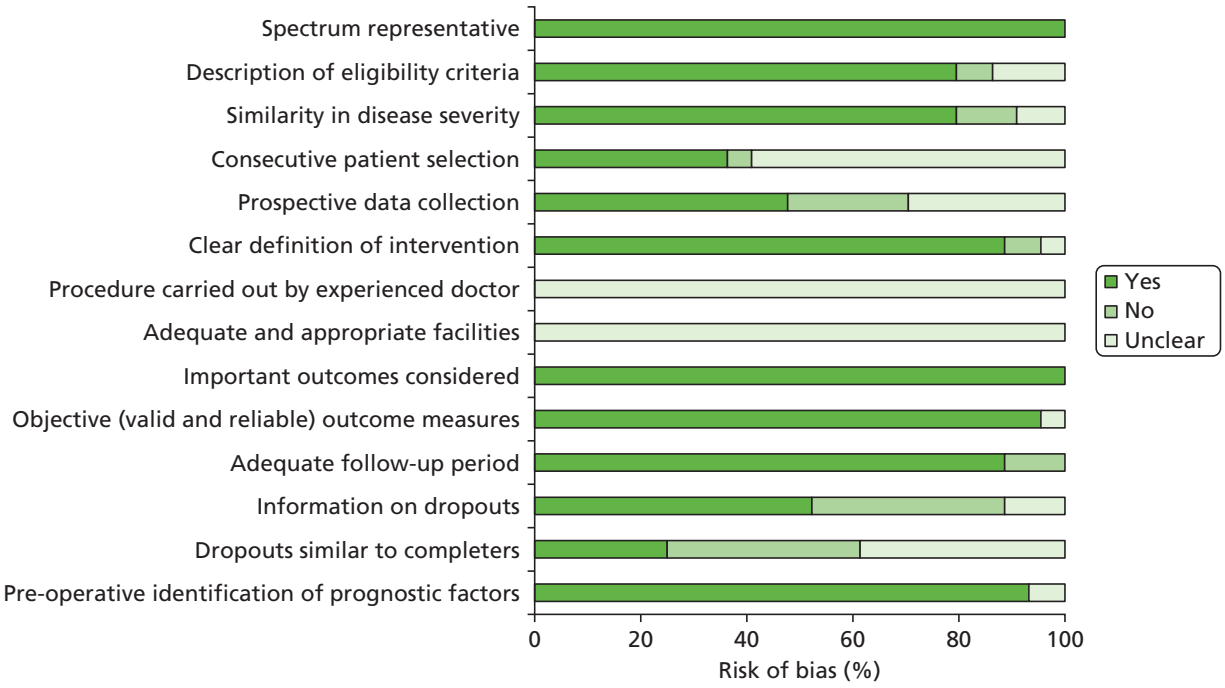

FIGURE 14 Summary of quality assessments of the case series in the primary review.

Salvage review (quantity and quality of included studies)

Number and types of studies included

All included studies were case series; six were studies of salvage RP,[209–211,213–215] two of salvage cryotherapy[208,212] and one of salvage HIFU.[120] Data were collected prospectively in three of the included studies[212,213,215] and retrospectively in a further three,[120,208,211] and in the remaining studies patient enrolment was unclear. *Table 7* summarises the number and types of included studies.

The study by Chin and colleagues[208] and that by Robinson and colleagues[212] were conducted in Canada; those by Gheiler and colleagues,[210] Neerhut and colleagues[211] and Tefilli and colleagues[214] were conducted in the USA; and those by Darras and colleagues,[209] Seabra and colleagues[213] and van der Poel and colleagues[215] were conducted in Belgium, Brazil and the Netherlands respectively.

TABLE 7 Characteristics of studies included in the salvage review

Intervention	Study design	Data collection	Number of studies
Salvage RP	Single-arm cohort	Prospective	2
		Retrospective	3
		Not reported	1
Salvage CRYO	Single-arm cohort	Prospective	1
		Not reported	1
Salvage HIFU	Single-arm cohort	Not reported	1
Total			9

CRYO, cryotherapy.

Characteristics of study participants

A total of 400 participants were enrolled in nine studies; 164 had salvage cryotherapy, 71 had salvage HIFU and 165 had salvage RP. Three hundred and eighty-eight (388) (97%) participants, encompassing 164 salvage cryotherapy, 71 salvage HIFU and 153 salvage RP patients, were included in the final outcome analyses. *Table 8* summarises the baseline characteristics of the study participants.

The mean age of salvage cryotherapy participants was comparable with that of salvage RP participants. All interventions were comparable in terms of participants with clinical stage T2 or less. The Gleason scores of enrolled participants were not comparable, as the proportion of participants with Gleason scores of 6 or less who underwent salvage RP was double that of those who underwent salvage cryotherapy, and vice versa for participants with Gleason scores of 8 or more. There was no information on Gleason score for participants who underwent salvage HIFU. It was not possible to comment on the PSA and prostate size because data were limited.

TABLE 8 Summary of the characteristics of the study participants included in the salvage review, where data were combinable, from the information reported by the study authors

Variable	Salvage CRYO	Salvage HIFU	Salvage RP
n enrolled	164	71	165
Mean age (years)	70		63.4
n (%)	46 (28.0)		165 (100.0)
Missing/unknown, *n* (%)	118 (72.0)	71 (100.0)	
Clinical stage, *n* (%)			
T1	16 (9.8)		40 (24.2)
T2	134 (81.7)		111 (67.3)
≤ T2[a]		71 (100.0)	
T3	14 (8.5)		14 (8.5)
PSA, *n* (%)			
≤ 10 ng/ml	65 (39.6)		
> 10 ng/ml	98 (59.8)		
Missing/unknown		71 (100.0)	165 (100.0)
Gleason score, *n* (%)			
≤ 6	23 (14.0)		53 (32.1)
7			23 (13.9)
8–10	24 (14.6)		9 (5.5)
Missing/unknown	117 (71.3)	71 (100.0)	80 (48.5)
Prostate size (ml)		21	
n (%)		71 (100.0)	
Missing/unknown, *n* (%)	164 (100.0)		165 (100.0)

CRYO, cryotherapy.
a Clinical stage for all patients as reported by Colombel 2006.[120] This group could not be included in any other category.

Overview of studies reporting the main outcomes of the review

Efficacy

Eight studies reported biochemical disease-free survival or treatment success using PSA level as an indicator,[120,179,208–210,213–215] two[179,209] reported both the overall and prostate cancer-specific mortality and three[210,211,215] reported the prostate cancer-specific mortality only.

Functional outcomes

Five studies reported data on erectile dysfunction or potency,[179,209,213–215] one reported sexual function,[179] seven reported data on urinary continence or incontinence,[120,208–210,213–215] one reported the urinary function status[179] and one reported the bowel function status.[179]

Adverse events

Seven studies presented data on adverse events;[120,208–211,213,215] two reported urinary obstruction,[208,213] one reported debris sloughing,[208] one reported epididymitis,[210] three reported strictures,[209,211,215] four reported bladder neck contracture and stenosis,[120,208–210] five reported rectourethral/rectovesical fistula,[120,208,210,211,213] and one each reported rectal injury,[211] vesicourethral fistula,[208] ureteral fistula,[210] ureteral transection,[211] deep-vein thrombosis,[210] prolonged postoperative ileus,[211] anastomotic stone formation,[211] mild acute tubular necrosis,[211] ureterovesical junction stricture and hydronephrosis,[211] grade 3 rectal complaints,[215] grade 4 rectal complaints,[215] intraoperative complications[209] and operative death.[211]

Quality of life

Two studies presented data on quality of life using validated tools.[212,214]

Quality assessment

All case series included in the salvage review were judged at high risk of bias as all methodological items were scored as 'no' or 'unclear' on the ReBIP checklist. The results of the quality assessment are summarised in *Figure 15* and further details are provided in *Appendix 9*.

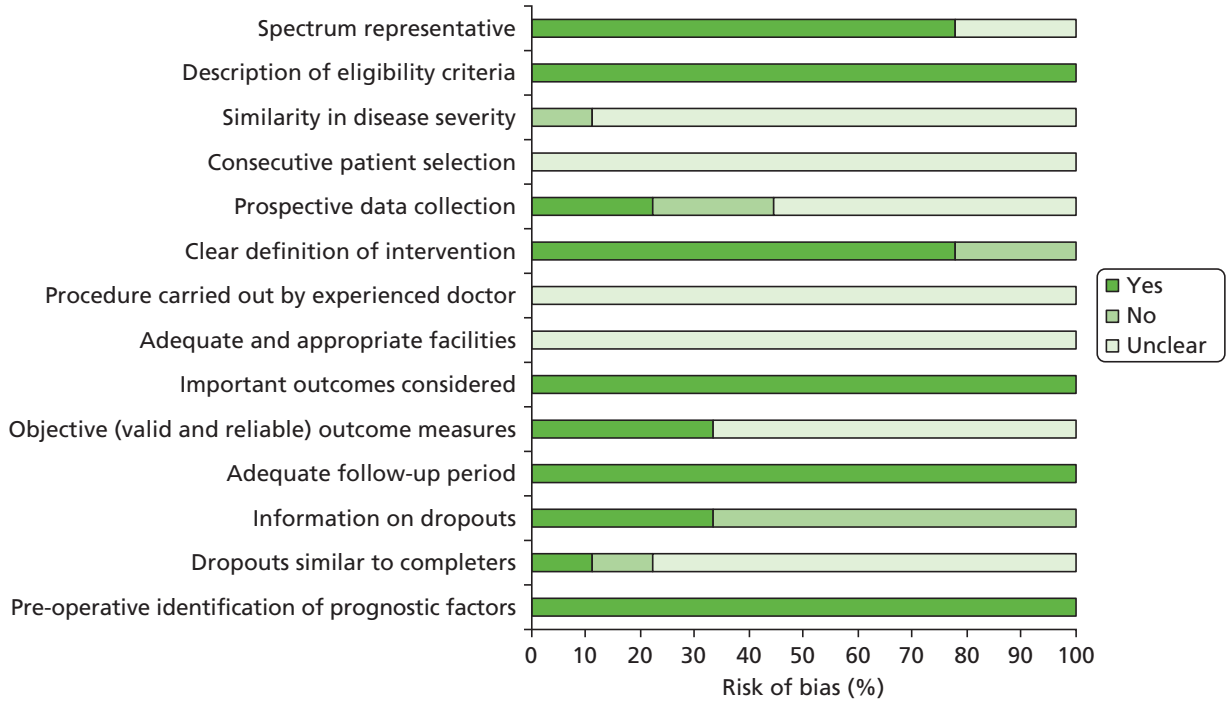

FIGURE 15 Summary of quality assessments of the case series in the salvage review.

Chapter 4 The comparative effectiveness of cryotherapy

Included studies

The characteristics of the included studies were described in *Chapter 3*, and are detailed in *Appendix 8* and summarised here.

There were 3995 enrolled and 3964 analysed patients undergoing cryotherapy from 19 studies included in the review.[52,102,103,114,122,124,125,128,129,138,139,154,158,160,188,202–204,216] The studies were mainly case series,[52,102,114,122,124,129,138,139,154,158,188,202,204,216] but with one RCT of cryotherapy versus EBRT[125] and one NRCS each on cryotherapy versus brachytherapy versus EBRT versus RP,[128] cryotherapy versus EBRT versus RP,[160] cryotherapy versus brachytherapy[203] and cryotherapy versus brachytherapy versus HIFU versus PDT.[103]

Assessment of effectiveness

Details of all outcomes, including those which were used in meta-analyses, are tabulated in *Appendix 10*.

Cancer-related efficacy outcomes

Biochemical failure

Four studies[125,138,175,188] provided data on biochemical failure following cryotherapy that could be used for meta-analysis (*Table 9*). Meta-analysis of these data showed a numerically increased risk of biochemical failure for cryotherapy compared with EBRT at all follow-up points, but this was not statistically significant (the probability that cryotherapy was superior to EBRT for this outcome was 0.07, 0.07 and 0.38 for years 1, 3 and 5 respectively). For the comparison with RP, cryotherapy showed a numerically decreased risk of biochemical failure at 1 year, but an increased risk thereafter. None of the differences were statistically significant (the probability that cryotherapy was superior to RP for this outcome was 0.60, 0.04 and 0.24 for years 1, 3 and 5 respectively). The 3-year time point had a higher number of studies contributing to the meta-analysis and the predicted rate of biochemical failure in the mixed-treatment comparison model at 3 years was 19% for cryotherapy, 5% for EBRT and 7% for RP.

Overall survival

Only two cryotherapy studies[124,125] provided information on overall survival that could be used for meta-analysis (*Table 10*). Meta-analysis of these data showed no evidence of a difference in survival for cryotherapy compared with EBRT at 4 years (the probability that cryotherapy was superior to EBRT was 0.73). The predicted rate of survival in the mixed-treatment comparison model at 4 years was 93% for cryotherapy and 91% for EBRT. There were no data available to estimate survival from the RP studies at 4 years.

Disease-free survival

Seven studies involving people undergoing cryotherapy[52,122,129,139,180,188,202] provided information on disease-free survival that could be used for meta-analysis (*Table 11*). Meta-analysis of these data showed a numerically lower rate of disease-free survival for people undergoing cryotherapy than for those treated with EBRT and RP at 1 year, and this was statistically significant (the probability that cryotherapy was superior to EBRT/RP was < 0.01). Findings for the 3-year time point were numerically similar to the 1-year results but the comparisons were no longer statistically significant. The 1-year time point had the greater number of studies contributing to the meta-analysis and the predicted rate of disease-free survival in the

TABLE 9 Meta-analysis of biochemical failure at 1-, 3- and 5-year follow-up

Follow-up	Cryotherapy, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	Cryotherapy vs. EBRT		Cryotherapy vs. RP	
				OR (95% CrI)	*p*(cryotherapy > EBRT)	OR (95% CrI)	*p*(cryotherapy > RP)
1 year	0.054 (0.01 to 0.24)	0.013 (< 0.01 to 0.07)	0.073 (< 0.01 to 0.55)	3.2 (0.70 to 15.9)	0.07	0.70 (0.02 to 20.7)	0.60
3 years	0.19 (0.06 to 0.40)	0.05 (0.01 to 0.16)	0.07 (< 0.01 to 0.44)	1.75 (0.85 to 3.81)	0.07	3.66 (0.84 to 29.8)	0.04
5 years	0.24 (0.03 to 0.78)	0.13 (0.05 to 0.25)	0.11 (0.02 to 0.38)	1.1 (0.60 to 2.03)	0.38	2.78 (0.11 to 52.9)	0.24

TABLE 10 Meta-analysis of overall survival at 4-year follow-up

Follow-up	Cryotherapy, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	Cryotherapy vs. EBRT		Cryotherapy vs. RP	
				OR (95% CrI)	*p*(cryotherapy > EBRT)	OR (95% CrI)	*p*(cryotherapy > RP)
4 years	0.93 (0.75 to 0.98)	0.91 (0.45 to 0.99)	–	0.75 (0.30 to 1.89)	0.73	–	–

TABLE 11 Meta-analysis of disease-free survival at 1- and 3-year follow-up

Follow-up	Cryotherapy, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	Cryotherapy vs. EBRT		Cryotherapy vs. RP	
				OR (95% CrI)	*p*(cryotherapy > EBRT)	OR (95% CrI)	*p*(cryotherapy > RP)
1 year	0.80 (0.62 to 0.90)	0.99 (0.98 to > 0.99)	0.95 (0.88 to 0.99)	27.7 (8.19 to 125.9)	< 0.01	5.46 (1.85 to 20.79)	< 0.01
3 years	0.83 (0.58 to 0.96)	0.95 (0.88 to 0.98)	0.90 (0.75 to 0.97)	3.44 (0.68 to 79.8)	0.07	1.62 (0.46 to 5.16)	0.22

mixed-treatment comparison model at 1 year was 80% for cryotherapy, 99% for EBRT and 95% for RP. These results from the meta-analysis were potentially conflicting with 4-year overall survival figures, which demonstrated no evidence of a difference between treatment by cryotherapy and EBRT (see *Table 10*).

Adverse effects

Urinary function: urinary incontinence

Six studies involving people treated with cryotherapy[52,114,124,138,139,202] provided information on urinary incontinence that could be used for meta-analysis (*Table 12*). Meta-analysis of these data showed a numerically decreased risk of incontinence for cryotherapy compared with EBRT at 1 year but this was not statistically significant (the probability that the outcome favoured cryotherapy was 0.67). For comparison with RP, cryotherapy showed a statistically significant decrease in risk of incontinence at 1 year (the probability that cryotherapy was superior to RP was > 0.99). By 5 years, the risk of incontinence was still numerically lower for people treated with cryotherapy, but was no longer statistically significant (the probability that the outcome favoured cryotherapy was 0.81). The predicted rate of incontinence in the mixed-treatment comparison model at 1 year was 3% for cryotherapy, 5% for EBRT and 66% for RP.

Sexual function: erectile dysfunction

As described in *Chapter 3*, *Overview of type of outcomes reported*, a total of 33 studies provided data on sexual function.[49,98–100,110,113,114,116,117,120,121,124,125,129,138,139,141,143,154,158,159,166,174,184,185,189,191,195,198,202,203,206,207]
The time point following intervention when the outcome was assessed and the measure used to quantify the outcome showed wide variation across the studies. Given the diversity of definitions and types of data (continuous or dichotomous), it was not possible to collate all the data from individual studies into a form suitable for meta-analysis. However, five studies involving people treated with cryotherapy[129,138,139,175,202] provided information on erectile dysfunction that could be used for meta-analysis (*Table 13*). Meta-analysis of these data showed a numerically lower rate of erectile dysfunction for people treated with cryotherapy than for those receiving RP at 1 year, but the difference was not statistically significant (the probability that cryotherapy was superior to RP was 0.58). The predicted rate of erectile dysfunction in the mixed-treatment comparison model at 1 year was 18% for cryotherapy and 33% for RP. There were no data available to estimate the rate of erectile dysfunction at 1 year in people treated with EBRT.

Bowel function

Disturbance in bowel function among people treated with cryotherapy was rarely measured as an outcome. In the single comparative study that compared cryotherapy with EBRT,[125] people treated with cryotherapy reported a lower rate of moderate or severe bowel problems, as measured by the University of California at Los Angeles – Prostate Cancer Index (UCLA-PCI),[217] than those receiving EBRT at 1-year follow-up (5% vs. 17%).

Procedural complications

Data on short-term adverse events related to the use of cryotherapy, including dysuria, urinary retention, urethral sloughing, infection, stricture, bladder neck contracture, bladder spasm, rectal pain/bleeding and fistula, are presented below. Abstracted data concerning other specific adverse events not included below are detailed in *Appendix 10*. Given the variety of definitions and periods of follow-up between studies, a degree of caution should be used in interpretation of these results.

Dysuria

One study[114] provided information on the occurrence of dysuria that could be used for meta-analysis (*Table 14*). Meta-analysis of these data showed a decrease in risk of dysuria for cryotherapy compared with EBRT and RP, but this was not statistically significant (the probabilities that cryotherapy was superior were 0.92 and 0.79 for EBRT and RP respectively). The predicted rate of dysuria in the mixed-treatment comparison model was 2% for cryotherapy, 14% for EBRT and 6% for RP.

TABLE 12 Urinary incontinence at 1- and 5-year follow-up

Follow-up	Cryotherapy, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	Cryotherapy vs. EBRT		Cryotherapy vs. RP	
				OR (95% CrI)	*p*(cryotherapy > EBRT)	OR (95% CrI)	*p*(cryotherapy > RP)
1 year	0.03 (< 0.01 to 0.12)	0.05 (< 0.01 to 0.46)	0.66 (0.12 to 0.96)	0.41 (0.02 to 19.0)	0.67	0.02 (< 0.01 to 0.39)	> 0.99
5 years	0.01 (< 0.01 to 0.16)	–	0.06 (< 0.01 to 0.42)	–	–	0.12 (< 0.01 to 16.8)	0.81

TABLE 13 Erectile dysfunction at 1-year follow-up

Follow-up	Cryotherapy, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	Cryotherapy vs. EBRT		Cryotherapy vs. RP	
				OR (95% CrI)	*p*(cryotherapy > EBRT)	OR (95% CrI)	*p*(cryotherapy > RP)
1 year	0.18 (0.04 to 0.49)	–	0.33 (0.04 to 0.85)	–	–	0.69 (< 0.01 to 13.1)	0.58

TABLE 14 Dysuria

Outcome	Cryotherapy, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	Cryotherapy vs. EBRT		Cryotherapy vs. RP	
				OR (95% CrI)	*p*(cryotherapy > EBRT)	OR (95% CrI)	*p*(cryotherapy > RP)
Dysuria	0.02 (< 0.01 to 0.20)	0.14 (0.03 to 0.52)	0.06 (< 0.01 to 0.35)	0.10 (< 0.01 to 2.8)	0.92	0.24 (< 0.01 to 15.9)	0.79

Urinary retention

Eight cryotherapy studies[52,103,114,138,154,188,202,203] provided information on urinary retention that could be used for meta-analysis (*Table 15*). Meta-analysis of the data reporting urinary retention showed a small increase in risk of urinary retention for cryotherapy compared with EBRT, but this was not statistically significant (the probability that the outcome favoured cryotherapy was 0.26 for EBRT). The predicted rate of urinary retention in the mixed-treatment comparison model was 4% for cryotherapy and 2% for EBRT. It was not possible to estimate the rate of urinary retention after RP.

Urethral sloughing

Urethral sloughing was reported by seven studies involving people undergoing cryotherapy.[52,114,125,138,139,154,204] The proportion of people suffering urethral sloughing ranged from 0%[138] to 38%[204] with a median of 5%.

Urethral stricture

Six studies involving people undergoing cryotherapy[103,114,128,139,154,203] provided information on urethral stricture that could be used for meta-analysis (*Table 16*). Meta-analysis of these data showed a similar risk of stricture following cryotherapy compared with EBRT and this was not statistically significant (the probability that cryotherapy was superior to EBRT was 0.34). For the comparison with RP, people treated with cryotherapy showed a statistically significant decrease in risk of stricture (the probability that cryotherapy was superior to RP was > 0.99). The predicted rate of stricture in the mixed-treatment comparison model was 1% for cryotherapy, 1% for EBRT and 8% for RP.

Rectal pain and bleeding

Three studies involving people undergoing cryotherapy provided information on rectal pain[114,188,203] and two provided information on rectal bleeding.[114,203] Meta-analysis of these data (*Tables 17* and *18*) showed a decreased risk of these adverse events following cryotherapy compared with EBRT, but neither reached statistical significance for rectal pain (the probabilities that cryotherapy was superior to EBRT were 0.89 and 0.94 for rectal pain and bleeding respectively). The predicted rate of rectal pain in the mixed-treatment comparison model was 3% for cryotherapy and 9% for EBRT. It was not possible to estimate rectal pain/bleeding after RP.

Other adverse events

Data on occurrence of fistula were reported in 13 studies involving people undergoing cryotherapy.[52,102,103,114,129,138,139,154,158,166,188,202,204] The rate of fistula reporting was low and ranged from 0% in eight studies[114,129,138,139,154,166,188,204] to 6% in one.[158] The median reported rate of fistula was 0%.

Bladder neck contracture was only reported in one study,[204] and the rate of contracture was 11% (8/71 patients). A single case of bladder spasm was also reported in the same study.

Rates of urinary tract infection were reported in four studies of people undergoing cryotherapy.[52,114,124,138] The rate of urinary tract infection ranged from 1%[52] to 6%.[114]

Quality of life

Only one case series of people having cryotherapy reported on quality of life outcomes.[124] The data were insufficient to enable us to assess any difference in this outcome compared with either EBRT or RP.

Further prostate cancer treatment

The need for reintervention within 2 years of initial procedure using further cryotherapy was reported by six studies of people undergoing primary cryotherapy.[114,122,125,129,154,204] The rates of reintervention ranged from 1% to 15% with a median rate of 9% across the studies.

Within 6 months of initial treatment, Donnelly and colleagues[125] reported that 11% of people treated with cryotherapy received hormonal androgen deprivation therapy and 3% were placed in a watchful waiting programme. In contrast, Caso and colleagues[114] reported the rate of further cancer treatment using any modality at a median follow-up of 2 years to be 12%.

TABLE 15 Urinary retention

Outcome	Cryotherapy, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	Cryotherapy vs. EBRT		Cryotherapy vs. RP	
				OR (95% CrI)	*p*(cryotherapy > EBRT)	OR (95% CrI)	*p*(cryotherapy > RP)
Urinary retention	0.04 (0.01 to 0.10)	0.02 (< 0.01 to 0.14)	–	2.1 (0.20 to 25.9)	0.26	–	–

TABLE 16 Stricture

Outcome	Cryotherapy, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	Cryotherapy vs. EBRT		Cryotherapy vs. RP	
				OR (95% CrI)	*p*(cryotherapy > EBRT)	OR (95% CrI)	*p*(cryotherapy > RP)
Stricture	0.01 (< 0.01 to 0.04)	0.01 (< 0.01 to 0.05)	0.08 (< 0.01 to 0.25)	1.2 (0.45 to 3.3)	0.34	0.24 (0.09 to 0.54)	0.99

TABLE 17 Rectal pain

Outcome	Cryotherapy, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	Cryotherapy vs. EBRT		Cryotherapy vs. RP	
				OR (95% CrI)	*p*(cryotherapy > EBRT)	OR (95% CrI)	*p*(cryotherapy > RP)
Rectal pain	0.03 (< 0.01 to 0.14)	0.09 (0.01 to 0.44)	–	0.16 (0.01 to 2.86)	0.89	–	–

TABLE 18 Rectal bleeding

Outcome	Cryotherapy, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	Cryotherapy vs. EBRT		Cryotherapy vs. RP	
				OR (95% CrI)	*p*(cryotherapy > EBRT)	OR (95% CrI)	*p*(cryotherapy > RP)
Rectal bleeding	0.01 (< 0.01 to 0.05)	0.04 (0.01 to 0.14)	–	0.22 (0.02 to 1.9)	0.94	–	–

Analysis of subgroups

Focal cryotherapy

Of the 19 studies describing the results of primary cryotherapy,[52,102,103,114,122,124,125,128,129,138,139,154,158,160,188,202–204,216] six used a focal ablative approach.[103,129,138,166,188,202] Given the low number of studies reporting on the use of focal cryotherapy and the diversity of outcomes reported in each study, no formal subgroup meta-analyses could be undertaken for most of the outcomes, and therefore a descriptive summary of reported findings in relation to the overall comparative meta-analysis is given below.

Biochemical failure

Two studies[138,188] reporting on the use of focal cryotherapy contributed data for the meta-analysis of our primary cancer-related outcome, biochemical failure. At 3-year follow-up, rerunning the mixed-treatment comparison model using the focal studies gave a non-significant numerical increase in biochemical failure using focal cryotherapy (OR 4.4, 95% CrI 0.5 to 39.5) versus EBRT. A similar result was observed in the comparison with RP (OR 4.3, 95% CrI 0.35 to 53.5). These findings were consistent with those estimated using all of the focal and non-focal studies.

Urinary incontinence

Two studies reporting the outcome of focal cryotherapy contributed to the meta-analysis of occurrence of urinary incontinence at 1 year.[138,202] The study by Ward and colleagues[202] contributed the majority of cryotherapy patients reporting on incontinence outcomes (1160 patients). The urinary incontinence rate from both focal cryotherapy studies was less than 1%, which was lower than that reported in the non-focal ablation studies (range from 2% to 20%). Rerunning the mixed-treatment comparison model using the focal studies gave an OR of 0.10 (95% CrI < 0.01 to 2.0) in favour of focal cryotherapy versus EBRT. Similarly, there was some evidence of a reduction in urinary incontinence rates using focal cryosurgery versus RP (OR 0.01, 95% CrI < 0.01 to 0.05). There is therefore a suggestion that urinary incontinence rates may be lower for focal cryotherapy, but caution is needed regarding this interpretation given the high risk of bias and quantity of the data.

Erectile dysfunction

Three studies reporting the outcomes of focal cryotherapy contributed to the meta-analysis of erectile dysfunction at 1 year.[129,138,202] The rates of erectile dysfunction were 0%,[138] 11%[202] and 40%.[129] There was no evidence of a reduction in erectile dysfunction rates using focal cryosurgery versus RP (OR 0.32, 95% CrI 0.02 to 12.6).

Procedural complications

Studies of the use of focal cryotherapy rarely reported data related to procedural adverse events. Urinary retention rates were reported in four studies[103,138,188,202] and ranged from 1.2%[202] to 8%.[103] The rate of urinary retention was consistent with the modelled rate of 4% in *Table 15*. The number of men with fistula was reported in all focal cryotherapy studies. Only two cases across the entire cohort of focal cryotherapy patients were reported, and such a low rate of reported fistula was consistent with the non-focal cryotherapy studies.

Use of cryotherapy versus active surveillance for people with low-risk prostate cancers

As described in the methods of the systematic review (see *Chapter 3*), any comparison with AS necessitated that the included studies contained low-risk patients only. Five studies reporting the outcome of cryotherapy met the low-risk disease criteria (described in *Chapter 3*) for inclusion.[103,129,138,160,202] The studies variably reported comparative outcomes of overall survival, functional outcomes (urinary incontinence and erectile dysfunction), quality of life and need for further cancer treatment.

Overall survival

None of the studies involving people undergoing cryotherapy for low-risk disease reported data for overall survival that could be compared with the included AS studies. Four AS studies reported the proportion surviving at 4 years as 92%,[146] 94%,[140] 96%[181] and 99%[111] respectively.

Functional outcomes

No data on urinary incontinence were reported in the included studies of people under AS. Three studies of people with low-risk disease treated with cryotherapy[129,138,202] and one of people under AS[141] provided information on erectile dysfunction that could be used for meta-analysis (*Table 19*). Meta-analysis of these data showed no statistical evidence of a difference in reported rate of erectile dysfunction at 1 year after cryotherapy compared with AS (the probability that cryotherapy was superior to AS was 0.41). The predicted rate of erectile dysfunction in the mixed-treatment comparison model at 1 year for people with low-risk prostate cancer was 11% for cryotherapy and 5% for AS.

Quality of life

Health status (quality of life) was measured in two studies of people under AS, one using the SF-36[199] and the other measuring anxiety using the State Trait Anxiety Inventory General Anxiety Measure.[198] Neither measure was used in any of the studies where men were treated with cryotherapy, preventing any comparison (see *Appendix 10, Table 88* for full details).

Need for further cancer treatment

Data on outcomes related to further cancer treatment were reported in six studies of people enrolled in an AS programme.[111,134,140,146,181,187] At 1-year follow-up of 2494 people enrolled in an AS programme, Bul and colleagues[111] reported that 21% received a prostate cancer therapy (10% RP, 10% EBRT). Two studies reported the rate of prostate cancer treatment at 3 years, with rates of 33%[187] and 14%.[140] Five-year follow-up data were reported in one study,[181] with 31% of people initially under AS switching to a prostate cancer treatment (19% EBRT or hormone therapy, 9% RP, 2% brachytherapy). Finally, after 6 years of follow-up, two studies reported rates of prostate cancer treatment as being 37% (curative aim: 24% RP, 7% EBRT; palliative aim: 5% hormone therapy)[134] and 30% (curative aim: 8% RP, 20% EBRT; palliative aim: 2% hormone therapy).[146]

Only one of these studies involved UK people.[181] The 5-year follow-up data described above may therefore be the closest representation of treatment implications in the NHS of using a strategy of AS for people with low-risk prostate cancer, but there must be caution in extrapolating results from a single study at high risk of bias. The AS protocol in the single UK study consisted of clinical assessment, with DRE and serum PSA levels taken at 3-month intervals in the first year, 4-month intervals in the second year and 6-month intervals thereafter. TRUS-guided prostate biopsy was repeated after 18–24 months of AS, and every 2 years thereafter. Treatment modality was selected according to local protocol, clinician judgement and patient preference.

TABLE 19 Erectile dysfunction at 1 year (AS)

			Cryotherapy vs. AS	
Year	Cryotherapy, proportion (95% CrI)	AS, proportion (95% CrI)	OR (95% CrI)	*p*(cryotherapy > AS)
1	0.11 (0.01 to 0.41)	0.05 (< 0.01 to 0.39)	1.51 (0.09 to 615)	0.41

Summary and conclusions from the evidence of the comparative effectiveness of cryotherapy

This review considered data from 3995 patients who received cryotherapy across 19 studies (14 case series,[52,102,114,122,124,129,138,139,154,158,166,188,202,204] one RCT[125] and four NRCSs[103,128,160,203]), with most studies considered to be at high risk of bias. Results should be interpreted cautiously to reflect the very poor quality of the evidence base and the variation in definition of many of the outcomes. There were limited published data on long-term efficacy of cryotherapy in achieving lower rates of morbidity and mortality compared with the standard options of RP and EBRT.

We found conflicting evidence relating to cancer-specific outcomes in the short term when cryotherapy is compared with either EBRT or surgery. The only finding that reached statistical significance was 1-year disease-free survival, which was worse for cryotherapy than for either EBRT or RP. However, none of the other cancer-specific outcomes, such as biochemical failure or overall survival, showed any significant differences. In fact, there was conflicting evidence relating to overall survival, with cryotherapy having a numerically better outcome than EBRT, although the difference did not reach statistical significance. As such, the findings in relation to cancer-specific outcomes are best regarded as inconclusive, and there is no robust evidence to suggest that mortality or other cancer-specific outcomes are different between cryotherapy and either EBRT or RP for people treated for localised prostate cancer.

There was evidence that the rate of urinary incontinence at 1 year was lower for people undergoing cryotherapy than for RP, but the size of the difference decreased with longer follow-up. Similarly, there was a reduction in erectile dysfunction following cryotherapy at 1 year. There were insufficient data to draw any conclusions on bowel problems.

There was a general trend for cryotherapy to have fewer procedural complications, apart from urinary retention. The difference reached statistical significance for stricture when compared with RP and the findings favoured cryotherapy.

Descriptive subgroup assessment restricted to studies reporting the use of focal cryotherapy was limited, but suggested that cancer-specific outcomes were at least comparable with those reported by full-gland cryotherapy studies. Urinary incontinence rates may be lower following focal cryotherapy, but a degree of caution is needed in light of the poor quality and quantity of the data.

It was not possible to compare the efficacy of cryotherapy with a programme of AS, apart from the rate of erectile dysfunction at 12 months, which showed no statistically significant difference.

In conclusion, the results of this review and meta-analysis were associated with a large degree of uncertainty due to the poor study quality and restricted number of studies identified. There was a lack of use of long-term direct measures of effectiveness and a serious lack of prospective comparative studies. The rates of short-term adverse events were, in general, favourable towards cryotherapy. The comparative effectiveness of cryotherapy against either EBRT or RP remains unclear.

Chapter 5 The comparative effectiveness of high-intensity focused ultrasound

Included studies

The characteristics of the included studies were described in *Chapter 3*, and are detailed in *Appendix 8* and summarised here.

There were 4000 enrolled and 3997 analysed patients undergoing HIFU from 21 studies included in the review.[98,99,103,106,107,116,120,127,132,133,142,143,150,159,161,162,173,174,185,191,195] The studies were predominantly case series, but with one NRCS on HIFU versus cryotherapy versus brachytherapy versus PDT.[103]

Assessment of effectiveness

A detailed description of all outcomes, including those which were used in meta-analyses, is provided in *Appendix 10*.

Cancer-related efficacy outcomes

Biochemical failure

Four studies[106,159,162,173] provided data on biochemical failure following HIFU that could be used for meta-analysis (*Table 20*). Meta-analysis of these data showed a numerically increased risk of biochemical failure for HIFU compared with EBRT at 1-year follow-up, which was statistically significant (21% for HIFU vs. 1.3% for EBRT, with a probability of 0.007 of HIFU being superior to EBRT). However, at 5-year follow-up, the differences were no longer statistically significant (the probability that HIFU was superior to EBRT was 0.039 at 5-year follow-up). For the comparison with RP, HIFU showed a numerically increased risk of biochemical failure at 1 and 5 years. None of the differences were statistically significant (the probabilities that HIFU was superior to RP were 0.097 and 0.106 for years 1 and 5 respectively). The 5-year follow-up had the higher number of studies contributing to the meta-analysis, and the predicted rate of biochemical failure in the mixed-treatment comparison model at 5 years was 34% for HIFU, 13% for EBRT and 11% for RP. A degree of caution is required in interpreting these findings given that none of the studies were comparative.

Overall survival

Only two studies[162,173] provided data on overall survival following HIFU that could be used for meta-analysis (*Table 21*). Meta-analysis of these data showed evidence of improved survival for HIFU compared with EBRT at 4 years (the probability that HIFU was superior to EBRT was 0.98). The predicted rate of survival in the mixed-treatment comparison model at 4 years was 99% for HIFU, 91% for EBRT. There were no data available to estimate survival from the RP studies at 4 years.

Disease-free survival

Five studies[107,132,133,161,191] provided data on disease-free survival following HIFU that could be used for meta-analysis (*Table 22*). Meta-analysis of these data showed a lower rate of disease-free survival for HIFU than for EBRT at 1 year and this was statistically significant (the probability that HIFU was superior to EBRT was < 0.01). There was no evidence of a difference between HIFU and RP at 1 year. Findings for the 3-year follow-up were numerically similar, but the results were no longer statistically significant. The 3-year follow-up had the higher number of studies contributing to the meta-analysis and the predicted rate of disease-free survival in the mixed-treatment comparison model at 1 year was 88% for HIFU, 95% for EBRT

TABLE 20 Meta-analysis of biochemical failure at 1- and 5-year follow-up

Follow-up	HIFU, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	HIFU vs. EBRT		HIFU vs. RP	
				OR (95% CrI)	*p*(HIFU > EBRT)	OR (95% CrI)	*p*(HIFU > RP)
1 year	0.21 (0.05 to 0.53)	0.013 (< 0.01 to 0.07)	0.073 (< 0.01 to 0.55)	20.3 (3.7 to 314)	0.007	3.3 (0.58 to 47.5)	0.097
5 years	0.34 (0.08 to 0.75)	0.13 (0.05 to 0.25)	0.11 (0.02 to 0.38)	3.8 (0.83 to 14.5)	0.039	3.7 (0.4 to 44.5)	0.106

TABLE 21 Meta-analysis of overall survival at 4-year follow-up

Follow-up	HIFU, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	HIFU vs. EBRT		HIFU vs. RP	
				OR (95% CrI)	*p*(HIFU > EBRT)	OR (95% CrI)	*p*(HIFU > RP)
4 years	> 0.99 (0.98 to > 0.99)	0.91 (0.45 to 0.99)	–	0.03 (< 0.01 to 0.79)	0.98	–	–

TABLE 22 Meta-analysis of disease-free survival at 1- and 3-year follow-up

Follow-up	HIFU, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	HIFU vs. EBRT		HIFU vs. RP	
				OR (95% CrI)	*p*(HIFU > EBRT)	OR (95% CrI)	*p*(HIFU > RP)
1 year	0.93 (0.75 to 0.98)	0.99 (0.98 to > 0.99)	0.95 (0.88 to 0.99)	13.8 (2.2 to 81.7)	< 0.01	1.8 (0.32 to 11.1)	0.23
3 years	0.88 (0.75 to 0.96)	0.95 (0.88 to 0.98)	0.90 (0.75 to 0.97)	2.2 (0.48 to 7.5)	0.13	1.1 (0.17 to 4.3)	0.46

and 90% for RP. As shown in *Table 6* (see *Chapter 3*), the observed differences may reflect a higher-severity disease profile at baseline in the HIFU studies compared with EBRT.

Adverse effects

Urinary function: urinary incontinence

Four studies[116,120,159,174] provided data on urinary incontinence following HIFU that could be used for meta-analysis (*Table 23*). Meta-analysis of these data showed a numerically increased risk of incontinence for HIFU compared with EBRT at 1 year, but this was not statistically significant (the probability that HIFU was superior to EBRT was 0.18). For the comparison with RP, HIFU showed a statistically significant decrease in risk of incontinence at 1 year (the probability that HIFU was superior to RP was > 0.99). By 5 years, the risk of incontinence was numerically larger for HIFU, but was not statistically significant (the probability that HIFU was superior to RP was 0.38). The predicted rate of incontinence in the mixed-treatment comparison model at 1 year was 10% for HIFU, 5% for EBRT and 66% for RP.

Sexual function: erectile dysfunction

As described in *Chapter 3*, *Overview of type of outcomes reported*, a total of 33 studies provided data on sexual function.[49,98–100,110,113,114,116,117,120,121,124,125,129,138,139,141,143,154,158,159,166,174,184,185,189,191,195,198,202,203,206,207]
The time point following intervention when the outcome was assessed and the measure used to quantify the outcome showed wide variation across the studies. Given the diversity of definitions and types of data (continuous or dichotomous), it was not possible to collate all the data from individual studies into a form suitable for meta-analysis. However, two studies[185,191] provided information on erectile dysfunction following HIFU that could be used for meta-analysis (*Table 24*). Meta-analysis of these data showed a numerical reduction in rates of erectile dysfunction following HIFU compared with RP at 1 year, but the difference was not statistically significant (the probability that HIFU was superior to RP was 0.72). The predicted rate of erectile dysfunction in the mixed-treatment comparison model at 1 year was 23% for HIFU and 33% for RP. There were no data available to estimate the rate of erectile dysfunction at 1 year in people treated with EBRT.

Bowel function

Bowel function following HIFU was only reported in one study.[191] Uchida and colleagues[191] reported a single case of stool incontinence in 72 people.

Procedural complications

Data on short-term adverse events related to the use of HIFU, including dysuria, urinary retention, urethral sloughing, infection, stricture, bladder neck contracture, bladder spasm, rectal pain/bleeding and fistula, are presented below. Abstracted data concerning other specific adverse events not included below are detailed in *Appendix 10*. Given the variety of definitions and periods of follow-up between studies, a degree of caution should be used in interpretation of these results.

Dysuria

Three studies[98,99,159] provided data on the occurrence of dysuria following HIFU that could be used for meta-analysis (*Table 25*). Meta-analysis of these data showed a numerical increase in risk of dysuria for HIFU compared with EBRT and RP, but this was not statistically significant (the probabilities that HIFU was superior were 0.29 and 0.16 for EBRT and RP respectively). The predicted rate of dysuria in the mixed-treatment comparison model was 20% for HIFU, 14% for EBRT and 6% for RP.

Urinary retention

Six studies[99,103,127,150,159,185] provided information on urinary retention following HIFU that could be used for meta-analysis (*Table 26*). Meta-analysis of these data showed a numerical increase in risk of urinary retention for HIFU compared with EBRT, but this was not statistically significant (the probability that HIFU was superior to EBRT was 0.08). The predicted rate of urinary retention in the mixed-treatment comparison model was 10% for HIFU and 2% for EBRT. There were no data available to estimate the rate of urinary retention after RP.

TABLE 23 Urinary incontinence at 1- and 5-year follow-up

Follow-up	HIFU, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	HIFU vs. EBRT		HIFU vs. RP	
				OR (95% CrI)	*p*(HIFU > EBRT)	OR (95% CrI)	*p*(HIFU > RP)
1 year	0.10 (0.01 to 0.57)	0.05 (< 0.01 to 0.46)	0.66 (0.12 to 0.96)	2.4 (0.28 to 19.5)	0.18	0.06 (0.01 to 0.48)	> 0.99
5 years	0.09 (0.01 to 0.57)	–	0.06 (< 0.01 to 0.42)	–	–	1.9 (0.04 to 121)	0.38

TABLE 24 Erectile dysfunction at 1-year follow-up

Follow-up	HIFU, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	HIFU vs. EBRT		HIFU vs. RP	
				OR (95% CrI)	*p*(HIFU > EBRT)	OR (95% CrI)	*p*(HIFU > RP)
1 year	0.23 (0.05 to 0.58)	–	0.33 (0.04 to 0.85)	–	–	0.57 (0.01 to 352)	0.72

TABLE 25 Dysuria

Outcome	HIFU, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	HIFU vs. EBRT		HIFU vs. RP	
				OR (95% CrI)	*p*(HIFU > EBRT)	OR (95% CrI)	*p*(HIFU > RP)
Dysuria	0.20 (< 0.07 to 0.43)	0.14 (0.03 to 0.52)	0.06 (< 0.01 to 0.35)	1.6 (0.19 to 12.9)	0.29	3.2 (0.32 to 53.3)	0.16

TABLE 26 Urinary retention

Outcome	HIFU, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	HIFU vs. EBRT		HIFU vs. RP	
				OR (95% CrI)	*p*(HIFU > EBRT)	OR (95% CrI	*p*(HIFU > RP)
Urinary retention	0.10 (0.01 to 0.10)	0.02 (< 0.01 to 0.14)	–	4.3 (0.53 to 40.4)	0.08	–	–

Urethral sloughing

Urethral sloughing was reported by three studies of people undergoing HIFU.[99,120,174] The proportion of people suffering with urethral sloughing ranged from 4%[120] to 34%.[99]

Urethral stricture

Eight studies[98,127,143,150,159,174,185,191] provided information on stricture following HIFU that could be used for meta-analysis (*Table 27*). Meta-analysis of these data showed a numerical increase in risk of stricture for HIFU compared with EBRT and this was statistically significant (the probability that HIFU was superior to EBRT was 0.01). HIFU showed no evidence of a difference in risk of stricture compared with RP (the probability that HIFU was superior to RP was 0.36). The predicted rate of stricture in the mixed-treatment comparison model was 8% for HIFU, 1% for EBRT and 8% for RP.

Rectal pain and bleeding

Only one study provided information on rectal pain and rectal bleeding following HIFU.[159] Meta-analysis of the data reporting rectal pain and bleeding (*Tables 28* and *29*) showed no evidence of a difference in risk for HIFU compared with EBRT. The predicted rate of rectal pain in the mixed-treatment comparison model was 11% for HIFU and 9% for EBRT. There were no data available to estimate rectal pain/bleeding after RP.

Other adverse events

Data on the occurrence of fistula following HIFU were reported in six studies.[98,143,150,159,161,185] The rate of fistula occurrence was low and ranged from 0% in two studies[98,143] to 5% in one study.[150] The median reported rate of fistula occurrence was 1%.

Bladder neck contracture was reported in three studies,[120,150,185] and the rates of contracture were 0%,[150] 10%[185] and 14%[120] respectively. A single case of bladder spasm was reported by Koch and colleagues.[150]

Rates of urinary infection were reported in nine studies of people undergoing HIFU.[99,116,127,142,150,159,161,185,191] The rate of urinary infection ranged from 0.6%[161] to 45%.[150] The median rate of urinary infection was 15%.

Quality of life

Two case series of people undergoing HIFU reported on a variety of quality of life outcomes,[98,195] but none of the measures were the same between studies. The data were, therefore, insufficient to inform on any difference in quality of life following HIFU compared with either EBRT or RP (see *Appendix 10*, *Table 88*, for full details).

Further prostate cancer treatment

The need for reintervention using further HIFU within 2 years of initial procedure was reported in three studies of people undergoing HIFU.[116,161,173] The rates of reintervention were 3%,[173] 12%[161] and 31%[116] respectively.

Within 6 months of initial treatment, Pinthus and colleagues[173] reported that 1% of patients treated with HIFU received hormonal androgen deprivation therapy and 7% were placed in an AS programme; 1.5% received RP and 1% EBRT. At 4 years, Misrai and colleagues[162] reported that 12% received EBRT, 6% received hormonal androgen deprivation therapy and 1% received RP. In contrast, at 8 years, Sumitomo and colleagues[185] reported that 2% received EBRT, 22% received hormonal androgen deprivation therapy and 2% received RP.

TABLE 27 Urethral stricture

Outcome	HIFU, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	HIFU vs. EBRT		HIFU vs. RP	
				OR (95% CrI)	*p*(HIFU > EBRT)	OR (95% CrI)	*p*(HIFU > RP)
Stricture	0.08 (0.02 to 0.15)	0.01 (< 0.01 to 0.05)	0.08 (< 0.01 to 0.25)	5.8 (1.2 to 24.5)	0.01	1.2 (0.23 to 4.0)	0.36

TABLE 28 Rectal pain

Outcome	HIFU, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	HIFU vs. EBRT		HIFU vs. RP	
				OR (95% CrI)	*p*(HIFU > EBRT)	OR (95% CrI)	*p*(HIFU > RP)
Rectal pain	0.11 (< 0.01 to 0.64)	0.09 (0.01 to 0.44)	–	0.96 (0.02 to 48.5)	0.51	–	–

TABLE 29 Rectal bleeding

Outcome	HIFU, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	HIFU vs. EBRT		HIFU vs. RP	
				OR (95% CrI)	*p*(HIFU > EBRT)	OR (95% CrI)	*p*(HIFU > RP)
Rectal bleeding	0.03 (< 0.01 to 0.36)	0.04 (0.01 to 0.14)	–	0.61 (< 0.01 to 18.9)	0.62	–	–

Analysis of subgroups

Focal high-intensity focused ultrasound

Of the 21 studies reporting outcomes in people receiving HIFU,[98,99,103,106,107,116,120,127,132,133,142,143,150,159,161,162,173,174,185,191,195] four used a focal HIFU approach.[98,99,103,127] Given the low number of studies reporting on the use of focal HIFU and the diversity of outcomes reported in each study, no formal subgroup meta-analyses could be undertaken, and therefore a descriptive summary of reported findings in relation to the overall comparative meta-analysis is given.

Cancer-related efficacy outcomes

No focal HIFU studies reported cancer-related efficacy data (biochemical failure, overall survival and disease-free survival) that could be compared with non-focal HIFU studies.

Incontinence or erectile dysfunction

No focal HIFU studies reported data on incontinence or erectile dysfunction that could be compared with non-focal HIFU studies.

Procedural complications

The focal HIFU studies reported data related to procedural adverse events. The dysuria rates were 22%[99] and 30%[98] in the focal HIFU studies, which were numerically higher than the pooled rate of 20% reported in *Table 25*. Urinary retention rates were 2%,[99] 8%[127] and 24%,[103] which were broadly similar to the pooled estimate of 10% in *Table 26*. Twenty-four per cent of people had urethral sloughing,[99] which was the highest rate across all the included HIFU studies. An infection rate of 17% was reported in two focal HIFU studies,[99,127] which was broadly similar to the median infection rate of all HIFU studies. Only three cases of stricture were reported across the cohort of focal HIFU patients, and such a low number of strictures was consistent with the non-focal HIFU studies.

Use of high-intensity focused ultrasound versus active surveillance for people with low-risk prostate cancer

As described in the methods of the systematic review (see *Chapter 3*), any comparison with AS necessitated that the included studies contained low-risk patients only. Two studies of people following HIFU met the low-risk patient criterion for inclusion.[116,162] The studies variably reported comparative outcomes of overall survival, functional outcomes (urinary incontinence and erectile dysfunction), quality of life and need for further cancer treatment.

Overall survival

One study[162] on people following HIFU reported data for overall survival at 4-year follow-up that could be compared with the included AS studies (*Table 30*). Meta-analysis of these data showed a numerical difference in survival for HIFU compared with AS at 4 years, but was not statistically significant (the probability that HIFU was superior to AS was 0.84). The predicted rate of survival in the mixed-treatment comparison model at 4 years was > 99% for HIFU and 95% for AS.

Functional outcomes

No data on urinary incontinence were reported in the included studies of people on AS. One study[116] of people following HIFU and two studies[141,198] of people on AS provided information on erectile function that could be used for meta-analysis (*Table 31*). Meta-analysis of the data showed no evidence of a difference in erectile dysfunction at 1 year for HIFU compared with AS (the probability that HIFU was superior to AS was 0.71). The predicted rate of erectile function in the mixed-treatment comparison model at 1 year was 65% for HIFU and 74% for AS.

TABLE 30 Meta-analysis of overall survival at 4-year follow-up (AS)

			HIFU vs. AS	
Follow-up	HIFU, proportion (95% CrI)	AS, proportion (95% CrI)	OR (95% CrI)	*p*(HIFU > AS)
4 years	> 0.99 (0.91 to > 0.99)	0.95 (0.80 to 0.99)	8.5 (0.15 to 861)	0.84

TABLE 31 Erectile function at 1 year (AS)

			HIFU vs. AS	
Outcome	HIFU, proportion (95% CrI)	AS, proportion (95% CrI)	OR (95% CrI)	*p*(HIFU > AS)
Erectile function	0.65 (0.13 to 0.96)	0.74 (0.35 to 0.93)	0.66 (0.06 to 5.7)	0.71

Quality of life

Health status (quality of life) was measured in two studies of people under AS, one using the SF-36[199] and the other measuring anxiety using the State Trait Anxiety Inventory General Anxiety Measure.[198] Neither measure was used in any of the studies in which people were treated with HIFU, preventing any comparison.

Need for further cancer treatment

Data related to the need for further cancer treatment in AS studies were described in *Chapter 4* (see *Use of cryotherapy versus active surveillance for people with low-risk prostate cancers*).

Summary and conclusions from the evidence of the comparative effectiveness of high-intensity focused ultrasound

This review considered data from 4000 patients who received HIFU across 21 studies (20 case series,[98,99,106,107,116,120,127,132,133,142,143,150,159,161,162,173,174,185,191,195] one NRCS[103]), with all studies considered to be at high risk of bias. Results should, therefore, be interpreted cautiously to reflect the very poor quality of the evidence base and the variation in definition of many of the outcomes. There were limited published data on the long-term efficacy of HIFU in achieving lower rates of morbidity and mortality compared with the standard options of RP and EBRT.

In the short term, there was some evidence that biochemical failure rates increased at 1 year when using HIFU compared with EBRT, and the difference was statistically significant. However, this was no longer statistically significant at 5 years. Similar findings were observed with regard to disease-free survival at 1 year, with a worse outcome for HIFU than for EBRT, which was statistically significant. The difference was no longer significant at 3 years. The biochemical result was in contrast to the overall survival which suggested that at 4 years HIFU had statistically significantly better survival. The early difference in biochemical failure may have been a reflection that participants in the EBRT studies in general had lower-risk prostate cancer at baseline than those in the HIFU studies that reported biochemical failure rates. There was no evidence of a difference in cancer-specific outcomes for HIFU versus RP.

There were insufficient data on any of urinary incontinence, erectile dysfunction or bowel problems to draw any robust conclusions, although at 1 year HIFU appeared to have lower incontinence rates than RP, with the differences statistically significant. However, there were no significant differences at 5 years. The safety profile for HIFU was generally good, apart from a potential numerical increase in urinary retention and dysuria, but the differences did not reach statistical significance. However, HIFU appeared to have a slightly higher incidence of urethral stricture than EBRT, and the difference was statistically significant. Descriptive subgroup assessment restricted to studies reporting the use of focal HIFU was too limited to draw any conclusions.

Limited data comparing outcomes in people following HIFU with a programme of AS suggested no evidence of a difference in either overall survival at 4 years or erectile dysfunction at 1 year.

In conclusion, the results of this review and meta-analysis were associated with a large degree of uncertainty due to the poor study quality and restricted number of studies identified. There was a lack of use of long-term direct measures of effectiveness and a lack of prospective comparative studies. The comparative effectiveness of HIFU against either EBRT or RP remains unclear.

Chapter 6 The comparative effectiveness of brachytherapy

Included studies

The characteristics of the included studies were described in *Chapter 3*, and are detailed in *Appendix 8* and summarised here.

There were 26,129 enrolled and 25,805 analysed patients undergoing brachytherapy from 41 studies (40 reports) included in the review.[36,49,100,101,103,105,108–110,113,117,119,121,123,126,128,130,131,135,136,144,145,149,151,153,156,160,163,170–172,176,182,184,186,189,203,205–207] The studies were predominantly non-randomised studies: nine on brachytherapy versus RP,[101,108–110,113,121,123,145,149] 13 on brachytherapy versus EBRT,[105,119,126,135,136,170–172,182,189,205–207] 13 on brachytherapy versus EBRT versus RP,[36,100,117,130,131,144,151,153,156,163,176,184,186] one study[128] on brachytherapy versus cryotherapy versus EBRT versus RP, one on brachytherapy versus cryotherapy versus RP,[160] one on brachytherapy versus cryotherapy versus HIFU versus PDT[103] and one on brachytherapy versus cryotherapy.[203] There were two RCTs on brachytherapy versus RP.[49,121]

Assessment of effectiveness

A detailed description of all outcomes, including those which were used in meta-analyses, is provided in *Appendix 10*.

Cancer-related efficacy outcomes

Biochemical failure

Seven studies[49,112,119,135,149,184,206] provided data on biochemical failure following brachytherapy that could be used for meta-analysis (*Table 32*). Meta-analysis of these data showed a numerically decreased risk of biochemical failure for brachytherapy compared with EBRT at 1-, 3- and 5-year follow-up and this was statistically significant at 5 years (the probability that brachytherapy was superior to EBRT for this outcome was > 0.99 for 5-year follow-up). For the comparison with RP, brachytherapy showed a numerically decreased risk of biochemical failure at 1, 3 and 5 years. All of the differences were statistically significant (the probabilities that brachytherapy was superior to RP for this outcome were 0.99, 0.99 and > 0.99 for years 1, 3 and 5 respectively). The 5-year time point had a higher number of studies contributing to the meta-analysis and the predicted rate of biochemical failure in the mixed-treatment comparison model at 5 years was 7% for brachytherapy, 13% for EBRT and 11% for RP.

Overall survival

There were no studies that provided information on overall survival that could be used for meta-analysis. The largest NRCS with longer-term follow-up[144] reported 10-year survival of 81.7% [95% confidence interval (CI) 78.7% to 84.4%] for brachytherapy, 82.6% (95% CI 79.8% to 85.0%) for EBRT and 88.9% (95% CI 87.5% to 90.1%) for RP.

Disease-free survival

Twelve studies involving people undergoing brachytherapy[36,49,109,119,126,135,136,151,170,171,204,206] provided information on disease-free survival that could be used for meta-analysis (*Table 33*). Meta-analysis of these data showed a higher rate of disease-free survival for people undergoing brachytherapy than for those treated with EBRT and RP at 1 and 3 years, and this was statistically significant (the probability that

TABLE 32 Meta-analysis of biochemical failure at 1-, 3- and 5-year follow-up

Follow-up	Brachytherapy, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	Brachytherapy vs. EBRT		Brachytherapy vs. RP	
				OR (95% CrI)	*p*(brachytherapy > EBRT)	OR (95% CrI)	*p*(brachytherapy > RP)
1 year	0.003 (< 0.001 to 0.04)	0.013 (< 0.01 to 0.07)	0.073 (< 0.01 to 0.55)	0.27 (0.01 to 2.6)	0.86	0.03 (< 0.01 to 0.52)	0.99
3 years	0.02 (< 0.01 to 0.11)	0.05 (0.01 to 0.16)	0.07 (< 0.01 to 0.44)	0.85 (0.41 to 1.7)	0.67	0.14 (< 0.01 to 0.74)	0.99
5 years	0.07 (0.03 to 0.15)	0.13 (0.05 to 0.25)	0.11 (0.02 to 0.38)	0.46 (0.32 to 0.67)	> 0.99	0.35 (0.21 to 0.56)	> 0.99

TABLE 33 Meta-analysis of disease-free survival at 1- and 3-year follow-up

Follow-up	Brachytherapy, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	Brachytherapy vs. EBRT		Brachytherapy vs. RP	
				OR (95% CrI)	*p*(brachytherapy > EBRT)	OR (95% CrI)	*p*(brachytherapy > RP)
1 year	0.99 (0.99 to > 0.99)	0.99 (0.98 to > 0.99)	0.95 (0.88 to 0.99)	0.41 (0.26 to 0.64)	> 0.99	0.13 (0.08 to 0.22)	> 0.99
3 years	0.96 (0.92 to 0.98)	0.95 (0.88 to 0.98)	0.90 (0.75 to 0.97)	0.43 (0.36 to 0.53)	> 0.99	0.42 (0.32 to 0.54)	> 0.99

brachytherapy was superior to EBRT/RP was > 0.99). The 3-year time point had the greater number of studies contributing to the meta-analysis and the predicted rate of disease-free survival in the mixed-treatment comparison model at 3 years was 96% for brachytherapy, 95% for EBRT and 90% for RP.

Adverse effects

Urinary function: urinary incontinence

Six studies involving people treated with brachytherapy[49,117,121,145,172,184] provided information on urinary incontinence that could be used for meta-analysis (*Table 34*). Meta-analysis of these data showed a numerically increased risk of incontinence for brachytherapy compared with EBRT at 1 year, but this was not statistically significant (the probability that the outcome favoured brachytherapy was 0.09). For comparison with RP, brachytherapy showed a statistically significant decrease in risk of incontinence at 1 year (the probability that brachytherapy was superior to RP was 0.94). By 5 years, the risk of incontinence was still numerically lower for people treated with brachytherapy and statistically significant (the probability that the outcome favoured brachytherapy was > 0.99). The predicted rate of incontinence in the mixed-treatment comparison model at 3 years was 11% for brachytherapy, 10% for EBRT and 28% for RP.

Sexual function: erectile dysfunction

As described in *Chapter 3*, *Overview of type of outcomes reported*, a total of 33 studies provided data on sexual function.[49,98–100,110,113,114,116,117,120,121,124,125,129,138,139,141,143,154,158,159,166,174,184,185,189,191,195,198,202,203,206,207] The time point following intervention when the outcome was assessed and the measure used to quantify the outcome showed wide variation across the studies. Given the diversity of definitions and types of data (continuous or dichotomous), it was not possible to collate all the data from individual studies into a form suitable for meta-analysis. However, four studies involving people treated with brachytherapy[113,117,121,184] provided information on erectile dysfunction that could be used for meta-analysis (*Table 35*). Meta-analysis of these data showed a numerically lower rate of erectile dysfunction for people treated with brachytherapy than for those receiving RP at 1, 3 and 5 years, and the difference was statistically significant at 3 and 5 years (the probability that brachytherapy was superior to RP was > 0.99 for 3 and 5 years). Only 3-year data were available for EBRT. Meta-analysis of these data showed a numerically lower rate of erectile dysfunction for people treated with brachytherapy than for those treated with EBRT at 3 years, and the difference was statistically significant (the probability that brachytherapy was superior to RP was > 0.99). The predicted rates of erectile dysfunction in the mixed-treatment comparison model at 3 years were 60% for brachytherapy, 81% for EBRT and 88% for RP.

Bowel function

Disturbance in bowel function among people treated with brachytherapy was rarely measured as an outcome, and when it was reported, the diversity of definitions used prevented meta-analysis. At 3-year follow-up, two NRCSs[117,184] compared brachytherapy with both EBRT and RP. In one study,[184] people treated with brachytherapy reported a lower rate of moderate or severe bowel problems as measured by the UCLA-PCI[217] at 3-year follow-up (0% vs. 14% and 35% for EBRT and RP respectively). In a second study,[117] 68% of people treated with brachytherapy reported bowel problems at 3-year follow-up using the Prostate Cancer Symptom Index.[217] The corresponding rates were 75% and 44% for EBRT and RP respectively.

Procedural complications

Data on short-term adverse events related to the use of brachytherapy, including dysuria, urinary retention, infection, stricture, bladder neck contracture, rectal pain/bleeding, fistula and toxicity, are presented below. Abstracted data concerning other specific adverse events not included below are detailed in *Appendix 10*. Given the variety of definitions and periods of follow-up between studies, a degree of caution should be used in interpretation of these results.

TABLE 34 Urinary incontinence at 1-, 3- and 5-year follow-up

Follow-up	Brachytherapy, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	Brachytherapy vs. EBRT		Brachytherapy vs. RP	
				OR (95% CrI)	*p*(brachytherapy > EBRT)	OR (95% CrI)	*p*(brachytherapy > RP)
1 year	0.27 (0.04 to 0.75)	0.05 (< 0.01 to 0.46)	0.66 (0.12 to 0.96)	2.7 (0.64 to 14.5)	0.09	0.66 (0.12 to 0.96)	0.94
3 years	0.11 (0.02 to 0.43)	0.10 (0.01 to 0.48)	0.28 (0.05 to 0.75)	0.71 (0.38 to 1.3)	0.87	0.25 (0.14 to 0.45)	> 0.99
5 years	0.03 (< 0.01 to 0.21)	–	0.06 (0.01 to 0.42)	–	–	0.24 (0.11 to 0.51)	> 0.99

TABLE 35 Erectile dysfunction at 1-, 3- and 5-year follow-up

Follow-up	Brachytherapy, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	Brachytherapy vs. EBRT		Brachytherapy vs. RP	
				OR (95% CrI)	*p*(brachytherapy > EBRT)	OR (95% CrI)	*p*(brachytherapy > RP)
1 year	0.28 (0.03 to 0.82)	–	0.33 (0.04 to 0.85)	–	–	0.78 (0.50 to 1.2)	0.87
3 years	0.60 (0.16 to 0.92)	0.81 (0.24 to 0.97)	0.88 (0.48 to 0.99)	0.35 (0.21 to 0.59)	> 0.99	0.21 (0.13 to 0.35)	> 0.99
5 years	0.50 (0.07 to 0.93)	–	0.70 (0.15 to 0.97)	–	–	0.41 (0.21 to 0.79)	> 0.99

Dysuria

Four studies[113,121,172,182] provided information on the occurrence of dysuria that could be used for meta-analysis (*Table 36*). Meta-analysis of these data showed an increase in risk of dysuria for brachytherapy compared with EBRT which was not statistically significant (the probability that brachytherapy was superior was 0.05). There was a statistically significant increase in risk of dysuria for brachytherapy compared with RP (the probability that brachytherapy was superior was < 0.01). The predicted rates of dysuria in the mixed-treatment comparison model were 22% for brachytherapy, 14% for EBRT and 6% for RP.

Urinary retention

Four studies involving people undergoing brachytherapy[49,182,203,206] provided information on urinary retention that could be used for meta-analysis (*Table 37*). Meta-analysis of these data showed a statistically significant increase in risk of urinary retention among people treated with brachytherapy compared with EBRT (the probability that brachytherapy was superior to EBRT for this outcome was < 0.01). The predicted rates of urinary retention in the mixed-treatment comparison model were 9% for brachytherapy and 4% for EBRT. It was not possible to estimate the rate of urinary retention after RP.

Urethral stricture

Six studies involving people undergoing brachytherapy[49,126,128,182,203,206] provided information on urethral stricture that could be used for meta-analysis (*Table 38*). Meta-analysis of these data showed a statistically significant increase in risk of stricture following brachytherapy compared with EBRT (the probability that brachytherapy was superior to EBRT was < 0.01). For the comparison with RP, people treated with brachytherapy showed a statistically significant decrease in risk of stricture (the probability that brachytherapy was superior to RP was > 0.99). The predicted rates of stricture in the mixed-treatment comparison model were 4% for brachytherapy, 1% for EBRT and 8% for RP.

Rectal pain and bleeding

Four studies involving people undergoing brachytherapy provided information on rectal pain[126,172,182,203] and six provided information on rectal bleeding.[113,172,182,203,206,207] Meta-analysis of these data (*Tables 39* and *40*) showed a decreased risk of these adverse events following brachytherapy compared with EBRT, and this was statistically significant for rectal pain (the probability that brachytherapy was superior to EBRT was > 0.99). The predicted rates of rectal pain in the mixed-treatment comparison model were 5% for brachytherapy and 9% for EBRT. It was not possible to estimate rectal pain/bleeding after RP.

Toxicity

Five studies involving people undergoing brachytherapy provided information on acute genitourinary toxicity[126,171,182,205,206] and four provided information on acute gastrointestinal toxicity.[126,171,182,205] Meta-analysis of these data (*Tables 41* and *42*) showed a statistically significant increased risk of acute genitourinary toxicity following brachytherapy compared with EBRT (the probability that brachytherapy was superior to EBRT was < 0.01). There was a numerical decrease in risk of acute gastrointestinal toxicity following brachytherapy compared with EBRT which was borderline statistically significant (the probability that brachytherapy was superior to EBRT was 0.95).

Other adverse events

Data on occurrence of fistula were reported in only one study involving people undergoing brachytherapy[203] and the rate of fistula occurrence was 0.3% (27/9985 patients).

Bladder neck contracture was only reported in one study,[126] and the rate of contracture was 0.6% (1/158 patients).

Urinary tract infection data were reported in one study of people undergoing brachytherapy[203] and the rate was 2.4% (237/9985 patients).

TABLE 36 Dysuria

Outcome	Brachytherapy, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	Brachytherapy vs. EBRT		Brachytherapy vs. RP	
				OR (95% CrI)	*p*(brachytherapy > EBRT)	OR (95% CrI)	*p*(brachytherapy > RP)
Dysuria	0.22 (0.06 to 0.57)	0.14 (0.03 to 0.52)	0.06 (< 0.01 to 0.35)	1.35 (0.94 to 1.9)	0.05	7.5 (4.3 to 13.2)	< 0.01

TABLE 37 Urinary retention

Outcome	Brachytherapy, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	Brachytherapy vs. EBRT		Brachytherapy vs. RP	
				OR (95% CrI)	*p*(brachytherapy > EBRT)	OR (95% CrI)	*p*(brachytherapy > RP)
Urinary retention	0.09 (0.03 to 0.20)	0.02 (< 0.01 to 0.14)	–	2.6 (1.8 to 3.7)	< 0.01	–	–

TABLE 38 Stricture

Outcome	Brachytherapy, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	Brachytherapy vs. EBRT		Brachytherapy vs. RP	
				OR (95% CrI)	*p*(brachytherapy > EBRT)	OR (95% CrI)	*p*(brachytherapy > RP)
Stricture	0.04 (0.02 to 0.08)	0.01 (< 0.01 to 0.05)	0.08 (< 0.01 to 0.25)	2.0 (1.4 to 2.9)	< 0.01	0.24 (0.15 to 0.37)	> 0.99

TABLE 39 Rectal pain

Outcome	Brachytherapy, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	Brachytherapy vs. EBRT		Brachytherapy vs. RP	
				OR (95% CrI)	*p*(brachytherapy > EBRT)	OR (95% CrI)	*p*(brachytherapy > RP)
Rectal pain	0.05 (0.01 to 0.22)	0.09 (0.01 to 0.44)	–	0.11 (0.07 to 0.17)	> 0.99	–	–

TABLE 40 Rectal bleeding

Outcome	Brachytherapy, proportion (95% CrI)	EBRT, proportion (95% CrI)	RP, proportion (95% CrI)	Brachytherapy vs. EBRT		Brachytherapy vs. RP	
				OR (95% CrI)	*p*(brachytherapy > EBRT)	OR (95% CrI)	*p*(brachytherapy > RP)
Rectal bleeding	0.03 (< 0.01 to 0.11)	0.04 (0.01 to 0.14)	–	0.76 (0.48 to 1.22)	0.88	–	–

TABLE 41 Acute genitourinary toxicity

Outcome	Brachytherapy, proportion (95% CrI)	EBRT, proportion (95% CrI)	Brachytherapy vs. EBRT	
			OR (95% CrI)	*p*(brachytherapy > EBRT)
Acute genitourinary toxicity	0.03 (< 0.01 to 0.09)	0.01 (< 0.01 to 0.03)	2.7 (1.8 to 4.1)	< 0.01

TABLE 42 Acute gastrointestinal toxicity

Outcome	Brachytherapy, proportion (95% CrI)	EBRT, proportion (95% CrI)	Brachytherapy vs. EBRT	
			OR (95% CrI)	*p*(brachytherapy > EBRT)
Acute gastrointestinal toxicity	< 0.001 (< 0.0001 to 0.004)	0.003 (< 0.001 to 0.01)	0.20 (0.01 to 1.3)	0.95

Quality of life

Quality of life was not reported consistently enough across studies to perform a meta-analysis. The most robust evidence came from a single RCT of brachytherapy versus RP.[49] The patients in the study reported similar significant decreases in some functional and symptom European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC-QLQ-C30) scales after 6 months and 1 year regardless of the treatment, and both groups of patients reported a normal global health after 1 and 5 years.

A similar pattern at 2-year follow-up was observed in the non-randomised study[130] that compared people receiving brachytherapy, RP and EBRT. Health-related quality of life (HRQoL) initially decreased across all the treatment modalities, and made a partial recovery by 2 years (see *Appendix 10*, *Table 88* for full details).

Further prostate cancer treatment

Within 3 months of initial treatment, Giberti and colleagues[49] reported that 2.5% of people treated with brachytherapy received hormonal androgen deprivation therapy, 2.5% received EBRT and 3% received RP. In contrast, Pickles and colleagues[171] reported a rate of hormonal androgen deprivation therapy at a follow-up of 5 years to be 5%, compared with 8% for people who initially received EBRT.

Analysis of subgroups

Focal brachytherapy

Of the 39 studies on brachytherapy, only Barret and colleagues[103] reported a focal technique and included 12 participants at enrolment and in the final outcome analyses. Given the low number of studies (and people) reporting on the use of focal brachytherapy, no further data exploration was undertaken.

Use of brachytherapy versus active surveillance for people with low-risk prostate cancers

As described in the methods of the systematic review (see *Chapter 3*), any comparison with AS necessitated that the included studies contained low-risk patients only. Twenty-four studies reporting the outcome of brachytherapy met the low-risk disease criterion for inclusion.[36,49,101,105,109,110,117,119,123,126,135,151,153,156,160,170–172,184,186,189,205–207] The studies variably reported comparative outcomes of overall survival, functional outcomes (urinary incontinence and erectile dysfunction), quality of life and need for further cancer treatment.

Overall survival

None of the studies involving people undergoing brachytherapy for low-risk disease reported data for overall survival that could be compared with the included AS studies.

Functional outcomes

No data on urinary incontinence were reported in the included studies of people under AS. Three studies of people with low-risk disease treated with brachytherapy[49,172,189] and two of people under AS[141,198] provided information on erectile function that could be used for meta-analysis (*Table 43*). Meta-analysis of these data showed a numerically lower chance of erectile function at 1 year after brachytherapy than under AS (the probability that brachytherapy was superior to AS was 0.22). The predicted rates of erectile function in the mixed-treatment comparison model at 1 year for people with low-risk prostate cancer were 52% for brachytherapy and 74% for AS.

Quality of life

Health status (quality of life) was measured in two studies of people under AS, one using the SF-36[199] and the other measuring anxiety using the State Trait Anxiety Inventory General Anxiety Measure.[198] Neither measure was used in any of the studies in which people were treated with brachytherapy, preventing any comparison.

Need for further cancer treatment

Data related to the need for further cancer treatment in AS studies were described in *Chapter 4* (see *Use of cryotherapy versus active surveillance for people with low-risk prostate cancers*).

Summary and conclusions from the evidence of the comparative effectiveness of brachytherapy

This review considered data from 26,129 patients who received brachytherapy across 41 studies (two RCTs[49,121] and 39 NRCSs[36,100,101,103,105,108–110,113,117,119,121,123,126,128,130,131,135,136,144,145,149,151,153,156,160,163,170–172,176,182,184,186,189,203,205–207]), with most studies considered to be at high risk of bias. Results should be interpreted cautiously to reflect the very poor quality of the evidence base and the variation in definition of many of the outcomes, but the data for brachytherapy were generally more robust than for other ablative therapies. There were limited published data on the long-term efficacy of brachytherapy in achieving lower rates of morbidity and mortality compared with the standard options of RP and EBRT.

In the short term, we found some evidence that the rate of biochemical failure was lower for brachytherapy than for EBRT or RP at 5-year follow-up. There was also some evidence that disease-free survival was better for brachytherapy at 3-year follow-up. These findings should be regarded cautiously as the one RCT of brachytherapy versus RP[49] did not identify a numerical difference in either of these outcomes. Nevertheless, there appeared to be some evidence that cancer-specific outcomes after brachytherapy were at least no worse than after EBRT or RP.

TABLE 43 Erectile function at 1 year (AS)

Outcome	Brachytherapy, proportion (95% CrI)	AS, proportion (95% CrI)	Brachytherapy vs. AS	
			OR (95% CrI)	*p*(brachytherapy > AS)
Erectile function	0.52 (0.19 to 0.84)	0.74 (0.35 to 0.93)	0.47 (0.05 to 3.5)	0.22

There was evidence that the rate of urinary incontinence at up to 5 years was lower for people undergoing brachytherapy than for those receiving RP, but the size of the difference decreased with longer follow-up. There was also a trend towards lower erectile dysfunction rates for brachytherapy than for EBRT or RP, and this reached statistical significance at 3-year follow-up. There were insufficient data to draw any conclusions on bowel problems.

The findings related to procedural complications were mixed. Dysuria rates were higher for brachytherapy and this reached statistical significance when compared with RP. Urinary retention was also statistically significantly higher for brachytherapy when compared with EBRT. Stricture rates were higher for brachytherapy than for EBRT, but were lower when compared with RP. The differences reached statistical significance for stricture when compared with RP. For rectal pain, there was significant evidence that rates were lower for brachytherapy than for EBRT. Acute genitourinary toxicity rates were statistically higher for brachytherapy than for EBRT, but acute gastrointestinal toxicity was lower for brachytherapy, though the difference was not statistically significant.

It was not possible to compare the efficacy of brachytherapy with a programme of AS apart from the rate of erectile dysfunction at 12 months; the rate of erectile dysfunction was lower for AS, but this was not statistically significant.

In conclusion, the results of this review and meta-analysis were associated with a degree of uncertainty due to the poor quality of studies identified, but the data were generally from higher-quality studies than the data on other ablative therapies. Although there was a lack of use of long-term direct measures of effectiveness, there was some evidence that the short-term cancer-related effects were generally better for brachytherapy. This review found no evidence to suggest that brachytherapy is inferior to the standard therapies of EBRT or RP, apart from a possible increased risk of dysuria and urinary retention.

Chapter 7 Effects of other ablative therapies

Included studies

Ablative therapies other than cryotherapy, HIFU and brachytherapy were considered separately and grouped together under 'other ablative therapies'. The characteristics of the included studies were described in *Chapter 3*, and are detailed in *Appendix 8* and summarised here.

Only two studies were included, which enrolled a total of 118 patients. One study[155] was a prospective single-arm case series involving focal laser ablative therapy ($n = 12$). The intervention involved interstitial laser ablation [Indigo® OPTIMA laser system (Ethicon Endo-Surgery, Inc., Cincinnati, OH)], which was delivered to a focal area of the prostate using TRUS guidance assisted by fusion software which linked cancer areas within the prostate pre-identified by MRI. The ablation process was monitored in real time using contrast-enhanced ultrasound scan. The participants all had low-risk localised prostate cancer. The assessment of effectiveness included extended repeat biopsies at 3 and 6 months to assess the presence of residual cancer, and assessment of urinary [International Prostate Symptom Score (I-PSS)] and erectile function (IIEF-5 score) at 3 and 6 months.

The other study[103] was a prospective NRCS ($n = 106$) involving four arms: focal brachytherapy ($n = 12$), cryotherapy ($n = 50$), HIFU ($n = 21$) and vascular-targeted PDT ($n = 23$). The intervention involved using laser probes inserted transperineally under TRUS guidance followed by injection of a photoactive substance (padeliporfin) intravenously. The PDT procedure was set for a 20-minute illumination period whereby the photoactive substance was activated by laser light. The participants all had low-risk localised prostate cancer. The assessment of effectiveness included the measurement of perioperative adverse events using the Clavien–Dindo system, measurement of urinary (I-PSS) and erectile function (IIEF-5 score), and continence status, at 3, 6 and 12 months.

The characteristics of the included studies and study participants are summarised in *Appendix 8*.

Assessment of effectiveness

A detailed description of all outcomes, including those which were used in meta-analyses, is provided in *Appendix 10*.

Cancer-related efficacy outcomes

Treatment failure

For focal laser ablative therapy,[155] 33% of patients (4/12) had treatment failure (defined as persistent cancer on repeat prostate biopsies in treated areas 3–6 months post treatment). One of the four patients underwent salvage RP.

The study on PDT[103] did not measure cancer-related outcomes.

Functional outcomes

For focal laser ablative therapy,[155] there was no significant change in urinary or erectile function at 3 and 6 months postoperatively compared with the preoperative status.

For PDT,[103] at a median follow-up of 9 months, there was no difference in urinary function nor erectile function between PDT and the other comparators (HIFU, cryotherapy and focal brachytherapy). However,

for the intragroup comparison of patients who underwent PDT, erectile dysfunction appeared to be worse after treatment than prior to treatment (a difference in median scores of 10 on the IIEF-5 score); the authors did not specify whether or not this result was statistically significant. There was no difference in urinary function between the pre- and postoperative states in patients who underwent PDT. In terms of continence, all patients were reportedly continent postoperatively.

Adverse events

For focal laser ablative therapy,[155] there were no perioperative complications. Postoperative morbidity was minimal and self-limiting; this included perineal discomfort (25% of patients), mild haematuria (16.7% of patients) and haematospermia (16.7% of patients).

For PDT,[103] the results for treatment-related complications were not reported separately. However, all of the reported complications involved patients who underwent either HIFU or cryotherapy; hence it is assumed that no patients who underwent PDT had any complications.

Summary and conclusions from the evidence of the comparative effectiveness of laser ablative therapy and photodynamic therapy

This review considered data from two studies, enrolling 106 patients who were treated with PDT within a four-arm non-randomised prospective study ($n = 23$ for PDT arm), and 12 patients who were treated with focal laser ablative therapy within a single-arm prospective case series. Both studies were considered as having a high risk of bias. Data were restricted to short-term outcomes, with virtually no data beyond 1 year. As a result, the findings should be interpreted with caution to reflect the very poor quality of the evidence base. Within these limitations, the review found that focal laser ablative therapy appeared to be reasonably effective in terms of cancer-related outcomes, with a 6-month treatment failure rate of 33%, which is comparable with the other ablative therapies. In the short term, the technology appeared to be associated with a reasonable functional outcome, and a low rate of adverse events. For PDT, data were restricted to short-term functional and adverse event outcomes. There appeared to be no difference in urinary and erectile function between PDT and the other ablative therapies (including cryotherapy, HIFU and focal brachytherapy) following treatment, and the procedure was associated with a low risk of adverse events.

In conclusion, the results of this review were associated with significant uncertainty due to the quality and quantity of the evidence base. Data were restricted to short-term outcomes only and there was a lack of good-quality prospective comparative studies. The comparative effectiveness of the newer ablative therapies, such as laser ablation and PDT, compared with established therapies remains uncertain.

Chapter 8 Effectiveness of salvage ablative therapy following primary external beam radiotherapy

Included studies

The characteristics of the included studies were described in *Chapter 3*, and are detailed in *Appendix 8* and summarised here.

The review included nine studies[120,208–215] which enrolled a total of 400 participants. All nine studies were single-arm cohort studies. Six were studies of salvage RP,[209–211,213–215] two of salvage cryotherapy[208,212] and one of salvage HIFU.[120] In only three of the studies were data collected prospectively.[212,213,215]

Assessment of effectiveness

A detailed description of all outcomes, including those which were used in meta-analyses, is provided in *Appendix 11*.

Cancer-related efficacy outcomes

Only two studies on salvage ablative therapies reported on cancer-related outcomes,[208,212] and both studies involved salvage cryotherapy. In contrast, all six studies on salvage RP[209–211,213–215] reported on cancer-related outcomes. The data were limited by heterogeneity of outcome definition, different time points of outcome measurement and different means of reporting (e.g. biochemical control vs. failure).

Biochemical disease-free survival

For salvage cryotherapy, one study[208] reported a biochemical disease-free survival (defined as PSA ≤ 2 ng/ml) ranging from 71% at 1 year to 54% at 4 years. The corresponding figures for salvage RP,[215] with biochemical disease-free survival defined as PSA ≤ 0.1 ng/ml, were 89% at 1 year and 54% at 4 years.

Biochemical control and failure

For salvage cryotherapy, the 2-year biochemical control rate was 51.6–55%, using different definitions of biochemical control.[179,208] For salvage RP, the 2-year biochemical control rate was 76%,[213] and the 3-year biochemical control rate was 50%,[210,214] with different definitions of biochemical control. One study provided a 10-year estimate of biochemical failure for salvage RP of 69%.[215]

Overall survival

For salvage cryotherapy, only one study reported on overall survival,[179] with a 2-year overall survival of 93%. For salvage RP, one study reported a 7-year overall survival of 91% (10/11 patients).[209]

Functional outcomes

Only three studies on salvage ablative therapies reported on functional outcomes: two studies on salvage cryotherapy[179,208] and one on salvage HIFU.[120] Six studies of salvage RP reported on functional outcomes.[209–211,213–215] The data were limited by heterogeneity of outcome definition, different time points of outcome measurement and different means of reporting (e.g. urinary continence vs. incontinence).

Urinary incontinence

For salvage cryotherapy, at a median of 18.6 months follow-up (range 3–54 months), the incontinence rate was 20%, whereas for salvage HIFU, at 15 months' follow-up, the incontinence rate was 7%. For salvage RP, at a median follow up of 18–20 months, the incontinence rate ranged from 25%[211] to 72%.[213]

The variability in results probably reflected the heterogeneity in outcome definition, which significantly limits the comparability of the results.

Sexual dysfunction

Using different definitions of sexual dysfunction, the sexual dysfunction rate for salvage cryotherapy[212] was 68.8% at 1 year and 51.9% at 2 years. The figures for salvage RP (based on different definitions) were 81% at 1 year[215] and 74% at a median of 18 months.[213]

Quality of life

Only one study on salvage ablative therapy reported on quality of life outcomes; this was Robinson 2006[212] on salvage cryotherapy. One study on salvage RP reported on quality of life outcomes.[214] The data were limited by heterogeneity of the different quality of life measures used, different time points of outcome measurement and different means of reporting (e.g. total score vs. individual component score).

Adverse events

Only three studies on salvage ablative therapies reported on adverse events: two studies on salvage cryotherapy[208,212] and one on salvage HIFU.[120] Six studies of salvage RP reported on adverse events.[209–211,213–215] For salvage cryotherapy, at a median follow-up of 18.6 months, the incidence of adverse events was relatively low, ranging from 2% (bladder neck stenosis) to 3% (rectourethral fistula). The corresponding figure for salvage RP, within a similar period of follow-up, was 4.8–6% (rectovesical fistula) and 3–25% (bladder neck stenosis or anastomotic stricture). For salvage HIFU, at 15 months follow-up, the incidence of rectourethral fistula was 6% and that of bladder neck stenosis was 17%. The data were limited by the relatively low number of patients and low event rates.

Summary and conclusions from the evidence of the comparative effectiveness of salvage ablative therapy

This review considered data from 400 participants treated with salvage therapy following primary EBRT across nine studies,[120,208–215] all of which were single-arm case series. Six studies involved salvage RP,[209–211,213–215] two involved salvage cryotherapy[208,212] and one involved salvage HIFU.[120] All of the studies were considered as having a high risk of bias. Consequently, the findings should be interpreted cautiously to reflect the extremely poor quality of the evidence base and the heterogeneity of outcome definition, different time points of outcome measurement and different means of outcome reporting. Data on the long-term effectiveness of salvage therapy were limited, with the majority of studies reporting on short-term data only.

In the short term, there was no robust evidence that mortality or other cancer-specific outcomes (biochemical disease-free survival or failure) differed between salvage cryotherapy and salvage RP. There were no data on cancer-specific outcomes for salvage HIFU.

With regard to functional outcomes, including urinary and sexual dysfunction and quality of life outcomes, the limited data prevented any valid conclusions from being made.

For adverse event outcomes, there was a general trend for salvage cryotherapy to have fewer procedure-related complications, especially for bladder neck stenosis (up to 2% at a median of 18.6 months), in comparison with salvage HIFU (up to 17% at a median of 15 months) and salvage RP (up to 25% at a median of 20 months). However, the data limitations render these findings uncertain at best.

In conclusion, the results of this review on salvage therapies were associated with large uncertainty owing to the quality and quantity of the evidence base. There was a lack of long-term direct measures of effectiveness and a lack of prospective comparative studies. There was no evidence to suggest that salvage ablative therapy was either better or worse than salvage RP following primary EBRT for any outcomes.

Chapter 9 Economic evaluation methods

The objective of this chapter is to present the economic evaluation of ablative therapies for the primary treatment of localised low-/intermediate-risk prostate cancer compared with AS, RP and EBRT. It was originally intended that we would also seek to look at these interventions for locally recurrent disease; however, a lack of effectiveness data, as reported in *Chapter 8*, has prevented any meaningful modelling.

Description of the care pathways compared

The cost-effectiveness of the different treatments and their subsequent care pathways was assessed using a modified Markov chain simulation model. This modelling approach allowed us to model the sequence of events that individual people would follow from their initial treatment until death. It also allowed for differences in the characteristics of the individual people who might alter their journey through the model to be incorporated.

The care pathways modelled within the modified Markov chain simulation model were based on care pathways which were developed in consultation with the study team and the expert panel (*Figure 16*). The main study team for this element of the work included two urologists (TL, RP), a health economist (LV) and two biological modellers (MS, SR). Over a number of meetings, the group mapped out the sequence of events for people potentially eligible for the interventions under consideration. Additional information came from our previous models in this area, notably our model comparing robotic with laparoscopic RP,[218] reviewed guidelines and expert opinion. These care pathways were then presented to the expert panel and revised to reflect the comments received.

Figure 16 describes the care pathways that were modelled. As noted above, the purpose of this model was to compare and contrast different ablative therapies for localised prostate cancer, and to compare and contrast ablative therapies with comparative whole-gland therapies. Within *Figure 16* a number of different initial managements are specified. In the subsequent modelling (described throughout this chapter), each of these had different monetary costs both for initial care and ongoing management, and for treatment of subsequent events (e.g. recurrence) associated with it. In addition, the events that might be experienced may affect not just length of life but also quality of life. Therefore, quality of life (utility) weights were also included. Combining these data with information on the probabilities of events occurring over time enabled cost, patient outcomes and quality-adjusted life-years (QALYs) to be estimated for hypothetical cohorts of patients undergoing each therapy.

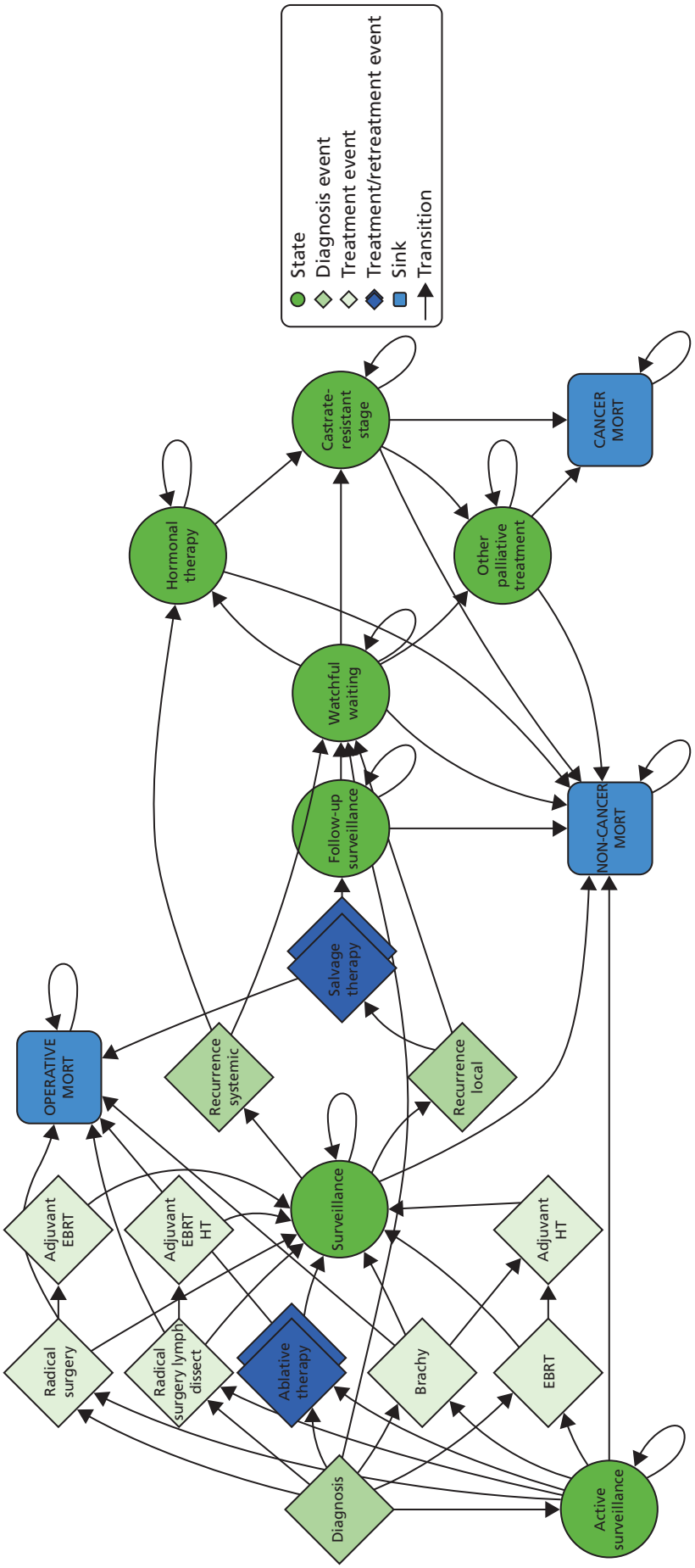

FIGURE 16 Complete care pathway. Note that depending on which primary therapy is experienced, not all subsequent aspects of care and events may be possible. HT, hormonal therapy; MORT, mortality.

Outline of the model

The model simulated the health status and treatment of a cohort of individuals. All individuals possessed two state variables: *age* and *severity of disease*. These variables were considered of relevance to the model given their potential effect on the clinical pathways experienced by patients. Severity was categorised as low, intermediate or high risk according to established definitions used in the UK NHS.[9]

Assumptions

Most of the assumptions inherent in the modelling process were derived from definitions and estimations of the driving parameters (see *Estimation of probabilities used within the model*). The importance of these assumptions in determining model output was estimated with elasticity analysis, as described in *Estimation of utilities used within the model*.

Process overview and scheduling

The structure of the simulation model is described in the care pathways constructed for all ablative and comparative therapies for prostate cancer (*Figure 16* in general and *Figures 17–20*). This care pathway forms the basis of a conceptual model of the processes to be simulated, and consists of three different elements: states, events and the transitions between them. A *state* is a stage in the model in which the patient spends at least one time step. *Events* are stages in the network that take up less than one time step. Each individual could therefore undergo one or more events plus a single state in each time step of the model. *Transitions* are the probability that an individual passes between different states and events. The care pathway does not claim to capture every possible patient trajectory (that is, a single route through the care pathway), as factors connected to the patient and their health-care team may result in treatment decisions that are unique to their individual circumstances. However, this care pathway was scrutinised by our expert advisory group and is considered to be definitive for 95% or more of all possible patient trajectories.

The conceptual model can be conceived as a network or graph. In mathematical terms, a network is expressed as a set of vertices and a set of edges which connect them. In this context, the vertices were states and events, and the edges were the transitions. This mathematical framework can be described in terms of an adjacency matrix for this network, and this adjacency matrix served as the transition matrix to determine the next event or state experienced in each modelled time step.

Beginning at the initial event of diagnosis, the state of each simulated patient at each time step was determined by the transition matrix. Within a modelled time step, a patient could also experience one or more events. Over time the patient could receive different types of therapy, experience different adverse events or spend time in one of three surveillance states: *AS* which occurs before primary therapy, *surveillance* which occurs after primary therapy and before biochemical failure, and *follow-up surveillance* which occurs following biochemical failure and salvage treatment. The simulation ended once all patients had entered one of the three 'sink' states: operative mortality, non-cancer mortality and cancer mortality.

The model employed a 6-month time step. All driving variables were probabilities that were usually calculated as yearly probabilities (P_{12m}); these were scaled to 6-month probabilities (P_{6m}) thus:

$$P_{6m} = 1 - \left((1 - P_{12m})^{\frac{6}{12}} \right). \quad (1)$$

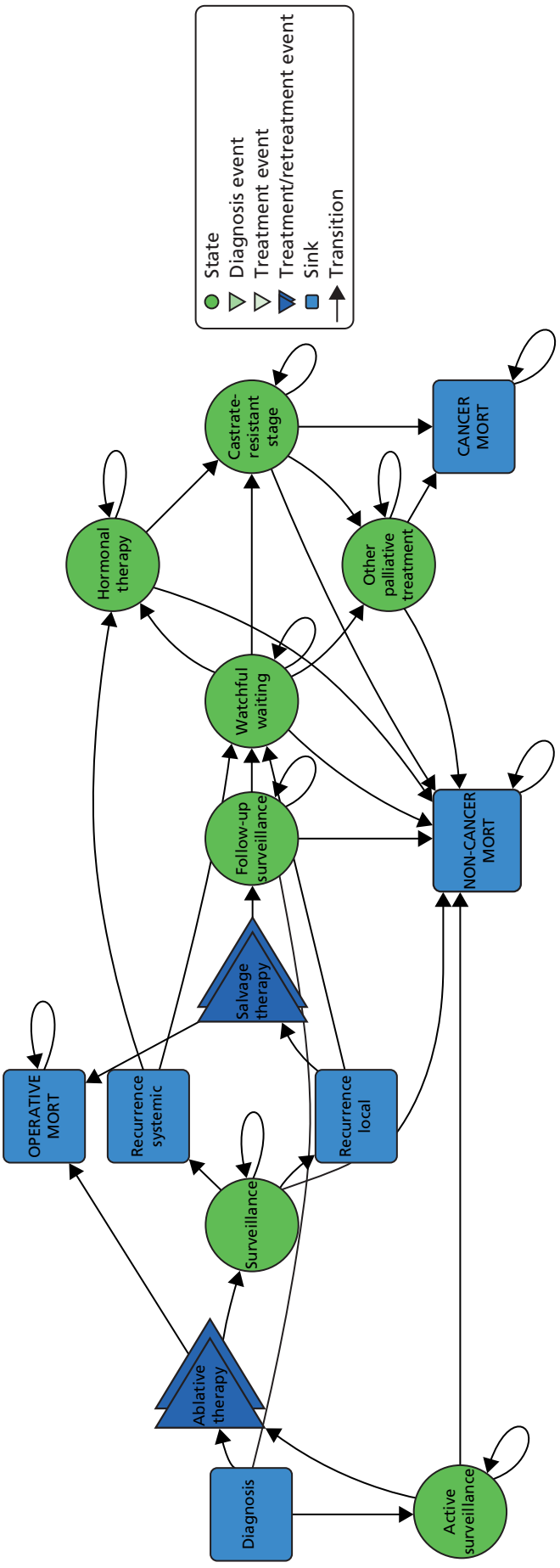

FIGURE 17 Model pathways for ablative therapies. MORT, mortality.

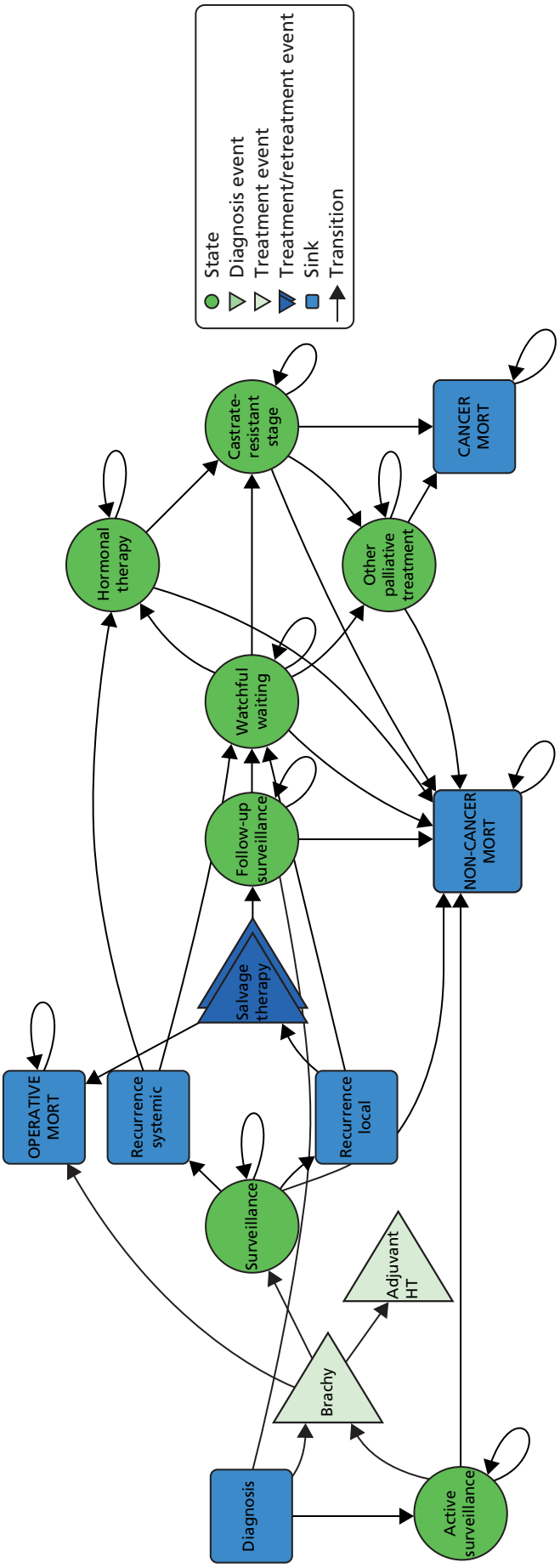

FIGURE 18 Care pathway for brachytherapy. HT, hormonal therapy; MORT, mortality.

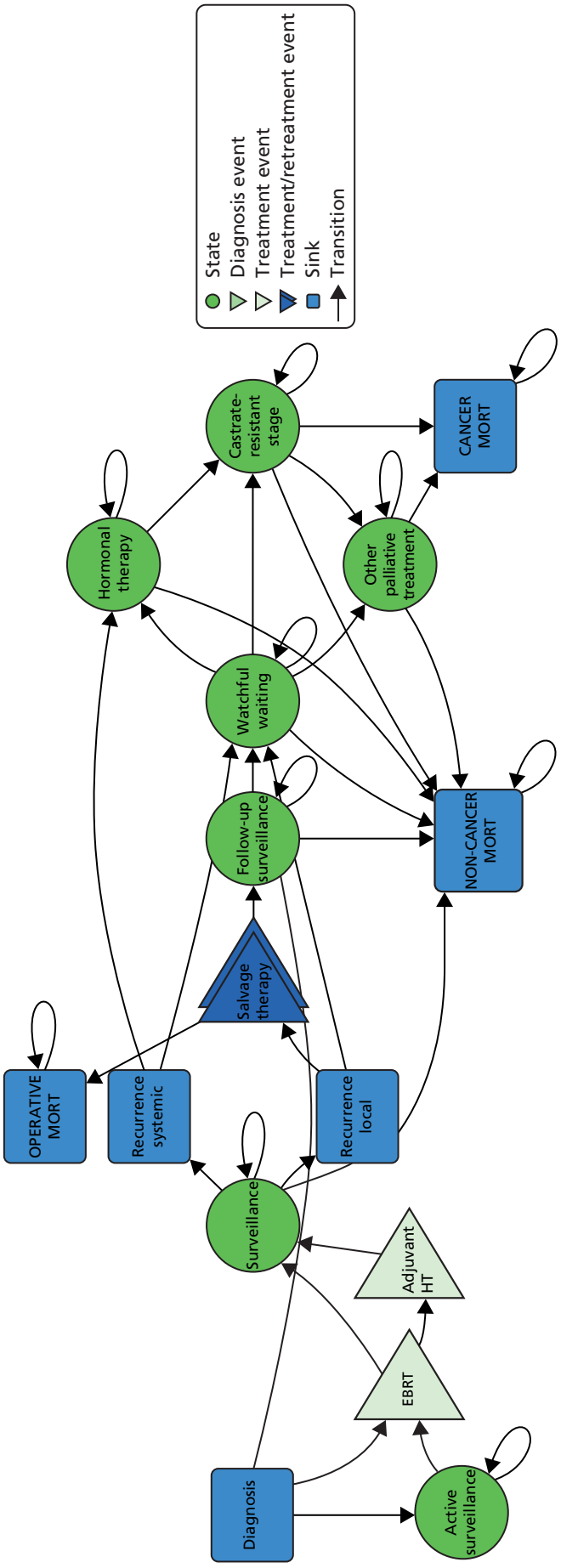

FIGURE 19 Care pathway for EBRT. HT, hormonal therapy; MORT, mortality.

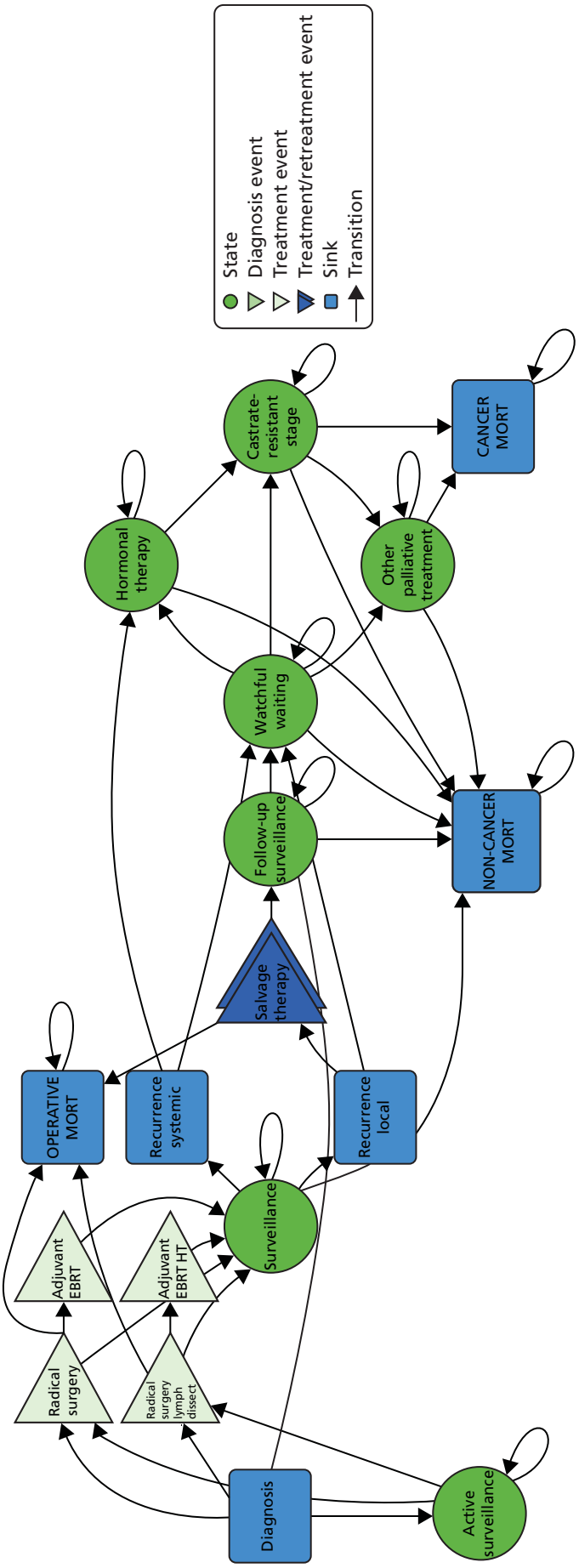

FIGURE 20 Care pathway for RP. HT, hormonal therapy; MORT, mortality.

Model design

Design concepts

The model was a modified Markov chain simulation model, where subsequent status was determined by current status multiplied by a matrix of transition probabilities. The basic design of a Markov chain model was altered to permit the state variables (age and severity) to have an impact on driving variables (transition probabilities).

Stochasticity

Stochasticity was incorporated into the model by simulating probabilities of changes in health status by sampling random deviates from a uniform distribution in the range of 0–1. Subsequent health status for each simulated patient trajectory was determined by the value of the random deviate compared with the cumulative probability of all destination states and events from the current health status. For states, remaining in the current state and entering the non-cancer-related mortality sink state were always possible destinations; neither of these options was available for events.

Observation

In each time step, the state of each simulated patient was recorded along with all events experienced during the time step. Each state and event was assigned a monetary cost. Utilities assigned to each state and event were converted into QALYs by calculating the product of all utilities experienced in each modelled year and then summing over the survival of the patient (i.e. the time before entering one of the three sink states).

Initialisation

The model was initialised with 1000 patients. Age of each patient was randomly sampled from a Poisson distribution with $\lambda = 70$ years. Severity for each patient was determined from data in the review of clinical effectiveness reported earlier [see *Chapter 3*, *Primary review (quantity and quality of included studies)*].

Inputs

There were two inputs to the model. The first input was an edge list of possible transitions in the model, with associated driving variables (transition probabilities). The second input was a vertex list of the monetary cost and the utility associated with each event or state. The data used for transitions, cost and utilities are described below (see *Estimation of probabilities used within the model*, *Estimation of costs used within the model* and *Estimation of utilities used within the model*).

Submodel: side effects

The three side effects of urinary incontinence (UI), erectile dysfunction (ED) and bowel dysfunction (BD) were each simulated independently with submodels. The side effects submodel was a Markov chain model dependent on the current state or event of the individual, or the current side effect status of the individual. Patients undergoing primary treatment had a probability of developing a dysfunction at an initial prevalence A, and therefore had a probability of maintaining function of 1 – prevalence A. In subsequent time steps, development of a dysfunction or recovery to functionality was determined by a second prevalence, B (*Table 44*). Patients in AS did not develop dysfunctions until after active treatment commenced (where their state is

TABLE 44 Transition matrix for the three side effects submodels

To/from	Primary treatment	AS	Dysfunction	Function	Deceased
Primary treatment	0	0	Prevalence A	1 – prevalence A	0
AS	0	1	0	0	0
Dysfunction	0	0	Prevalence B	1 – prevalence B	0
Function	0	0	Prevalence B	1 – prevalence B	0
Deceased	0	0	0	0	1

changed to primary treatment by the main model), and so were unable to develop or recover from dysfunctions prior to this. Patients in one of the three deceased states also remained in their current state (unable to develop or recover from dysfunctions).

The two prevalences, A and B, allowed for an initial post-treatment prevalence of a side effect that was different from the long-term prevalence of the side effect; typically, prevalence A was higher than prevalence B, but this was not always the case.

Characterisation of the risk profile of the simulated cohort

Severity was categorised as low, intermediate and high risk according to the distribution of patients at each stage, as found in the studies identified in the review of clinical effectiveness described in *Chapters 4–6*.

Estimation of probabilities used within the model

This section summarises the parameter values used in the model. All probabilities in the following tables are given as yearly probabilities for better concordance with the data tables in this report. Probabilities were converted into 6-monthly estimates prior to use. For most variables parameter ranges were not available, and point estimates were used throughout rather than a distribution of variables.

All probabilities originating at the same state or event must sum to unity. As some probabilities depend on the state variables of the patient, it is not always possible in these tables to provide exact parameter values, and 'balance' has been used to denote where the difference between unity and the sum of the other driving variables for that state or event was used.

Age distribution of cohort being modelled and the probability of death from causes other than prostate cancer

The age distribution of the cohort was randomly sampled from a Poisson distribution with a λ value of 70.

At any point in the model, there is a risk of death from all causes, including prostate cancer. The interventions under investigation might alter the prostate cancer-specific component of this mortality but would not be expected to affect other causes of mortality. Non-cancer mortality was calculated from age- and sex-specific UK life expectancy and mortality tables for the UK produced by the Office for National Statistics (ONS).[219,220] These data were resolved into a lognormal equation of male age-specific mortality rates using generalised linear modelling. This equation explained 97% of the variation in the published data.

Selection of primary treatment or active surveillance on diagnosis

Five separate model runs were conducted using the entire cohort of 1000 simulated patients, one model run for each of the main treatments (HIFU, cryotherapy, brachytherapy, EBRT and RP). Separate model runs meant that it was not necessary to use routine data sources to estimate the relative proportions of patients diagnosed with localised disease receiving each treatment as their primary therapy.

However, routine data sources were required to derive an estimate for parameter values regarding the proportion of patients receiving adjuvant treatments (e.g. EBRT or hormone therapy), and the proportion of people who received AS prior to any primary therapy.

Data from the National Cancer Intelligence Network provide information on treatments given to 18,839 diagnosed patients in 2009 (for a further 16,008 the initial treatment strategy was reported as unknown).[221] These data were not available separately for patients in different stages of disease at diagnosis.

However, the British Association of Urological Surgeons (BAUS) Cancer Registry has published information on the initial treatment strategies used for patients diagnosed in 2007, and these data are available separately for various PSA level thresholds (0–5, 6–10, 11–15, 16–20, 21–50, 50 +).[222] We used a threshold PSA of ≤ 20 as a proxy for localised disease and used both sources to estimate the required parameter values.

In 2009, approximately 5104 patients received AS as their primary treatment strategy following diagnosis.[221] This equates to 27.1% of the 18,839 patients for whom primary treatment was known.

The probability of staying in AS rather than moving to a primary therapy was determined from data in the review of clinical effectiveness described in *Chapters 4–6* (*Table 45*).

Probabilities related to primary treatment

Ablative therapy (including retreatment)

For ablative therapies, some data from the systematic review reported in *Chapters 4–6* were available on the proportion of recipients needing reintervention, although reintervention was often ill-defined and in some instances may be more likely to be describing salvage treatment using the same intervention as was used initially. We assumed that a constant rate of 10% of those receiving each ablative therapy would need reintervention as part of that same primary therapy for localised disease, based on the review of effectiveness data reported earlier (*Table 46*).

The probability of operative mortality (as opposed to perioperative mortality, which was parameterised separately) was considered to be 0.00054% of all operations performed.[223] This predominantly reflects the risk of anaesthesia alone. Additional risks of perioperative death for procedures were modelled separately as perioperative adverse events.

Radical prostatectomy

As shown in *Figures 16* and *20*, the model assumes that patients having RP can do so either with or without a lymph node dissection (lymphadenectomy) as part of this surgery, and that any RP patient (regardless of lymphadenectomy status) may or may not also receive adjuvant EBRT. However, the model also assumes that only those receiving radical surgery alongside a lymphadenectomy would receive adjuvant hormone therapy alongside any adjuvant EBRT received.

TABLE 45 Transition probabilities for AS

From	To	All therapies	Source
AS	Primary therapy	0.271	See *Chapter 4*
AS	AS	Balance[a]	
AS	Non-cancer mortality	Non-cancer mortality	ONS

a Non-cancer mortality is approximately 0.008255, so balance is about 0.72.

TABLE 46 Transition probabilities for ablative therapy

From	To	HIFU and cryotherapy	Source
Ablative therapy	Ablative therapy retreatment[a]	0.1	See *Chapter 5*[b]
Ablative therapy	Operative mortality	5.4E-06	Aitkenhead 2005[223]
Ablative therapy	Surveillance	0.899995	Balance

a It was assumed that all patients experiencing retreatment of ablative therapies would then pass on to surveillance with a probability of 1.
b Median for HIFU reintervention rate given in studies reporting this outcome reported in *Chapter 5*.

For RP patients, we assumed that the probability of pelvic lymphadenectomy during surgery was 0.582.[218] Using data from the BAUS 2007 survey for those with a PSA of ≤ 20, we estimated that for patients receiving RP with a lymphadenectomy, 38.1% would receive the adjuvant EBRT and hormone therapy, based on the probability of radical surgery being the sole treatment for 61.9% (for those with a PSA of 16–20, that is the highest-risk proportion of the 'localised' groups). Of those undergoing a prostatectomy without lymphadenectomy, we assumed that 33.3% would receive adjuvant EBRT, based on the probability of radical surgery being the sole treatment for 66.7% of those with a PSA of 11–15 (i.e. the next highest-risk proportion of the localised groups) (*Table 47*).[222]

Brachytherapy and external beam radiotherapy

Patients receiving either brachytherapy or EBRT as their primary treatment could also receive adjuvant hormone therapy. However, the model did not allow the combination of brachytherapy and EBRT as a primary treatment. The information from the BAUS survey allowed us to estimate that around 46% of brachytherapy patients receive adjuvant hormone therapy, based on the fact that brachytherapy was reported as being provided as the sole treatment in 53.7% of diagnosed patients with a PSA of ≤ 20.

However, using the same method to calculate the frequency with which EBRT was used as an adjuvant treatment, it was noted that 16% received solely EBRT, thus suggesting that EBRT is rarely provided as the sole primary treatment for localised disease, and we assumed that adjuvant hormone therapy was provided to 84% of EBRT patients (*Table 48*).[222]

All patients experiencing adjuvant therapies following primary therapy (adjuvant EBRT for radical surgery, and adjuvant hormonal therapy for radical surgery, brachytherapy and EBRT) pass on to surveillance with a probability of 1. This means that for these patient subgroups, both operative mortality and non-cancer mortality are not considered possible within this part of the model.

TABLE 47 Transition probabilities for RP

From	To	Radical surgery	Source
Radical surgery	Adjuvant EBRT	0.3333	
Radical surgery	Operative mortality	5.4E-06	
Radical surgery	Surveillance	0.666695	
Radical surgery: lymph node dissection	EBRT and adjuvant HT	0.381	
Radical surgery: lymph node dissection	Operative mortality	5.4E-06	
Radical surgery: lymph node dissection	Surveillance	0.618995	

HT, hormonal therapy.

TABLE 48 Transition probabilities for brachytherapy and EBRT

From	To	Brachytherapy	Source
Brachytherapy	Adjuvant HT	0.463	BAUS 2007[222]
Brachytherapy	Operative mortality	5.4E-06	Aitkenhead 2005[223]
Brachytherapy	Surveillance	0.536995	
From	**To**	**EBRT**	**Source**
EBRT	Adjuvant HT	0.84	
EBRT	Surveillance	0.16	BAUS 2007[222]

HT, hormonal therapy.

Perioperative adverse events

The systematic review of clinical effectiveness identified studies that had reported information on perioperative adverse events. Two clinicians (RP and TL) graded each of these adverse events based on expected severity and subsequent management. This rating system informed the Clavien–Dindo rating approach.[80] An average probability for the occurrence of a perioperative adverse event for each grade was calculated using the reported information from the review. The model accounted for differences between the treatments in terms of perioperative adverse events by costing additional days in hospital caused. Information on additional length of stay in hospital for different Clavien–Dindo ratings was taken from a study by Prentis and colleagues,[224] whereby ratings of < 3 and ≥ 3 resulted in 4 and 15 additional days' stay respectively (*Table 49*).

Biochemical recurrence after primary treatment

Recurrence

The probability of recurrence following primary treatment was calculated from patient severity and primary treatment. The probability of PSA success for 1 year for all five primary treatments was used as input, categorised further by low-, intermediate- and high-risk groups. These probabilities were converted into the probability of a recurrence after 6 months. In most cases, the decline in PSA success beyond 1 year could be explained by assuming a constant rate over time.

Informing the probability of recurrence were data from the systematic review reported in *Chapters 4–6*. At each 6-month time step the individual modelled would either continue surveillance without recurrence or (i) have a local recurrence identified that would lead to further treatment; (ii) have a systemic recurrence identified that would lead to further treatment; or (iii) die from causes other than prostate cancer.

Although the systematic review of clinical effectiveness reported in *Chapters 4–6* provided details of recurrence, it was not always clear for each intervention whether that recurrence was local or systemic. Therefore, we used the European Association of Urology (EAU) guidance for RP, which informed judgements about the likelihood of a recurrence being local or systemic (*Table 50*).[73] This likelihood was dependent on the time at which a recurrence occurred, with a shorter time frame indicating a higher likelihood of the recurrence being systemic.

TABLE 49 Probability of perioperative adverse events by Clavien–Dindo score of < 3 or ≥ 3

Primary treatment	Probability of an adverse event with Clavien–Dindo score of < 3	Probability of an adverse event with Clavien–Dindo score of ≥ 3	Source
Cryotherapy	0.018	0.04775	See *Chapters 4–6*
HIFU	0.05	0.05	See *Chapters 4–6*
Brachytherapy	0.32	0.08575	See *Chapters 4–6*
EBRT	0.057	0.033	See *Chapters 4–6*
RP	0.184	0.0325	See *Chapters 4–6*

TABLE 50 Annual probability that a recurrence, if identified, was localised disease

Recurrence at time point	Value	Source
Recurrence at ≤ 1 year indicating localised disease	0.07	EAU[73]
Recurrence at 1–2 years indicating localised disease	0.1	EAU[73]
Recurrence at > 2 years indicating localised disease	0.61	EAU[73]
Recurrence at > 3 years indicating localised disease	0.74	EAU[73]

For the base-case analysis, the probability of remaining free from recurrence was derived from the prevalences reported in the meta-analysis reported in *Chapters 4–6*. Under the assumption of a constant rate of biochemical failure per year, the raw data from the meta-analysis were converted into yearly rates by raising the probability of biochemical failure to the *n*th root, where *n* was the number of years that the patients had remained recurrence-free. The assumption that there was a constant rate of biochemical failure was tested using linear mixed-effects regression modelling. The response was the yearly estimate of biochemical failure, the predictor was the time point from which the yearly estimate was derived and the random effect was the treatment type. The intercept was significantly different from zero (estimate = 0.041, $p = 0.0008$) but the predictor of time of the estimate was not (estimate = –0.001, $p = 0.4699$). This indicated that the assumption of constant rates of biochemical failure over time was valid. This conversion of the meta-analysis data resulted in the yearly probabilities of remaining free from recurrence, reported in *Table 51*.

Alternatively, the data contributing to the values in *Table 51* regarding the probability of remaining free from recurrence were divided into low, intermediate and high risk for each treatment type; these were assigned to simulated patients with severity state variables of 1, 2 and 3 respectively (*Table 52*).

These data were combined with the information from the EAU on the link between the time to recurrence and the probability of that recurrence being local or systemic, to estimate the proportion of the cohort entering the local and systemic recurrence states respectively (*Table 53*).

TABLE 51 Yearly probabilities of remaining free from recurrence for each therapy

Primary therapy	Minimum estimate	Median estimate	Maximum estimate
Ablative: HIFU	0.994	0.973	0.943
Ablative: cryotherapy	0.923	0.978	0.949
Brachytherapy	0.999[a]	0.994	0.986
EBRT	0.997	0.992	0.973
Radical surgery	0.996	0.989	0.957

a The minimum estimate was actually unity for this probability, but a more conservative value was used to permit biochemical failure as an extremely rare event.

TABLE 52 Yearly probabilities of remaining free from recurrence for each therapy by risk level

Primary therapy	Low risk	Intermediate risk	High risk
Ablative: HIFU	0.989	0.934	0.926
Ablative: cryotherapy	0.740	0.700	0.600
Brachytherapy	0.984	0.970	0.731
EBRT	0.992	0.990	0.908
Radical surgery	0.980	0.920	0.965

TABLE 53 Transition probabilities for surveillance

From	To	All therapies	Source
Surveillance	Non-cancer mortality	Non-cancer mortality	ONS[219]
Surveillance	Recurrence: local	Year 1: 0.07 × recurrence	See *Tables 47* and *52*
		Year 2: 0.10 × recurrence	
		Year 3: 0.61 × recurrence	
		Year 4 +: 0.74 × recurrence	
Surveillance	Recurrence: systemic	Year 1: 0.93 × recurrence	See *Tables 47* and *52*
		Year 2: 0.90 × recurrence	
		Year 3: 0.39 × recurrence	
		Year 4 +: 0.26 × recurrence	
Surveillance	Surveillance	Balance	

Treatment options following biochemical recurrence

Table 54 shows the yearly transition probabilities for those who move from recurrence to subsequent events. These data were then converted to 6-monthly rates.

Salvage treatment for localised recurrence

Salvage therapies (including retreatment)

The choice of salvage treatment for localised recurrence may depend on the choice of initial/primary treatment. For example, patients whose initial treatment was radical surgery could not receive radical surgery again as a salvage treatment as the prostate would already have been removed during the initial operation. Therefore, the probability of receiving a specific salvage treatment is conditional on the primary treatment received. Lacking detailed studies of salvage therapy, for HIFU, cryotherapy and brachytherapy the retreatment rate of salvage therapy was assumed to be the same as for primary therapy with HIFU (0.1). For radical surgery and EBRT, the retreatment rate of salvage therapy was assumed to be the average retreatment rate of primary therapy with HIFU and cryotherapy. The probability of avoiding retreatment with salvage therapy was the difference between unity and the retreatment rate plus operative mortality. *Table 55* reports the transition probabilities for movements from salvage therapy.

For salvage therapy patients who reach the follow-up surveillance state, *Table 56* outlines the probabilities of the possible options for future movement from this state.

TABLE 54 Transition probabilities for movement from recurrence events

From	To	All therapies	Source
Recurrence: local	Salvage therapy	0.958	
Recurrence: local	Watchful waiting	0.042	BAUS 2007[222]
Recurrence: systemic	HT	0.9703	
Recurrence: systemic	Watchful waiting	0.0297	BAUS 2007[222]

HT, hormonal therapy.

TABLE 55 Transition probabilities for movements from salvage therapy

From	To	HIFU, cryotherapy, brachytherapy	Radical surgery and EBRT	Source
Salvage therapy	Follow-up surveillance	0.899995	0.907995	
Salvage therapy	Operative mortality	5.4E-06	5.4E-06	Aitkenhead 2005[223]
Salvage therapy	Salvage therapy retreatment[a]	0.1	0.092	Systematic review data[b]

a All patients experiencing retreatment with salvage therapies pass on to follow-up surveillance with a probability of 1.
b This is based on retreatment rate following primary treatment with HIFU.

TABLE 56 Transition probabilities for follow-up surveillance following salvage treatment

From	To	Radical surgery	All other therapies	Source
Follow-up surveillance	Follow-up surveillance	Balance	Balance	
Follow-up surveillance	Non-cancer mortality	Non-cancer mortality	Non-cancer mortality	
Follow-up surveillance	Watchful waiting	0.11[a]	0.0297	See *Chapters 4–8* BAUS 2007[222]

a This is 1 minus the probability of progression-free survival, from salvage data for RP.

Watchful waiting

From watchful waiting, treatment options for patients become limited to those generally used to treat metastatic disease. *Table 57* reports the transition probabilities from the watchful waiting state to such treatments.

Treatment for systemic recurrence after primary or salvage treatment

It was assumed that on progression following salvage treatment, or on systemic recurrence following primary treatment, patients would be treated for advanced disease, with 'watchful waiting' being conducted initially and alternative treatment options (which in clinical practice will depend on individual patient circumstances) being hormonal therapy and castrate-resistant stage therapies (including chemotherapy) as well as palliative treatment. Palliative treatment might also involve drug treatment, but to treat sequelae of the prostate cancer (e.g. bone metastases) rather than the prostate cancer itself.

TABLE 57 Transition probabilities from the watchful waiting state

From	To	All therapies	Source
Watchful waiting	Castrate-resistant stage	0.335[a]	Tangen 2003[225]
Watchful waiting	HT	Balance	
Watchful waiting	Non-cancer mortality	Non-cancer mortality	
Watchful waiting	Other palliative treatment	0.1	Assumption
Watchful waiting	Watchful waiting	0.0297	BAUS 2007[222]

HT, hormonal therapy.
a Assuming that if 0.77 survived < 5 years, then the failure rate per year can be taken to be 0.77 × (1/5). Similarly, 5–10 years is 0.16 × (1/10), and survival for > 10 years is 0.07 × (1/15). Add all these up to get overall/average failure rate of 0.335.

Table 58 shows the yearly transition probabilities for those who move from hormonal therapy, castrate-resistant disease and other palliative treatments to subsequent care and events.

We used guidelines on the treatment of the disease at this stage to estimate the typical processes of care at this stage in the care pathway. We assumed that patients at this point would initially receive hormonal therapy, with the rate of progression to hormone refractory disease taken from available guideline evidence on treatment for metastatic disease.[73] The initial probability of response was estimated at 80%, with 60% still showing progression-free response at 3 years.[73]

Overall survival has been separately estimated at a median of 5 years,[226] with 7% surviving beyond 10 years.[225] Similarly, further review evidence on survival following chemotherapy treatment for advanced cancer was used to inform the model for castrate-resistant disease. On progression with hormone therapy, the probability of staying in the castrate-resistant stage for ≥ 1 time step was considered equivalent to the yearly probability of response to chemotherapy (0.52).[226] Palliative treatment was considered to confer a 6-month survival on average (though cancer mortality could also occur prior to having any palliative treatment).[227]

Probability of longer-term adverse events (used in submodels of adverse events)

Values for the two prevalences (A and B) were calculated from data in the systematic review. For each of the three adverse events it was assumed that within the first 6 months the rate would differ from any longer-term trend. Prevalence A was calculated as the median for all sources reporting the prevalence of the adverse event at a follow-up time of ≤ 6 months. It was assumed that after 6 months, the prevalence would settle to a constant rate. All data on each adverse event that were reported for a follow-up time of beyond 6 months were converted to a yearly rate and then the average was taken to calculate prevalence B. The results are summarised in *Table 59*.

TABLE 58 Yearly transition probabilities: metastatic disease

From	To	All therapies	Source
HT	Castrate-resistant stage	0.335	See *Table 57*
HT	HT	Balance	
HT	Non-cancer mortality	Non-cancer mortality	
From	**To**	**All therapies**	**Source**
Castrate-resistant stage	Cancer mortality	0.2499	See note[a]
Castrate-resistant stage	Castrate-resistant stage	0.52 × balance	Shelley 2008[226]
Castrate-resistant stage	Non-cancer mortality	Non-cancer mortality	
Castrate-resistant stage	Other palliative treatment	0.48 × balance	Shelley 2008[226]
From	**To**	**All therapies**	**Source**
Other palliative treatment	Cancer mortality	0.2499	See note[a]
Other palliative treatment	Non-cancer mortality	Non-cancer mortality	
Other palliative treatment	Other palliative treatment	Balance	

HT, hormonal therapy.
a Estimating from a median overall survival (1.37 years), we turned this into a rate of death per year (1/1.37), then subtracted the probability of going on to palliative care (0.73 – 0.48) to get the final probability of 0.2499.

TABLE 59 Prevalences for each side effect, by primary treatment

Side effect	Primary treatment	Prevalence A	Prevalence B
Urinary incontinence	Ablative: HIFU	0.116	0.033
	Ablative: cryotherapy	0.099	0.041
	Brachytherapy	0.332	0.363
	EBRT	0.092	0.111
	Radical surgery	0.248	0.278
Erectile dysfunction	Ablative: HIFU	0.430	0.383
	Ablative: cryotherapy	0.807	0.561
	Brachytherapy	0.268	0.262
	EBRT	0.486	0.406
	Radical surgery	0.645	0.706
Bowel disorder	Ablative: HIFU	0.010	0.010
	Ablative: cryotherapy	0.106	0.061
	Brachytherapy	0.055	0.116
	EBRT	0.152	0.181
	Radical surgery	0.040	0.128

Estimation of costs used within the model

All costs were estimated based on resource-use inputs and unit costs for the 2011–12 financial year, and are reported in UK pounds sterling. All resource inputs, unit costs and their sources for each treatment, associated care pathways and management of events are shown in *Appendix 13*. With the exception of costs of radical surgery and palliative treatments, which were taken from the literature, costs included in the model were estimated using a micro-costing exercise. The data used in this exercise were then subsequently approved by the external advisory group. Specific costs to the NHS, relevant to the treatments, care pathways and events, included diagnostic tests and imaging, staff time, equipment (including consumables), theatre time and capital (for reusable equipment) costs. With the exception of consumables and theatre time, which were sourced from relevant NHS providers, and capital costs, which were sourced from specific commercial providers, most unit costs were sourced from NHS reference costs,[228] unit costs of health and social care[229] and the NHS *Agenda for Change*.[230] Where costs were not reported in 2011–12 values, they were inflated by the Hospital and Community Health Sector inflation index.[229]

All capital costs for each of the treatment pathways were costed using current market prices obtained from various commercial providers to the NHS. A lower and upper estimate of these prices was provided by each relevant supplier (as the cost to each NHS provider is dependent on individual contractual arrangements) to provide a distribution around the market price. These initial outlay costs were annuitised over the useful working lifespan of the piece of equipment (assumed to be 10 years for all equipment), applying an annual discount factor of 3.5%[231] to account for the opportunity cost of the investment over time. The equivalent annual cost of each piece of equipment was divided by its estimated number of uses per annum (from NHS providing units and expert opinion) to give cost-per-use estimates. If capital equipment was used for procedures other than the treatment in question, the timings of each procedure were checked for equality in order that a cost-per-use estimate would be valid.

Treatment costs associated with primary treatments

Table 60 shows the cost estimates used in the model for AS, *Table 61* the cost estimates for primary treatment costs and *Table 62* the cost estimates for the follow-up surveillance state.

Active surveillance

As noted above, the costs of AS were estimated using a micro-costing (bottom-up) approach, with treatment pathways and associated resource inputs being identified by clinical experts within the research team. The costs of AS were estimated for each of the first 5 years, then annually thereafter, based on the assumption that there were no changes in the condition of a patient such that they had to leave active monitoring and be given a different primary radical treatment. In year 1, patients would attend four nurse-led urology outpatient appointments with PSA tests conducted at each appointment. The unit costs of non-consultant-led follow-up outpatient appointments were obtained from the NHS reference costs[228] and the unit costs for the PSA test were obtained from Ramsay and colleagues (2012).[218]

TABLE 60 Annual AS costs

Year	Resource inputs	Value (£)	Lower limit (£)[a]	Upper limit (£)[a]
1	4 nurse-led outpatient appointments	442.24	283.68	574.80
	4 PSA tests			
	1 DRE			
	1 MDT meeting			
2	1 TRUS-guided biopsy	368.12	233.84	499.40
	2 nurse-led outpatient appointments			
	2 PSA tests			
	1 DRE			
3	2 nurse-led outpatient appointments	169.12	117.84	228.40
	2 PSA tests			
	1 DRE			
4	1 TRUS-guided biopsy	368.12	233.84	499.40
	2 nurse-led outpatient appointments			
	2 PSA tests			
	1 DRE			
5	2 nurse-led outpatient appointments	169.12	117.84	228.40
	2 PSA tests			
	1 DRE			
Annually thereafter	1 practice nurse appointment	19.81	14.86	24.76
	1 PSA test			
	1 DRE			

MDT, multidisciplinary team.
a Upper and lower limits of triangular distribution calculated at ±25% of the point estimate.

TABLE 61 Primary treatment costs

Costs	Value (£)	Source	Distribution (values used to define the distribution) (£)[a]
Radical surgery (with and without lymphadenectomy)	3848.76	Ramsay[218]	
Cryotherapy	6407.72	Micro costed	4802.61–7986.62
HIFU	4277.98	Micro costed	3208.48–5347.48
Brachytherapy alone	6756.61	Micro costed	5024.95–9121.70
EBRT	2508.58	Micro costed	1881.44–3135.73
Adjuvant and salvage EBRT	2356.46	Micro costed	1767.34–2945.58
Adjuvant hormone therapy	555.00	Micro costed	416.25–693.75

a Upper and lower limits of triangular distribution calculated at ±25% of the point estimate.

TABLE 62 Annual surveillance costs

Year	Resource inputs	Value (£)	Lower limit (£)[a]	Upper limit (£)[a]
1	4 nurse-led outpatient appointments	340.40	255.30	425.50
	4 PSA tests			
	1 DRE			
2–5	2 nurse-led outpatient appointments	170.20	127.65	212.75
	2 PSA tests			
	1 DRE			
Annually thereafter	1 practice nurse appointment	19.81	14.86	24.76
	1 PSA test			

a Upper and lower limits of triangular distribution calculated at ±25% of the point estimate.

Following this, at 12 months, a multidisciplinary team (MDT) cancer meeting would take place to review each patient, the unit cost of which was obtained from the NHS reference costs (cost code CMDT_Oth).[228] Patients in year 2 of AS would attend two nurse-led urology outpatient appointments, again with PSA tests performed at each appointment. In addition, patients would undergo a standard TRUS-guided biopsy, the unit cost of which was taken from the NHS reference costs[228] using the appropriate Healthcare Resource Group (LB27Z). Year 4 of AS was assumed to be identical to this, and years 3 and 5 were assumed to be the same with the exception of the TRUS-guided needle biopsy. Patients would also have an annual DRE for years 1–5. However, we assumed that the costs of this would be minimal and that it could effectively be included within the cost of the nurse-led outpatient appointment. After the first 5 years, it was assumed that patients would receive an annual PSA test conducted by a practice nurse in a general practice setting. The unit cost of a practice nurse appointment was taken from the unit costs of health and social care.[229]

Radical surgery (with and without lymphadenectomy)

The costs of radical surgery were taken from the recent HTA comparing laparoscopic and robotic RP.[218] Given the likelihood of higher future use of robotic compared with laparoscopic surgery (based on clinical opinion within the research team), it was assumed that all radical surgery within the model would be performed using robotic surgery. The cost per procedure was based on the assumption that 200 procedures per annum

would be carried out at any providing unit and the cost per procedure was the same regardless of whether or not a lymphadenectomy had taken place.

External beam radiotherapy

The costs of EBRT by a NHS unit carrying out the IMRT procedure were calculated on the basis of 37 sessions within a 7-week time frame. A list of staff time by grade and specialty involved in the procedure was provided by the Newcastle upon Tyne Hospitals NHS Foundation Trust (Edgar Paez, consultant urologist and Gill Lawrence, Head of Radiotherapy Physics, Northern Centre for Cancer Care, 2013, personal communication). UK capital costs for a Varian radiotherapy solution incorporating a TrueBeam™ linear accelerator (Varian Medical Systems, Palo Alto, CA), a treatment planning system, an oncology management system and associated maintenance costs were obtained from Varian Medical Systems (www.varian.com). The expected number of uses per annum for linear accelerator equipment was based on 37 fractions per day based on a 253-day working year, and for the treatment planning and oncology management systems this was based on 4500 patients per year. These estimates were provided by the Newcastle upon Tyne Hospitals NHS Foundation Trust (Debbie Bennett, Radiotherapy Service Manager at the Northern Centre for Cancer Research, 2013, personal communication).

Adjuvant external beam radiotherapy

The costs of adjuvant and salvage EBRT were considered by expert opinion to be the same in terms of the treatment pathway and associated resource inputs. Furthermore, the expert advisory group advised that the only difference between this and primary EBRT was the reduced number of fractions that each patient received, from 37 to 33. Thus, the costs for adjuvant and salvage EBRT were based on the same micro-costing approach conducted for EBRT, albeit with a reduction in capital cost per patient for the accelerator to allow for the reduction in fractions and a reduction in radiographer's time in the delivery of the fractions.

Brachytherapy

The costs of brachytherapy were estimated from a treatment pathway and associated resource inputs being identified by a NHS unit carrying out the procedure (Newcastle upon Tyne Hospitals NHS Foundation Trust). This was subsequently checked with the external advisory group. The costs associated with brachytherapy were calculated on the basis of a two-stage procedure with a 1-night length of stay, and a list of all resource inputs relevant to the procedure was provided by Newcastle upon Tyne Hospitals NHS Foundation Trust (Ian Pedley, clinical director/clinical oncologist at the Northern Centre for Cancer Care, and Gill Lawrence, 2013, personal communication). A list of reusable equipment and consumables used during the procedure, along with their unit costs [including Isostrand® seeds (Eckert & Ziegler BEBIG GmbH, Berlin, Germany) and implantation needles] came from Newcastle upon Tyne Hospitals NHS Foundation Trust (Steve Locks, Consultant Clinical Scientist in Radiotherapy Physics, 2013, personal communication). Clinical audit showed that between 60 and 110 seeds were used per patient at this centre, with an average of 80 seeds per patient, and between 17 and 46 implantation needles were used per procedure, with an average of 28 needles used per patient. UK capital costs for the VariSeed™ treatment planning system (Varian Medical Systems, Palo Alto, CA; equipment version 8.0.2.), ancillary equipment and maintenance costs were obtained from Eckert & Ziegler BEBIG (www.bebig.eu). The expected number of uses per annum for this treatment planning system was based on 100 patients per annum, with a range of 25–250 patients. These figures are based on numbers of patients treated in each UK centre obtained from the UK Prostate Brachytherapy Advisory Group's website.[232,233]

Cryotherapy

The costs of cryotherapy were estimated from the treatment pathway and associated resource inputs being identified by a NHS unit carrying out the procedure (City Hospitals Sunderland Foundation Trust). This was subsequently checked by the external advisory group. A list of all resource inputs relevant to the procedure was provided by City Hospitals Sunderland Foundation Trust (Sue Asterling, urology research nurse; Damien Greene, consultant urologist; and Mark Kelly, Acting Divisional General Manager – Theatres, 2013, personal communication). UK capital costs for the Visual-Ice® cryoablation system (Galil Medical, Arden Hills, MN), ancillary equipment and maintenance costs were obtained from Galil Medical (www.galil-medical.com).

The expected number of uses per annum for this treatment system was based on an estimate of 200 patients per annum. Cryotherapy was assumed to require a 2-night length of stay.

High-intensity focused ultrasound

The costs of HIFU were estimated from a NHS unit carrying out the procedure (University College London Hospitals NHS Foundation Trust). The costs associated with HIFU were calculated on the basis of a focal procedure with patients returning home on the day of surgery. A list of all resource inputs relevant to the procedure was provided by University College London Hospitals NHS Foundation Trust (Mark Emberton, Professor in Interventional Oncology, and Lois Roberts, General Manager, Division of Surgical Specialties, 2013, personal communication). UK capital costs for the Sonablate® 500 HIFU surgical ablation system (SonaCare Medical, Charlotte, NC) (including maintenance and ancillary costs) were provided by Nuada Medical Prostate Care. The expected number of uses per annum for this treatment system was based on 200 patients per annum. Although most patients return home the same day the treatment is given, it was acknowledged that some patients do have an overnight stay in secondary care. We therefore assumed that 20% of patients would have a 1-night length of stay (Mark Emberton, personal communication).

Adjuvant hormone therapy

A proportion of patients who receive either brachytherapy or EBRT as a primary radical treatment subsequently have adjuvant hormone therapy. It was assumed (based on advice from our expert advisory group) that these patients would be treated with 3 weeks of cypoterone acetate (Androcur®, Bayer) (100 mg) at a cost of £58.50,[234] and two courses, each of 3 months, of the LHRH agonist goserelin (Zoladex® LA, AstraZeneca) (10.8-mg 3-month injection), at a total cost of £470. It was assumed that goserelin would be administered by a practice nurse in a primary care setting at a cost of £13.25 per visit.[229]

Surveillance

The costs of surveillance following primary treatment were estimated using treatment pathways and associated resource inputs identified by clinical experts within the research team. Costs were estimated for each of the first 5 years then annually thereafter, based on the assumption that there were no changes in a patient's condition nor evidence of biochemical recurrence such that the patient had to leave the surveillance state. In the first year of surveillance, patients would attend four nurse-led urology outpatient appointments, with PSA tests conducted in each of these. The unit costs of non-consultant-led follow-up outpatient appointments were obtained from the NHS reference costs[228] and the unit costs for the PSA test were obtained from Ramsay and colleagues.[218] For the second through to the fifth year it was assumed that patients would attend two nurse-led urology outpatient appointments with PSA testing at each outpatient appointment. After the first 5 years, it was assumed that patients would receive an annual PSA test conducted by a practice nurse in a primary care setting. The unit cost of a practice nurse appointment was taken from the unit costs of health and social care.[229] Patients would also have an annual DRE (with the exception of those who have undergone RP) each year for the first 5 years, but the cost of this was subsumed in the cost of the nurse-led outpatient appointment.

Treatment costs associated with biochemical recurrence after primary treatment

Based on elevated PSA levels observed while under surveillance state, biochemical recurrence can entail two different types of diagnosis event: local recurrence and metastatic recurrence. *Table 63* shows the costs of diagnosing local and metastatic recurrence.

TABLE 63 Costs of diagnosis of local and metastatic recurrences

Diagnosis event	Value (£)	Lower limit (£)[a]	Upper limit (£)[a]
Local recurrence	569	392	641
Metastatic recurrence	755	523	873

a Upper and lower limits of triangular distribution calculated at ± 25% of the point estimate.

Local recurrence

Resource inputs regarding diagnosis of local recurrence were based on expert opinion. It was assumed that patients would have two consultant-led outpatient appointments: one before diagnostic testing and one after to discuss further treatment options. Each patient would undergo a MRI scan, which would be followed by a MDT cancer meeting and a nurse-led urology outpatient appointment.

Metastatic recurrence

It was assumed on the basis of expert opinion that the only difference between diagnosing local and metastatic recurrence would be that patients with suspected metastasis would also have to undergo a bone scan.

Costs associated with local progression following treatment for localised disease

A proportion of the cohort might experience biochemical recurrence following primary radical treatment for localised prostate cancer. Depending on the primary treatment received, these patients were modelled to receive any one of the following salvage therapies: ablative therapy, radical surgery, brachytherapy or EBRT. The cost and utility for salvage therapies was calculated from the combination of the possible salvage therapies following the primary therapy modelled. Primary radical surgery could be followed by salvage EBRT or salvage ablative therapy. Primary brachytherapy or EBRT could be followed by salvage surgery or salvage ablative therapy. Primary ablative therapy could be followed by salvage ablative therapy, salvage EBRT, salvage brachytherapy or salvage radical surgery. When combining multiple salvage therapies into an average treatment, the lower limit was taken to be the minimum of the calculated lower limits, the upper limit to be the maximum of the calculated upper limit and the point estimate to be the mean of the point estimates. With the exception of salvage EBRT, the costs associated with these salvage treatments were assumed to be the same as for the primary treatments. The costs of salvage EBRT per patient, as specified in *Table 61*, were considered to be lower than those of the primary treatment owing to a lower number of fractions received (33 sessions over a 6-week time frame). Following salvage therapy, patients were modelled to enter into a follow-up surveillance state. The costs for this were assumed to be the same for the first 5 years of the surveillance state in *Table 62*. Provided the patient's disease did not progress, after 5 years patients were modelled to enter into a watchful waiting state, the costs of which were assumed to be the same as the annual costs after 5 years specified in the surveillance state described above (see *Table 62*).

Costs associated with metastatic progression

Patients with metastatic recurrence were modelled initially to receive either hormone therapy or watchful waiting. Following this, patients could either remain in this state or enter into other states (which in clinical practice will depend on individual patient circumstances), these being hormonal therapy, castrate-resistant stage therapies (including chemotherapy) or palliative treatment.

Watchful waiting

The costs of watchful waiting were assumed to be the same as the annual costs after 5 years specified in the surveillance state described above, that is patients would receive an annual PSA test conducted by a practice nurse in a primary care setting at a cost of £19.81.

Hormonal therapy

It was assumed (based on advice from our clinical experts in the research team) that these patients would be treated with 3 weeks of cypoterone acetate (100 mg) at a cost of £58.50[234] and a 3-month course of the LHRH agonist goserelin (10.8-mg 3-month injection) at a cost of £235 until the patient either died or entered into the castrate-resistant stage. It was assumed that goserelin would be administered by a practice nurse in a primary care setting at a cost of £13.25 per visit.

Castrate-resistant stage

We assumed that 50% of patients would undergo a first-line docetaxel-based (Taxotere®, Sanofi-Aventis) chemotherapy regimen (£10,450) and that 70% of these patients would go on to receive a second-line abiraterone-based (Zytiga®, Janssen) regimen (£24,670) prior to death, as per the assumptions in the costing template for the NICE abiraterone technical appraisal.[235]

Other palliative treatment

These costs were taken from Collins and colleagues[236] and were estimated to be £4454 per annum.

Summary of costs used in the model

Costs used in the model are all summarised in *Table 64*.

Costs and utilities used in the submodel of adverse events

Time in each state of dysfunction for all three side effects incurred a cost which was added to the yearly costs to obtain lifetime totals for each patient. Costs used are listed in *Table 65*.

TABLE 64 Summary of costs used in the model

State or event	Cost (£)	Source
Primary therapy events		
Ablative therapy: HIFU	4277.98	See *Treatment costs associated with primary treatments*; *Table 61*
Ablative therapy: cryotherapy	6407.72	See *Treatment costs associated with primary treatments*; *Table 61*
Brachytherapy	6756.61	See *Treatment costs associated with primary treatments*; *Table 61*
EBRT	2508.58	See *Treatment costs associated with primary treatments*; *Table 61*
Radical surgery	3848.76	See *Treatment costs associated with primary treatments*; *Table 61*
States		
AS	Year 1: 442.24 Years 2, 4: 368.12 Years 3, 5: 169.12 Years 6+: 19.81	See *Treatment costs associated with primary treatments*; *Table 61*
Surveillance	Year 1: 340.40 Years 2–5: 170.20 Years 6+: 19.81	See *Treatment costs associated with primary treatments*; *Table 61*
Follow-up surveillance	(Same as surveillance)	See *Treatment costs associated with primary treatments*
Watchful waiting	(Same as surveillance)	See *Treatment costs associated with primary treatments*
Castrate-resistant stage	50% of patients: 10,450.00+ 70% of these: 24,670.00	See *Costs associated with metastatic progression, Castrate-resistant stage*
Hormonal therapy	Cypoterone acetate: 58.50+ Goserelin: 235.00+ Delivery: 13.25	See *Costs associated with metastatic progression, Hormonal therapy*
Other palliative treatment	4454.00	Collins[236]

continued

TABLE 64 Summary of costs used in the model (*continued*)

State or event	Cost (£)	Source
Events		
Adjuvant EBRT	2356.46	See *Treatment costs associated with primary treatments*; *Table 61*
Adjuvant hormonal therapy	555.00	See *Treatment costs associated with primary treatments*; *Table 61*
Local recurrence	569.00	See *Treatment costs associated with biochemical recurrence after primary treatment, Metastatic recurrence*; *Table 63*
Salvage therapy	Brachytherapy: 5342.85 Cryotherapy: 4172.89 EBRT: 4844.82 HIFU: 4705.32 Radical surgery: 4812.63	See *Treatment costs associated with biochemical recurrence after primary treatment, Costs associated with local progression following treatment for localised disease*
Systemic recurrence	755.00	See *Treatment costs associated with biochemical recurrence after primary treatment, Metastatic recurrence*; *Table 63*
Mortality states		
Cancer mortality	0.00	N/A
Non-cancer mortality	0.00	N/A
Operative mortality	0.00	N/A

N/A, not applicable.

TABLE 65 Costs used for adverse events

Side effect	Cost (£)	Source
UI	Self-management (94.8%): 263.59 (per year) AUS device (5.2%): 3928.00 (implantation) + 4918.00 (cost of device)	Ramsay 2012[218]
ED	No treatment (43%) Treatment (57%) Sildenafil (82.2% of treated): 5.88 (per week) Alprostadil (15.4% of treated): 11.94 (per week) Penile prosthesis (2.4% of treated): 2262.00 (implantation) + 5023.00 (cost of device)	Ramsay 2012[218]
BD	Annual monitoring cost: 368.50 Mean treatment cost: 2352.90	Ara 2009;[237] Shimizu 2008[238]

Estimation of utilities used within the model

Quality-adjusted life-years are calculated by weighting life-years with utility values, to reflect patients' preferences for the HRQoL that they experience. There are various methods and tools that can be used to elicit utility values. In its methods guide,[231] NICE recommends the use of the European Quality of Life-5 Dimensions (EQ-5D).

Sources of utility data for patient states and events in the model related to diagnosing and treating prostate cancer were identified from systematic searches of several databases, including MEDLINE, EMBASE, NHS Economic Evaluation Database (NHS EED), Health Economic Evaluations Database (HEED) and the Cost-effectiveness Analysis (CEA) Registry. Search strategy details are available in *Appendix 1*. Two reviewers independently screened the titles and abstracts of the studies identified from all searches and sources. A full paper copy of any study judged to be relevant by either reviewer was obtained where possible. A total of 306 references were identified. Of these, 56 were selected for potential inclusion in terms of reporting utility values by any method. An iterative method of study selection was planned to identify the best evidence regarding utility values:

1. values obtained by the EQ-5D
2. values obtained using other public preference-based weights of HRQoL scores [e.g. Health Utilities Index, Short Form questionnaire-6 Dimensions (SF-6D)]
3. values obtained by direct preference elicitation methods (e.g. time trade-off, standard gamble).

The final studies used to calculate utilities included in the model are reported in more detail in *Appendix 12*, together with a detailed summary of the methods and results for each study. Final utility values used in the model are specified in the summary results (*Table 66*).

The availability of data regarding utilities for health states and events included in the model was poor. For many treatment events there were no available data. Furthermore, where data did exist, there was heterogeneity in methods used to elicit utilities across all relevant studies. Therefore, utility values used in the model were calibrated in the model to the EQ-5D by using the value measured using the EQ-5D at initial diagnosis of prostate cancer.[238]

Diagnosis events

Where multiple sources of utility values for particular parameters were available, median values from the literature reviewed were used, which were then calibrated to the EQ-5D. For local recurrence, utility values were estimated on the basis of values taken from four studies.[243,247–249] For systemic recurrence, utility values were estimated on values taken from two studies.[247,250]

Primary treatments

For many primary treatment events, such as brachytherapy, cryotherapy, etc., there were no utility data available. It was assumed that the utility values for these treatment events were the same as that used for surveillance. This seemed a reasonable assumption as this was estimated to be the same as the utility value for EBRT.

Where EQ-5D scores were available from one source for multiple time points (as with EBRT),[239] the percentage improvement from baseline to 6 months post intervention was calculated. This was then calibrated by the EQ-5D value of initial diagnosis. It was assumed that the utility values for adjuvant EBRT with and without hormone therapy were the same as this. The utility value for RP with lymphadenectomy was assumed to be the same as that for RP alone owing to the absence of data.

TABLE 66 Utility values used in the model

Event/treatment	Value	Source
Diagnosis events		
Initial diagnosis	0.9	Shimizu 2008[238]
Local recurrence	0.63	See *Estimation of utilities used within the model, Diagnosis events*
Systemic recurrence	0.45	See *Estimation of utilities used within the model, Diagnosis events*
Primary treatments		
Cryotherapy	0.88	See *Estimation of utilities used within the model, Primary treatments*
HIFU	0.88	See *Estimation of utilities used within the model, Primary treatments*
Brachytherapy	0.88	See *Estimation of utilities used within the model, Primary treatments*
EBRT	0.88	Korfage 2005[239]
Radical surgery with and without lymphadenectomy	0.60	Stewart 2005[240]
Adjuvant EBRT with and without hormone therapy	0.88	See *Estimation of utilities used within the model, Primary treatments*
Surveillance states		
AS	0.87	Zeliadt 2005[241]
Surveillance	0.88	Krahn 1994[242]
Follow-up surveillance	0.88	Krahn 1994[242]
Watchful waiting	0.648	Cowen 1996[243]
Further cancer treatment		
All salvage treatments		See *Costs associated with local progression following treatment for localised disease*
Brachytherapy	0.88	
Cryotherapy	0.81	
EBRT	0.79	
HIFU	0.81	
Radical surgery	0.88	
General states		
All-cause mortality	0	Value assigned to death in EQ-5D
Hormone therapy	0.8 (range 0.4–0.9)	Bayoumi 2000[244]
Castrate-resistant stage	0.58	Hummel 2010[245]
Palliative treatment stage	0.46	Sandblom 2004[246]

Further cancer treatment

There were no utility data for any of the salvage treatments included in the model. We therefore estimated this (for all salvage treatments), taking the average of utility values for local recurrence, 6 weeks post RP and surveillance at 12 weeks.

General states

For the palliative stage of disease, we used the utility value for people with prostate cancer in the last 4 months of their lives, as reported by Sandblom and colleagues.[246]

Summary of costs and utilities used in the submodel of adverse events

Time in each state of dysfunction for all three side effects incurred a cost and utility which were (respectively) added to/multiplied by the yearly costs and utilities to obtain lifetime totals for each patient. Costs and utilities used are listed in *Tables 65* and *67*.

Elasticity analysis

The sensitivity of a model parameter is its potential to affect the overall model outcomes. A small change in a variable to which the model is highly sensitive may have a large impact on model outcomes, whereas the effect of a variable with a low sensitivity may go unnoticed amid the random noise of a stochastic model. An elasticity analysis examines the individual sensitivities of each driving variable to a given outcome, in this case survival, and is sometimes called a sensitivity analysis; however, this term is avoided here to avoid confusion with sensitivity analyses of the form more commonly reported in economic evaluations (we note, however, that this approach is consistent with the multiparameter probabilistic sensitivity analyses typically conduced in economic evaluations, the main difference being in the representation of results).

In addition to highlighting variables to which the model is most sensitive (and that hence should be the focus of greater efforts to obtain the best available data), the elasticity analysis also has a role in exploring the internal consistency of the model (see *Model validation*). This is because, as a precursor to any attempt to explore the sensitivity of the model to a change in parameters, we needed first to ensure that the internal logic of the model was correct.

There is no accepted procedure for testing the elasticity of a stochastic model. Swartzman[251] recommends that a successful method meets the following criteria: (a) it must be clearly defined, straightforward and specify the number of model runs required; (b) it must account for the effects of interactions between parameters; (c) it must include information on the variability associated with parameter estimates; and (d) it must allow interpretation for several output variables. Here we present our protocol for a sensitivity analysis of a Markov chain simulation model which includes all of these features. We use Latin hypercube sampling to sample the data range of each input variable, using the restricted pairing technique of Iman and Conover[252] to eliminate correlation between input variables. In addition, the calculation of partial correlation coefficients for each input variable takes into account the variance in model results caused by other input variables and calculates the proportion of the variance in the output which is uniquely accounted for by each input variable.

TABLE 67 Utilities used for adverse events

Side effect	Utility	Source
UI	0.830	Ramsay 2012[218]
ED	0.840	Ramsay 2012[218]
BD	0.720	Hummel 2010[245]

An elasticity analysis was performed on each of the nine primary treatment pathways. The pathways for these nine treatments differ in terms of the primary and subsequent treatments employed; for example, all ablative therapies follow the same treatment pathway because they share the same options for salvage treatments, even though some of these treatments may have different frequencies of use with different primary ablative treatments. The nine treatment pathways considered were:

- radical surgery
- radical surgery with adjuvant radiotherapy
- radical surgery with pelvic lymphadenectomy
- radical surgery with pelvic lymphadenectomy and adjuvant radiotherapy and hormonal therapy
- ablative therapy
- brachytherapy
- brachytherapy with adjuvant hormonal therapy
- EBRT
- EBRT with adjuvant hormonal therapy.

Latin hypercube sampling[253] was used to generate sets of parameter values from uniform distributions of known or estimated ranges. The aim was to provide a range of input values for each variable that could potentially occur under clinical conditions. In other words, the model would be run a sufficiently large number of times to encompass the potential range of conditions that occur naturally, rather than simply worst- and best-case scenarios.[254] In this method, sample values of the input parameters were selected by a randomisation procedure subject to constraints on the extent of correlation of input variables that were imposed by the modeller. There were insufficient data available to identify the distribution function for all parameters; furthermore, there were no data available to assess the extent to which each of the life history parameters was correlated with the others. A uniform distribution was therefore assumed for each variable, with upper and lower limits derived from the literature, and variables were also assumed to be independent of each other. This approach will lead to an overestimate of the size of the likely universe of possible values that each life history parameter could take. This is because, firstly, it is likely to lead to the selection of values for parameters that are near the extremes of their distributions more frequently than would be expected in reality. Secondly, the assumption of non-independence between the life history variables will lead to variable pairs being selected in the model that are unlikely to occur in the field (e.g. high mortality and high fecundity). On the other hand, it also ensures that all potential values (within the known range of observed behaviours for each variable) are sampled. In other words, although we know that the hyperspace of possible values for each parameter in the model will be larger than reality, we know that reality lies somewhere in that space and not outside it.

There is a trade-off to consider when choosing the number of simulations to perform in a sensitivity analysis. In assessing the effects of individual parameters on model output, it is critical not only to be able to accept the alternative hypothesis of an effect with confidence (i.e. significance, α), but also to have sufficient confidence in the predictions to avoid mistakenly rejecting the null hypothesis (i.e. power, $1 - \beta$). The power of a statistical test is reliant on the effect size looked for (that is, the posited difference between the sampled test statistic and the true test statistic) and the number of samples.[255] Thus, the number of input parameter sets generated by the Latin hypercube sampling can be chosen to achieve the required criteria for significance and power (i.e. minimise type I and type II errors).

In an ideal world, millions of replicates would be performed, producing high statistical power and, therefore, high confidence in the results. On the other hand, computer run-time dictates the maximum number of replicates possible, as does the capacity of statistical programs to analyse the data. With a Latin hypercube sampling procedure, there is a maximum of $(n!^{k-1})$ parameter sets, where n is the number of simulations and k is the number of variables. Iman and Helton (1985)[256] suggest $n > 4/3k$ as a minimum number of simulations; however, this number was reached from experience with their models, and is not necessarily a portable rule.

Therefore, to investigate the effect of number of simulations on the elasticity analysis, a heuristic approach was used. The Latin hypercube sampling procedure was used to generate 250 sets of the driving variables in the model. The restricted pairing technique of Iman and Conover (1982)[252] was used, rejecting parameter sets with significant correlations. The model was then run 250 times, once for each parameter set. Each model run consisted of a cohort of 1000 patients. Another 250 sets of input parameters were then generated using the Latin hypercube sampling procedure and the model was run again. This process was repeated to 250,000 model runs (i.e. 1000 replicates × 250 sets of random driving variables). Each replicate used the same random seeds to generate probabilities, to maximise the variation caused by changing the parameter values and minimise the variation caused by random noise. The life history outputs generated by each parameter set were recorded.

Partial correlation coefficients were calculated between the sets of driving variables and each of the output variables. Partial correlation coefficients represent the proportion of the correlation coefficient that is due only to the predictor, having removed variation caused by interactions with the other variables in the model. Significant partial correlation coefficients therefore indicated which parameter values had a significant effect on the output variable. Significant partial correlation coefficients were ranked in order of their *F*-value, and their sign (positive or negative) was recorded. The power of the partial correlation coefficients was calculated exactly using the method of Cohen and Cohen.[257]

Data analysis

Each state and event in the model had a cost and a utility associated with it. For a state, the cost and utility were incurred in each time step of the model in which the simulated patient remained in the state; for some states there was an additional cost when the state was first entered. For an event, the cost and utility were incurred during any time step of the model in which the simulated patient experienced the event. The sum of the cost in each year and the product of the utilities in each year were summed over the lifetime of the simulated patient to compute total cost and QALY for that individual.

In all cases, costs and utilities were drawn from a triangular distribution with the listed value as the peak value, and ± 25% used as the minimum and maximum values (utilities were truncated at zero and unity respectively). A triangular distribution was chosen as it makes minimal assumptions about the spread of values within the distribution while still acknowledging the presence of a peak around the calculated cost, utility or other estimated outcome. The model compared alternative treatments for localised prostate cancer by simulating for each treatment pathway the following outcomes.

Economic outputs

The economic outputs of the model included:

- Total costs per patient over the patient lifetime. These data tended to be highly skewed as some patients survived in the model for a long time but also experienced a number of very high-cost events. These were then summarised at a population level to produce average total cost over the patient lifetime for each initial treatment.
- Total QALYs of each patient. As noted earlier, this was calculated by summing the yearly products of the within-year utilities for each state and event. QALYs also tended to have a highly skewed distribution as some patients experienced an early death or experienced events that greatly reduced the amount of QALYs they could gain. These were then summarised at a population level to produce average QALYs for each initial treatment.
- Incremental mean costs.
- Incremental mean QALYs.
- Incremental cost per QALY gained.
- Net monetary benefits.

Within the base-case analysis, we adopted a NHS perspective and discounted costs and QALYs at the recommended 3.5% discount rate.[231] All costs and QALYs are for a lifetime time horizon and all monetary values are expressed in 2011–12 prices.

The base-case analysis has assumed that biochemical recurrence does not differ across the procedures, which is consistent with the evidence in the review of effectiveness presented in *Chapters 4–7*. However, an alternative analysis where biochemical recurrence varies according to the results of the meta-analysis of clinical effectiveness is also reported.

Sensitivity analysis

We addressed uncertainty by conducting probabilistic sensitivity analyses and deterministic (e.g. one-way) sensitivity analyses. The probabilistic sensitivity analysis involved running 1000 iterations of the model for each intervention considered for each analysis. These data were then used to prepare cost-effectiveness plots and cost-effectiveness acceptability curves.[258] These curves provide an estimate of the likelihood that an intervention would be considered cost-effective at different threshold values for society's willingness to pay for either a recurrence avoided or a day at usual activities.

The following deterministic sensitivity analyses were considered. A new intervention, AS, was introduced as an alternative to initial active therapy for localised prostate disease. In effect, this is a policy of delayed and selective treatment, which might be a viable option where disease is unlikely to become symptomatic over the expected lifetime of the individual or where the expected harms (in terms of side effects) would be worse than any symptoms currently experienced. This analysis was facilitated because it was assumed in the base-case analysis that, for each active treatment, a period of AS would take place for approximately 20% of people. In the modelling, this means that approximately 20% of the model runs for each active treatment involved AS. These data have been used to construct an additional comparator, AS, to allow cost-effectiveness analysis to be explored.

Model validation

Internal consistency checks

With respect to face validity the structure of the model and all data inputs were scrutinised by the research team and the external advisory group to ensure that the model structure suitably reflected the decision problem addressed and that data inputs and methods to assemble these inputs seemed plausible.

The elasticity analysis provided a further computational validity in that it explored the importance of model transitions. This provided a check on the mathematical logic of the model and allowed the modelling code to be tested for errors. Counterintuitive results became the focus of further investigation. Further, sensitivity analysis (not reported) was used to explore whether or not data had been incorporated correctly.

External validity

Alternative models comparing the cost-effectiveness of these interventions are not available and so this approach was not available to check external validity. However, the results of the model were checked with experts to assess their face validity. The model was also used to produce outputs that could be compared with data not used in the model (because it was not reported in sufficiently disaggregated form to be incorporated into the model).

Any issues with the internal or external validity of the model or its outputs were resolved prior to producing the final results reported in the next chapter.

Chapter 10 Economic evaluation results

Elasticity analysis

An illustration of the elasticity analysis output can be found in *Figure 21*. It is evident that all edges which lead to non-cancer mortality reduced the number of cancer-related deaths (coloured dark grey), whereas those which lead an individual closer to the cancer mortality sink state increased the number of cancer-related deaths (coloured black). These results are to be expected; what is informative from the elasticity analysis is that these driving variables are the ones that have the largest impact on the predicted costs and output for each initial treatment. From this we can identify for which variables it might be most important to obtain good data in order to estimate outcomes for each intervention and differences between interventions.

For all nine treatment pathways under consideration, the same processes appeared in the 'top three' (*Table 68*). A diagrammatic illustration of the elasticity analysis for ablative therapies is shown in *Figure 21*. The output under consideration was the proportion of individuals dying of cancer-related mortality. In this figure, transitions (edges) coloured dark grey indicate those processes which decreased the mortality from cancer; those coloured black increased the mortality from cancer. Edges coloured light grey had no significant impact on this output. The thickness of the edges indicates the relative importance of that process in cancer-related mortality.

Table 68 and *Figure 21* show variables that drive decreases in cancer mortality, which were the probabilities of patients succumbing to non-cancer mortality during the watchful waiting, castrate-resistant and other palliative treatment states and the probability of patients proceeding to active monitoring before undergoing primary treatment. Variables driving any increases in cancer mortality were the probabilities of patients suffering cancer mortality during the castrate-resistant and palliative care stages, and the probability of patients proceeding to watchful waiting from diagnosis, and bypassing primary treatment altogether.

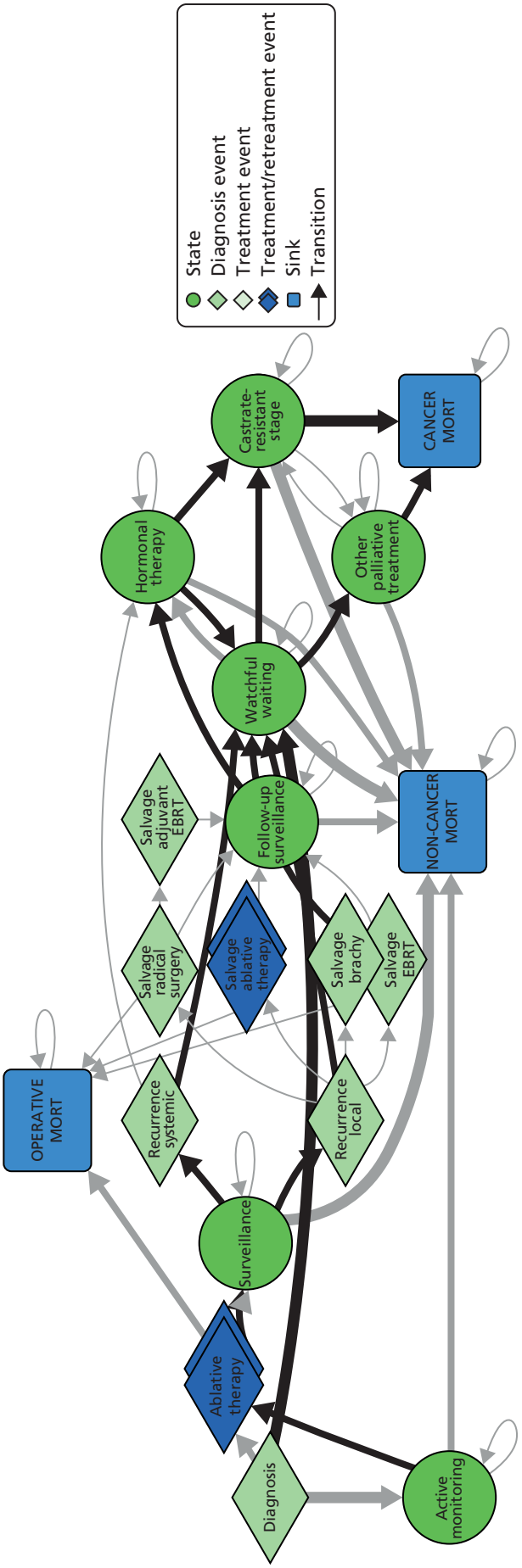

FIGURE 21 Diagrammatic illustration of the elasticity analysis for ablative therapies. MORT, mortality.

TABLE 68 Top three processes increasing and decreasing cancer mortality in all nine treatment pathways. The processes are listed in descending order for each pathway

	Top Three processes decreasing cancer mortality		Top Three processes increasing cancer mortality	
Treatment Pathway	From	To	From	To
Ablative therapy	Castrate-resistant stage	Non-cancer mortality	Diagnosis	Watchful waiting
	Watchful waiting	Non-cancer mortality	Castrate-resistant stage	Cancer mortality
	Diagnosis	Active monitoring	Other palliative treatment	Cancer mortality
Brachytherapy	Castrate-resistant stage	Non-cancer mortality	Diagnosis	Watchful waiting
	Watchful waiting	Non-cancer mortality	Castrate-resistant stage	Cancer mortality
	Diagnosis	Active monitoring	Other palliative treatment	Cancer mortality
Brachytherapy with adjuvant hormonal therapy	Watchful waiting	Non-cancer mortality	Diagnosis	Watchful waiting
	Castrate-resistant stage	Non-cancer mortality	Castrate-resistant stage	Cancer mortality
	Other palliative treatment	Non-cancer mortality	Other palliative treatment	Cancer mortality
EBRT	Castrate-resistant stage	Non-cancer mortality	Castrate-resistant stage	Cancer mortality
	Watchful waiting	Non-cancer mortality	Diagnosis	Watchful waiting
	Other palliative treatment	Non-cancer mortality	Other palliative treatment	Cancer mortality
EBRT with adjuvant hormonal therapy	Watchful waiting	Non-cancer mortality	Other palliative treatment	Cancer mortality
	Castrate-resistant stage	Non-cancer mortality	Castrate-resistant stage	Cancer mortality
	Other palliative treatment	Non-cancer mortality	Diagnosis	Watchful waiting
Radical surgery	Castrate-resistant stage	Non-cancer mortality	Diagnosis	Watchful waiting
	Watchful waiting	Non-cancer mortality	Castrate-resistant stage	Cancer mortality
	Diagnosis	Active monitoring	Other palliative treatment	Cancer mortality
Radical surgery with adjuvant radiotherapy	Castrate-resistant stage	Non-cancer mortality	Diagnosis	Watchful waiting
	Watchful waiting	Non-cancer mortality	Castrate-resistant stage	Cancer mortality
	Diagnosis	Active monitoring	Other palliative treatment	Cancer mortality

continued

TABLE 68 Top three processes increasing and decreasing cancer mortality in all nine treatment pathways. The processes are listed in descending order for each pathway (*continued*)

	Top Three processes decreasing cancer mortality		Top Three processes increasing cancer mortality	
Treatment Pathway	From	To	From	To
Radical surgery with pelvic lymphadenectomy	Castrate-resistant stage	Non-cancer mortality	Diagnosis	Watchful waiting
	Watchful waiting	Non-cancer mortality	Castrate-resistant stage	Cancer mortality
	Diagnosis	Active monitoring	Other palliative treatment	Cancer mortality
Radical surgery with pelvic lymphadenectomy and adjuvant radiotherapy and hormonal therapy	Watchful waiting	Non-cancer mortality	Diagnosis	Watchful waiting
	Other palliative treatment	Non-cancer mortality	Other palliative treatment	Cancer mortality
	Castrate-resistant stage	Non-cancer mortality	Castrate-resistant stage	Cancer mortality

Incremental cost-effectiveness

Base-case analysis: equal risk of biochemical recurrence

When making the assumption that biochemical recurrence is equivalent, the choice between interventions is driven by three factors: (i) the cost of the interventions; (ii) perioperative complications; and (iii) the impact of long-term complications. *Table 69* shows the incremental cost-effectiveness analysis for the comparison of the different interventions. These data are derived from the Monte Carlo simulations. As this table illustrates, HIFU is, on average, less costly per patient and results in more QALYs than any of the other interventions. However, this analysis is potentially misleading as it does not display the imprecision surrounding estimates of costs, QALYs and cost-effectiveness. This imprecision can be portrayed by plotting the costs and QALYs for each intervention (*Figure 22*) and, as was described in *Chapter 9*, these data can be displayed as cost-effectiveness acceptability curves (*Figure 23*).

TABLE 69 Base-case analysis: equal biochemical recurrence (probabilistic analysis)

Intervention	QALYs	Cost (£)	Incremental cost per QALY (£)
EBRT	3.69	19,363	
HIFU	3.86	19,860	2915
Cryotherapy	3.78	23,010	Dominated[a]
Brachytherapy	3.75	24,456	Dominated
RP	3.44	26,507	Dominated

a Intervention is more costly but less effective than an intervention that is less costly.

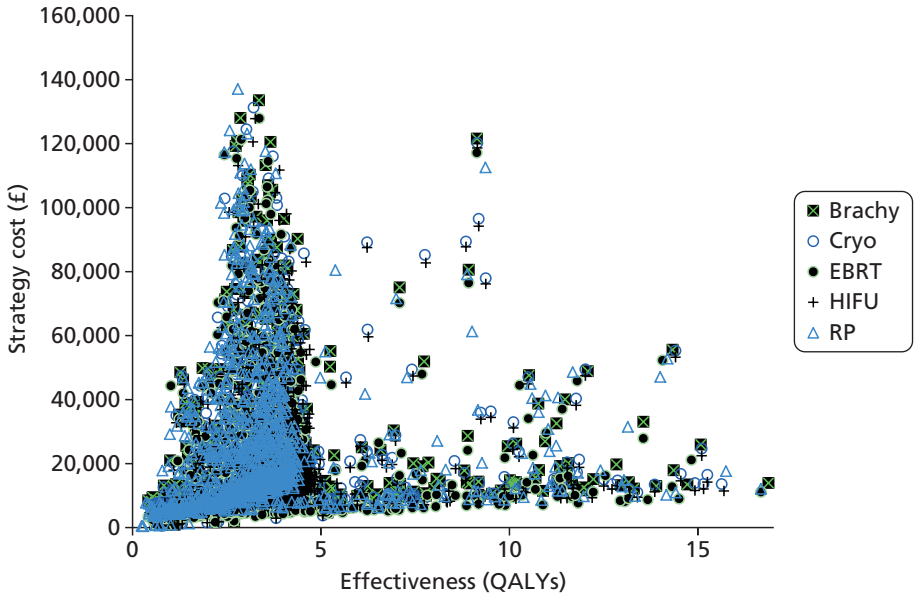

FIGURE 22 Base-case analysis: plots of costs and QALYs for each intervention.

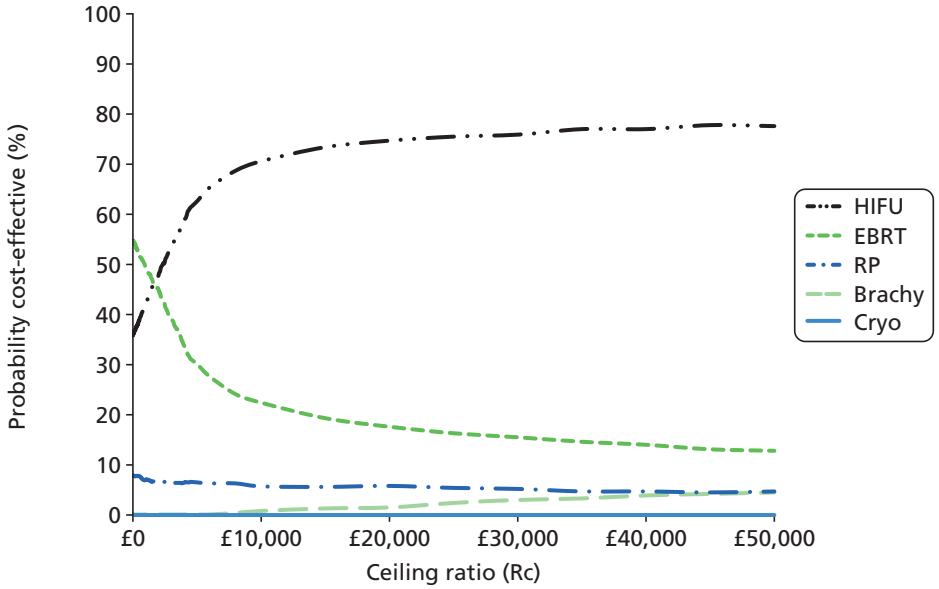

FIGURE 23 Base-case analysis: cost-effectiveness acceptability curves.

As *Figure 22* illustrates, there is a wide variation in cost and QALYs for each intervention. For all interventions, the majority of individuals in the Monte Carlo simulation have relatively modest QALYs (< 5) but with considerably more variation in cost, which reflects the varying intensities of care that they receive over time. However, a small number of individuals for each intervention experience very low cumulative costs and considerably more QALYs, reflecting the possibility that some prostate cancers will not necessarily be problematic and might require considerably less care.

Figure 23 shows that should society not be willing to pay anything for an additional QALY, the intervention most likely to be cost-effective is EBRT, with an approximately 50% likelihood of being considered cost-effective. HIFU is more likely to be more costly than EBRT but provides more QALYs, hence as society's willingness to pay for a QALY increases, the likelihood that HIFU would be considered cost-effective also increases. Thus, at threshold values for society's willingness to pay for a QALY that might be considered worthwhile – for example, between £20,000 and £30,000 per QALY[231] – there is a 70% likelihood that HIFU would be considered cost-effective. Over the same range, the other interventions (RP, cryotherapy and brachytherapy) have a very low likelihood of being considered cost-effective. It should be noted, however, that, as *Figure 22* illustrates, the interventions are in fact similar and the results shown in *Figure 23* are driven by small differences in costs and QALYs.

Alternative analysis using the results from the meta-analysis for biochemical recurrence

As an alternative to the base-case analysis, the results in this subsection assume that the results of the meta-analysis of biochemical recurrence are the most appropriate to use in the model. *Table 70* shows that the rank ordering of interventions has now changed and that EBRT is now the least costly and least effective intervention, but with HIFU dominating the other treatments. In this analysis, HIFU is associated with an incremental cost per QALY that is beyond the threshold level generally considered acceptable for society.[231] However, these average data are very sensitive to the skewed data and do not illustrate the precision surrounding the estimates.

Figure 24 shows the plots of costs and QALYs for each intervention and these are broadly similar to the plots shown in *Figure 22*. Likewise, the cost-effectiveness acceptability curve for this analysis (*Figure 25*) shows a broadly similar pattern to that shown in *Figure 23*. Again, HIFU is most likely to be considered cost-effective at the threshold values for willingness to pay for a QALY that society might be willing to pay. However, the same caveats as noted above also apply.

TABLE 70 Incremental cost-effectiveness when estimates of biochemical recurrence come from the meta-analysis (probabilistic analysis)

Intervention	QALYs	Cost (£)	Incremental cost per QALY (£)
EBRT	3.99	11,250	
HIFU	4.04	15,648	85,762
Brachytherapy	3.94	18,782	Dominated[a]
RP	3.60	22,461	Dominated
Cryotherapy	3.39	29,954	Dominated

a Intervention is more costly but less effective than an intervention that is less costly.

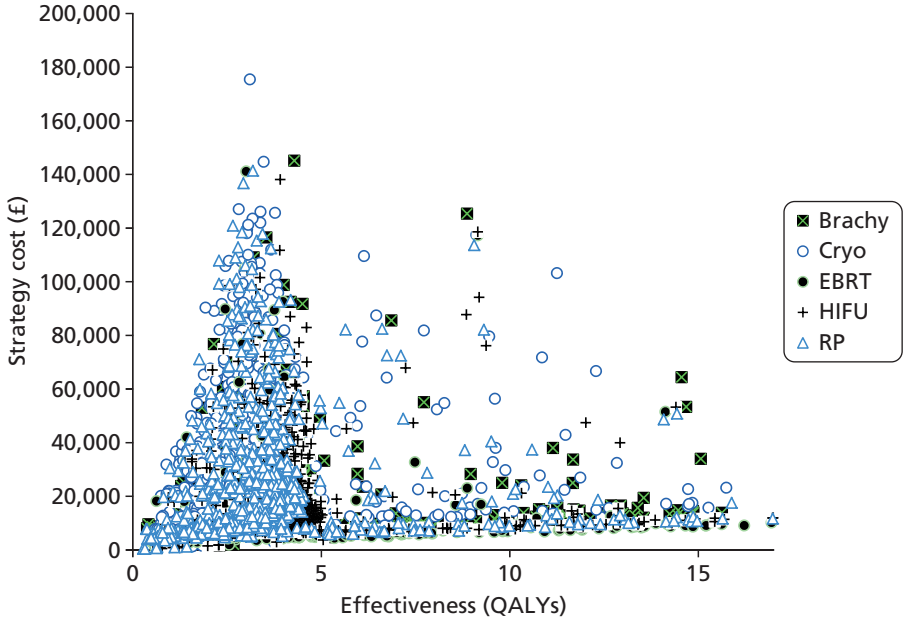

FIGURE 24 Plots of costs and QALYs for each intervention when risk of biochemical recurrence is based on the results of the meta-analysis.

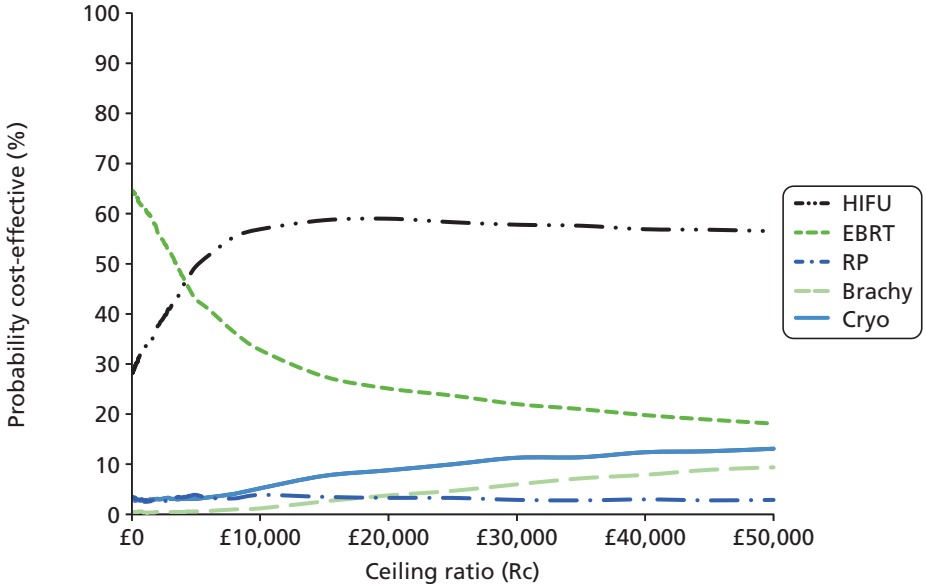

FIGURE 25 Cost-effectiveness acceptability curves when risk of biochemical recurrence is based on the results of the meta-analysis.

Sensitivity analyses

As there are considerable uncertainties within the data used in the model, analyses have been conducted where parameters have been changed to plausible extreme values. The results of these analyses for both probabilistic and deterministic results are shown in *Table 71*. Of note in the sensitivity analyses is the reduction in the likelihood that HIFU would be considered cost-effective compared with the base-case analysis and the analysis using the data from the meta-analysis. This helps illustrate the degree of uncertainty surrounding some of the data inputs to the model.

In one sensitivity analysis we attempted to construct a new comparator, 'active surveillance'. The introduction of an AS option was, on average, less costly and more effective than the immediate use of an active treatment. However, although interesting, these data need to be treated exceptionally cautiously and hence they are not further reported.

TABLE 71 Summary of sensitivity analyses results

Sensitivity analysis	Intervention	QALYs	Cost (£)	Incremental cost per QALY (£)	Probability of cost-effectiveness for different threshold values for society's willingness to pay for a QALY (%)			
					£10,000	£20,000	£30,000	£50,000
Base-case model: equal biochemical recurrence	EBRT	3.69	19,363		55	18	16	13
	HIFU	3.86	19,860	2915	36	75	76	78
	Cryotherapy	3.78	23,010	Dominated[a]	0	0	0	0
	Brachytherapy	3.75	24,456	Dominated	0	2	3	5
	RP	3.44	26,507	Dominated	8	6	5	5
Biochemical recurrence based on meta-analyses data	EBRT	3.99	11,250		65	25	22	18
	HIFU	4.04	15,648	85,762	28	59	58	57
	Brachytherapy	3.94	18,782	Dominated[a]	1	4	6	9
	RP	3.60	22,461	Dominated	4	3	3	3
	Cryotherapy	3.39	29,954	Dominated	3	9	11	13
Parameters set at a plausible best case	EBRT	4.02	10,861		51	16	13	12
	HIFU	4.22	11,670	4020	43	71	70	70
	Brachytherapy	4.01	17,882	Dominated[a]	0	1	2	3
	RP	3.75	17,521	Dominated	3	4	4	4
	Cryotherapy	3.42	30,764	Dominated	2	7	10	12
Parameters set at a plausible worst case	EBRT	3.72	19,550		54	22	19	17
	HIFU	3.92	19,692	690	22	60	61	60
	Brachytherapy	3.41	31,003	Dominated[a]	3	6	6	9
	RP	3.03	34,322	Dominated	14	4	4	4
	Cryotherapy	3.33	31,651	Dominated	6	9	10	10

a Intervention is more costly but less effective than an intervention that is less costly.

Summary

The economic evaluation suggests that HIFU might be the intervention that is most likely to be considered cost-effective when assessed against threshold values for a cost per QALY that society might be willing to pay. There is marked uncertainty within the analyses as plausible extremes would suggest that EBRT may also be most likely to be considered cost-effective in some circumstances. Over the limited range of analyses, cryotherapy, brachytherapy and RP were unlikely to be viewed as cost-effective over the threshold values considered. It is, however, important to note that given the uncertainties surrounding parameter estimates and the similarities in costs and QALYs estimated, as illustrated by *Figure 22*, it is not impossible that plausible combinations of data inputs could be identified that could make these interventions appear cost-effective.

Thus, the results presented here are unlikely to be sufficient to form recommendations to change practice, but they do indicate that further robust studies around HIFU and EBRT as treatment options for localised prostate cancer may be useful.

Chapter 11 Discussion

Clinical effectiveness and harms

Primary ablative therapy

Statement of principal findings

The systematic review assessed the evidence for the clinical effectiveness and cost-effectiveness of ablative therapies in comparison with standard interventions for the management of localised prostate cancer, in a comprehensive and robust manner. Meta-analysis of studies was performed whenever the data allowed for it, which, unfortunately, was not often, with the majority of studies suffering from clinical and methodological heterogeneity. A total of 34,159 patients who underwent ablative therapy were included across 76 studies.[36,49,52,98–103,105–110,113,114,116,117,119–133,135,136,138,139,142–145,149–151,153–156,158–163,166,170–174,176,182,184–186,188,189,191,195,202–207] Brachytherapy accounted for 76.5% of patients, with all brachytherapy studies being either NRCSs (39/41 studies)[36,100,101,103,105,108–110,113,117,119,121,123,126,128,130,131,135,136,144,145,149,151,153,156,160,163,170–172,176,182,184,186,189,203,205–207] or RCTs (2/41 studies).[49,121] As such, the evidence base for brachytherapy is inherently more reliable. In contrast, for non-brachytherapy ablative therapies, the majority of studies (35/40) were case series.[52,98,99,102,106,107,114,116,120,122,124,127,129,132,133,138,139,142,143,150,154,155,158,159,161,162,166,173,174,185,188,191,195,202,204]

The majority of included ablative studies involved total gland ablation. For the newer development of focal ablative therapy (incorporating hemigland, nerve-sparing or focal ablation), 10 studies were included,[52,98,99,103,127,129,138,166,188,202] recruiting a total of 1525 patients; more than 90% of these patients underwent focal cryotherapy. The majority of these studies (9/10) were case series.[52,98,99,127,129,138,166,188,202]

Clinical effectiveness and harms of ablative therapies (whole-gland or non-focal intention)

For cryotherapy and HIFU, the evidence relating to cancer-specific outcomes, such as biochemical recurrence or survival, was limited by the lack of long-term follow-up data and by contradictory findings. There were some observed differences in biochemical recurrence in the short-term favouring EBRT over HIFU, but these differences were lost in the longer term beyond 1 year, and probably reflect clinical heterogeneity between the studies, whereby patients in the EBRT studies, in general, had lower-risk prostate cancer at baseline than those in the HIFU studies. At best, the review found no robust evidence to suggest that mortality or other cancer-specific outcomes were significantly different between either cryotherapy or HIFU, versus either EBRT or RP, for people treated for localised prostate cancer. In terms of functional outcomes, both cryotherapy and HIFU appeared to have a better rate of urinary incontinence at 1 year than RP, but this apparent benefit was lost in the longer term. There were insufficient data to comment on ED. Cryotherapy was associated with fewer short-term adverse effects or periprocedural complications than either RP or EBRT, whereas HIFU, although it appeared to have a reasonable safety profile, was associated with a slightly higher urethral stricture rate than EBRT.

The data concerning brachytherapy were more robust and reliable than for either cryotherapy or HIFU. There was some evidence that cancer-specific outcomes following brachytherapy were no worse than those following either EBRT or RP, at least in the short term. It was quite encouraging to note that brachytherapy appeared to be associated with better functional outcomes, with lower incontinence and ED rates in the medium term (up to 5 years) than either EBRT or RP. However, brachytherapy carried a higher risk of some adverse effects, especially dysuria, urinary retention, genitourinary toxicity and urethral stricture.

Apart from cryotherapy, HIFU and brachytherapy, only two other ablative therapies were identified in the review, namely focal laser ablative therapy and vascular-targeted PDT. Data were too scarce (the total number of patients included in studies for these two procedures was 35) for any definitive conclusions to

be made, apart from the observation that there was no evidence to suggest that the procedures were not safe or were not associated with a low risk of adverse events.

Clinical effectiveness and harms of focal ablative therapy (hemigland, nerve-sparing or focal ablation)

The evidence for focal ablative therapy, although limited, was largely obtained from studies involving focal cryotherapy. This suggested that cancer-specific outcomes for focal cryotherapy were at least comparable with those observed in full-gland cryotherapy studies. There was a suggestion that urinary incontinence rates may be lower following focal cryotherapy than following whole-gland cryotherapy, but this assertion may be unreliable owing to the poor quality and quantity of data. For focal HIFU, no comparative data were available to make any judgements regarding most effectiveness outcomes, apart from adverse events, for which there did not appear to be any significant difference between focal and whole-gland HIFU.

Clinical effectiveness and harms of ablative therapies versus active surveillance for low-risk localised disease

For low-risk localised prostate cancer, there is an increasing trend towards adopting AS as a viable management option in current clinical practice. As such, comparative evidence involving ablative therapies versus AS for low-risk localised disease is potentially important, especially for focal ablative therapies. Subgroup analysis from the review found that there was no evidence of any significant difference in any of the outcomes, including cancer-specific, functional and adverse event outcomes, between any of the focal ablative therapies and AS, although data were scarce, with significant heterogeneity of outcome definition and measurement.

In summary, the results of this review and meta-analysis regarding clinical effectiveness and harms were associated with a considerable degree of uncertainty owing to the poor quality of studies identified. There was a lack of data on long-term direct measures of effectiveness, and a lack of prospective comparative studies, which considerably limited the quality of the evidence synthesised from the review.

Salvage ablative therapy

Statement of principal findings

This review included data from 400 participants who were treated with salvage therapy following primary EBRT across nine studies.[120,208–215] All studies were single-arm case series, which severely limits the reliability and strength of the conclusions. Six studies involved salvage RP,[209–211,213–215] whereas two involved salvage cryotherapy,[208,212] and one salvage HIFU.[120] In the majority of studies (six out of nine[120,208–211,214]), data were not collected prospectively, and were restricted to short-term outcomes only. As such, all of the studies were considered as having a high risk of bias. With those limitations in mind, there was no robust evidence that mortality or other cancer-specific outcomes (i.e. biochemical disease-free survival or failure) differed between salvage cryotherapy and salvage RP in the short term. There were no data on cancer-specific outcomes for salvage HIFU. With regard to functional and quality of life outcomes, the paucity of data prevented any definitive conclusions from being made. In terms of adverse event outcomes, salvage cryotherapy appeared to be associated with fewer periprocedural complications (especially for bladder neck stenosis) than salvage HIFU or salvage RP, but there was a high level of uncertainty with this observation.

In summary, the findings for salvage ablative therapy were associated with significant uncertainty on account of the very limited quality and quantity of the evidence base. There was a lack of long-term direct measures of effectiveness and a lack of prospective comparative studies. Data on the long-term effectiveness of salvage therapy were limited, with the majority of studies reporting on short-term data only. In addition, the evidence base was seriously marred by heterogeneity of outcome definition, different time points of outcome measurement and different means of outcome measurement and reporting.

Cost-effectiveness of primary ablative therapies

Statement of principal findings

The first stage of the economic analysis was an elasticity analysis. The elasticity analysis helped identify which transition probabilities were the principal determinants of survival. This analysis was conducted for each intervention and showed that many of the principal determinants of survival were related to the characteristics of the initial cancer and many of the probabilities of outcomes following recurrence. Of moderate importance was the performance of individual therapies in preventing or delaying recurrence. In the economic evaluation that compared alternative interventions, the probabilities of events following recurrence were generally the same for all interventions and hence their effect on estimates of cost-effectiveness would be entirely caused by differences in recurrence rates between interventions.

With respect to the economic evaluation itself, the results of this analysis suggest that HIFU might be the intervention that is most likely to be considered cost-effective when assessed against threshold values for a cost per QALY that society might be willing to pay.[231] There is marked uncertainty within the analyses as plausible extremes would suggest that EBRT may also be most likely to be considered cost-effective in some circumstances. Over the limited range of analyses, cryotherapy, brachytherapy and RP were unlikely to be viewed as cost-effective over the threshold values for society's willingness to pay for a QALY that were considered. It is, however, important to note that given the uncertainties surrounding parameter estimates and the similarities in costs and QALYs estimated (as illustrated by *Figure 22*), it is quite possible that plausible combinations of data inputs could be identified that could make these interventions appear cost-effective.

Thus, the results presented here are unlikely to be sufficient to form recommendations to change practice, but they do indicate that further robust studies around the relative effectiveness and cost-effectiveness of HIFU and EBRT as treatment options for localised prostate cancer may be most useful.

Strengths and limitations of the assessment

Clinical effectiveness

The main strength of the study is the systematic approach taken to review the literature. Exhaustive systematic searches were made of the major electronic databases. All potentially relevant studies were reviewed for eligibility. The risk of bias of included comparative studies and quality assessment of included case series were assessed using the best available tools. To prevent any biases caused by selective data abstraction, all outcomes were predetermined by both expert panel and patient focus group consensus. Any data were extracted using standard forms. Despite these efforts it is possible that some relevant data remained hidden as a result of non-publication.

In total, 121 reports were included.[36,49,52,98–215] Although this number of studies seems impressive, not every study contributed data to each outcome. Furthermore, differences in reporting between studies also limited the opportunities for robust meta-analysis. Given the limited evidence base, the CrIs around many of the estimates of differences were wide and included differences that would be clinically important but could favour any of the therapies under investigation. Another major limitation resulted from the majority of comparisons using case series, with few head-to-head comparisons of ablative therapies against current practice. The estimates were therefore generated using indirect comparisons. Like all analyses, they require assumptions to be made that may or may not be reasonable. In the context of this analysis, an important assumption is that the studies in each meta-analysis were representative of a similar population (i.e. the clinical and demographic characteristics of the people were similar across studies). Data in *Table 2* demonstrated that the assumption had broad face validity, but that there were some differences, such as a slight increase in the average clinical stage for people in the EBRT study. Accordingly, the results should be interpreted with a large degree of caution.

A further methodological limitation that frustrated pooled analysis was the use of differing definitions and measures of functional outcomes for urinary, erectile and bowel dysfunction. The variety of different ways of measuring dysfunction reduced the ability to narratively compare data or to conduct a comprehensive meta-analysis. Although in part the difficulty is reflected by changing measurement methodology over time, it will remain a problem until consensus on important outcome measurements in this clinical area can be agreed. Initiatives such as the UK Medical Research Council- and European Union-funded Core Outcome Measures in Effectiveness Trials (COMET) or Consensus-based Standards for the Selection of Health Measurement Instruments (COSMIN) may be useful in this context. Such initiatives help patients, clinicians and researchers to develop a standardised set of outcomes that should be measured and reported as a minimum in all clinical trials of a specific condition, thereby making it easier to contrast and synthesise the results of trials.

Identifying outcomes that can be used to compare ablative therapies with both AS and RP or EBRT was challenging. Long-term survival is a key outcome that could be used consistently across studies, but it is limited because differences are unlikely to be observed for at least 10–15 years, and few of the ablative studies had such length of follow-up. Dysfunctional and quality of life outcomes can be used for comparison, but were limited for the reasons given previously. Need for further (systemic) treatment may also be used to contrast all therapies, but again this was rarely reported in the studies. All of these issues contributed to the review providing little information on the comparative effectiveness of AS and active treatment.

Cost-effectiveness

The cost-effectiveness analysis shares the strengths and limitations of the review of effectiveness, as the estimates derived from the review of effectiveness were important input parameters into the economic model. The data on relative effectiveness are, however, only one component of the estimation of cost-effectiveness. Rigorous attempts were made to develop a model of the disease and care pathways for localised prostate cancer. Within an elasticity analysis, the importance of individual probability parameters was explored to help prevent the distorted assembly of data and focus the research effort on the assembly of data inputs into the model on the most important elements. Computationally, the elasticity analysis is very demanding and in this analysis the focus was on survival. A similar elasticity analysis could, however, have been performed for other key outcomes, but both total costs and QALYs are closely related to survival and hence might not provide further information of sufficient value to warrant the additional costs of conducting the research. What would, however, be of value would be to consider the elasticity analysis in a comparative analysis of different therapies, as many of the probabilities identified in the elasticity analysis as being important are, or are assumed to be, the same between treatments.

The rigorous attempts to assemble other data inputs have reduced some of the uncertainties that are faced. The probabilistic sensitivity analysis that was performed attempted to explore the imprecision around model outputs. Largely this was accomplished by using triangular distributions. Ordinarily, such an approach would not be recommended, but the use of alternative distributions would have required an additional set of assumptions, given the lack of data, to define the distribution. Therefore, in this analysis we have assumed a simpler triangular distribution.

The assembly of data on costs of interventions was based on an intensive micro-costing exercise, and other cost data were derived so as to be most applicable to this decision-making context. The assembly of data on health state utilities was likewise systematic and focused on identifying the most applicable data for the decision problem. Nevertheless, the extant data were, in places, sparse or not well suited to the study and necessitated a number of strong assumptions to be made. Among these are the utilities that would be applicable during the recovery phase. Within the model, these were derived based on expert advice and consideration of data for related events. It is questionable how accurate these assumptions actually are. Ideally, an exercise to systematically derive empirical estimates of relevant health state utilities would be undertaken.

A further limitation imposed by the nature of the clinical evidence is the limited data that are available to explore clinical uncertainties. Three distinct clinical questions have not been addressed. These are: (i) what is the role of AS as opposed to immediate treatment with an active therapy?; (ii) are focal therapies more cost-effective than whole-gland ablative therapies?; and (iii) what is the optimal form of salvage therapy? With respect to (i), some exploratory analysis around the value of AS was performed. The results of this analysis appeared to suggest that AS would be associated with a substantial survival benefit. However, given the structure of the model and the data used, these results were judged to be unreliable as it was felt that given the data available, AS was essentially just adding a delay in the development of the disease. With respect to (ii), we would expect little difference in the costs of focal compared with whole-gland ablation, and some gains in QALYs and reductions in costs if the probabilities of incontinence were avoided. However, the impact on costs and QALYs of 'early' reoperation and of difference in recurrence rates in the medium and long term are unknown. For the third clinical question that remained unanswered, regarding which is the best salvage therapy, the model structure was designed to be able to address this but too few data were available to populate the model. These three clinical questions remain options for further primary research.

Chapter 12 Conclusions

Implications for health care

The increasing incidence of low- and medium-risk localised prostate cancer indicates that demand for treatment interventions which are less aggressive than the established radical treatments will likely increase over the next decade in the UK. Such interventions include ablative therapy, which appears to be the ideal intervention because, unlike AS, it actively treats cancer while being minimally invasive and potentially organ-sparing, unlike either RP or EBRT. This review was tasked with assessing the evidence base regarding the clinical effectiveness and cost-effectiveness of ablative therapy for people with localised prostate cancer in the NHS.

For primary ablative therapy, neither cryotherapy nor HIFU had sufficiently robust data to enable any definitive conclusions to be made in regard to their clinical effectiveness, harms or cost-effectiveness in comparison with RP, EBRT or AS. The data on brachytherapy were more robust, although there were some limitations which resulted in some uncertainties surrounding the estimates. Nevertheless, there was some evidence that cancer-specific outcomes in the short term were either better than or equivalent to those of either EBRT or RP, with comparable adverse effect profiles apart from a possible increased risk of dysuria and urinary retention. The findings on focal ablative therapy were mostly derived from data on focal cryotherapy, which suggested that cancer-specific outcomes were at least comparable with those of full-gland cryotherapy, and there was a suggestion that UI outcome may be better following focal cryotherapy than whole-gland cryotherapy. In terms of the economic analysis, the findings suggest that of all the ablative interventions, HIFU is the most likely to be considered cost-effective when assessed against threshold values for a cost per QALY that society might be willing to pay. However, marked uncertainties within the analyses, and the lack of reliable estimates of its clinical effectiveness and harms, mean that the cost-effective advantage needs to be interpreted cautiously. At best, the data highlight that this modality might be a good target for further robust primary research.

For salvage ablative therapy following primary EBRT, a lack of reliable and robust data prevented any meaningful conclusions from being made, in comparison with salvage RP.

The findings from the review indicate that there is insufficient evidence to form any clear recommendations on the use of ablative therapies which either influence or change current clinical practice.

Implications for research

The main gaps in the evidence base are the lack of direct comparative studies of ablative therapies, the role of focal ablative therapies and the lack of longer-term data on cancer control, such as overall and cancer-specific mortality. To investigate if the evidence base will improve, we conducted a search for ongoing studies. We found the following ongoing studies as of 3 October 2013.

Brachytherapy

Five case series of focal brachytherapy;[259–263] four case series of whole-gland brachytherapy;[264–267] one RCT of brachytherapy versus EBRT;[268] one RCT of brachytherapy versus RP;[269] and one RCT of brachytherapy versus radiotherapy versus RP versus AS;[270] and one NRCS of RP versus EBRT versus brachytherapy versus AS versus cryotherapy.[271]

Cryotherapy

Two case series of focal cryotherapy;[272,273] one case series of whole-gland cryotherapy;[274] one case series of whole-gland salvage cryotherapy,[275] one NRCS of cryotherapy versus RP versus radiotherapy;[276] and one case series of focal salvage cryotherapy and HIFU.[277]

High-intensity focused ultrasound

Three case series of focal HIFU[278–280] and one case series of whole-gland HIFU.[281]

Other ablative therapies

One case series of focal laser ablation;[282] one case series of whole-gland laser ablation;[283] one case series of whole-gland PDT;[284] and one RCT of focal PDT versus AS.[285] In addition, we identified two case series of cyberknife;[286,287] one RCT of hemi versus total irreversible electroporation [Nanoknife® (AngioDynamics, Latham, NY)] ablation;[288] one case series of focal irreversible electroporation;[289] one case series of irreversible electroporation 30 days prior to prostatectomy;[290] and one case series of transurethral ultrasound ablation[291] and one case series of hypofractionated radiosurgery.[292]

In general, the ongoing studies clearly illustrate that the evidence base for ablative therapies is following an upwards trajectory, and, in particular, the evidence for focal ablative therapies is likely to increase in quantity. However, it is also clear that the quality of the evidence base will not be substantially improved given that the majority of the ongoing studies are case series. Research efforts in the use of ablative therapies in the management of prostate cancer should now be concentrated on the performance of more rigorous, high-quality studies. Lessons from our systematic review lead us to the following areas in which further research would be important:

1. HIFU and brachytherapy seem the most promising newer interventions but they lack high-quality evaluation. Such evaluation should ideally be by multicentre RCT with long-term follow-up, and would include predefined assessment of cancer-specific, dysfunction and HRQoL measures. Such studies should incorporate economic evaluations and also inform economic modelling.
2. The role of focal therapies in the management of people with localised prostate cancer should be investigated. It may be desirable to incorporate the focal approach into the design described above. It is noted, however, that use of focal therapies is dependent on prior precise localisation of the cancer for which the technology remains developmental.
3. AS is an increasingly used strategy for people with localised prostate cancer that is deemed to be at low initial risk of spread. The results of ongoing studies are required to assess its safety, acceptability to people with prostate cancer and cost-effectiveness.
4. Agreed definitions of outcomes in urology and agreed measures for recording them are urgently needed. Partnership between governing bodies and international initiatives such as COSMIN and COMET may be desirable.

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Craig R Ramsay (co-principal investigator, Health Care Assessment Programme Director) oversaw and co-ordinated all aspects of the study and wrote the scientific summary, methods and results for the systematic review of clinical effectiveness, and the discussion and conclusion chapters.

Temitope E Adewuyi (research assistant) led the day-to-day running of the study, reviewed the evidence for clinical effectiveness of the technologies and wrote the results for the systematic review of clinical effectiveness.

Joanne Gray (senior lecturer), **Jenni Hislop** (research fellow) and **Mark DF Shirley** (research associate) developed the care pathways, conducted the economic evaluation and wrote the method and results for the economic evaluation.

Shalmini Jayakody (research fellow) assisted in reviewing the evidence for clinical effectiveness of the technologies.

Graeme MacLennan (research fellow) provided statistical support.

Cynthia Fraser (information specialist) developed and ran the search strategies and was responsible for obtaining full-text papers and for reference management.

Sara MacLennan conducted a focus group with men living with and beyond localised prostate cancer and analysed data to identify outcomes of importance from a patient perspective.

Miriam Brazzelli (senior research fellow) provided guidance and expert advice on reviewing the evidence for clinical effectiveness.

James N'Dow (Professor of Urology) provided expert clinical advice on service and surgical aspects.

Robert Pickard (Professor of Urology) classified reported adverse events into the Clavien–Dindo classification of surgical complications and provided expert clinical advice on service and surgical aspects.

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Kieran Rothnie (research assistant) assisted in reviewing the evidence for clinical effectiveness of the technologies.

Stephen P Rushton (Professor of Biological Modelling) and **Luke Vale** (Professor of Health Economics) supervised the economic evaluation and wrote the methods and results for the economic evaluation.

Thomas B Lam (co-principal investigator, senior specialist registrar and honorary clinical lecturer) jointly co-ordinated the study with Craig Ramsay, provided clinical advice on the care pathways, classified reported adverse events into the Clavien–Dindo classification of surgical complications, co-ordinated the expert advisory group participation and wrote the background, description of care pathways, results for the systematic review of the clinical effectiveness of salvage ablative therapies, discussion and conclusion chapters.

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274. ClinicalTrials.gov. *Prostate Conformal Cryotherapy*. URL: http://clinicaltrials.gov/show/NCT00877682 (accessed 3 October 2013).

275. ClinicalTrials.gov. *Salvage Cryotherapy in Recurrent Prostate Cancer (SCORE)*. URL: http://clinicaltrials.gov/ct2/show/NCT00824928 (accessed 3 October 2013).

276. ClinicalTrials.gov. *Immune Profiles and Circulating Tumor Cell Status Following Prostate Cryotherapy*. URL: http://clinicaltrials.gov/show/NCT01454037 (accessed 3 October 2013).

277. ClinicalTrials.gov. *FOcal RECurrent Assessment and Salvage Treatment (FORECAST)*. URL: http://clinicaltrials.gov/show/NCT01883128 (accessed 3 October 2013).

278. ClinicalTrials.gov. *Focal MR-guided Focused Ultrasound Treatment of Localized Low-risk Prostate Cancer: Feasibility Study*. URL: http://clinicaltrials.gov/show/NCT01226576 (accessed 3 October 2013).

279. ClinicalTrials.gov. *High-intensity Focused Ultrasound in Treating Patients With Localized Prostate Cancer*. URL: http://clinicaltrials.gov/ct2/show/NCT01194648 (accessed 3 October 2013).

280. ClinicalTrials.gov. *Focal MR-guided Focused Ultrasound Treatment of Localized Low-risk Prostate Cancer*. URL: http://clinicaltrials.gov/show/NCT01657942 (accessed 3 October 2013).

281. ClinicalTrials.gov. *High-intensity Focused Ultrasound Focal Ablation in Treating Patients With Progressive Prostate Cancer*. URL: http://clinicaltrials.gov/show/NCT00988130 (accessed 3 October 2013).

282. ClinicalTrials.gov. *MR Image Guided Therapy in Prostate Cancer*. URL: http://clinicaltrials.gov/show/NCT01377753 (accessed 3 October 2013).

283. ClinicalTrials.gov. *MR-guided Laser Interstitial Thermal Therapy in Treating Patients With Prostate Cancer*. URL: http://clinicaltrials.gov/show/NCT01792024 (accessed 3 October 2013).

284. ClinicalTrials.gov. *Efficacy, Safety and Quality of Life After TOOKAD® Soluble Vascular Targeted Photodynamic Therapy for Localized Prostate Cancer (PCM304)*. URL: http://clinicaltrials.gov/show/NCT01875393 (accessed 3 October 2013).

285. ClinicalTrials.gov. *Efficacy and Safety Study of TOOKAD® Soluble for Localised Prostate Cancer Compared to Active Surveillance. (PCM301)*. URL: http://clinicaltrials.gov/show/NCT01310894 (accessed 3 October 2013).

286. ClinicalTrials.gov. *CyberKnife Radiosurgery For Low & Intermediate Risk Prostate Cancer: Emulating HDR Brachytherapy Dosimetry*. URL: http://clinicaltrials.gov/show/NCT00643617 (accessed 3 October 2013).

287. ClinicalTrials.gov. *CyberKnife Radiosurgery for Organ-confined Prostate Cancer: Homogenous Dose Distribution*. URL: http://clinicaltrials.gov/show/NCT00643994 (accessed 3 October 2013).

288. ClinicalTrials.gov. *Multi-center Randomized Clinical Trial Irreversible Electroporation for the Ablation of Localized Prostate Cancer*. URL: http://clinicaltrials.gov/show/NCT01835977 (accessed 3 October 2013).

289. ClinicalTrials.gov. *Focal Therapy for Localised Prostate Cancer Using Irreversible Electroporation (Nano)*. URL: http://clinicaltrials.gov/show/NCT01726894 (accessed 3 October 2013).

290. ClinicalTrials.gov. *Safety and Efficacy of Irreversible Electroporation in Ablation of Prostate Cancer in Humans*. URL: http://clinicaltrials.gov/ct2/show/NCT01790451 (accessed 3 October 2013).

291. ClinicalTrials.gov. *Safety Study of MRI-guided Transurethral Ultrasound Ablation of Prostate Tissue to Treat Localized Prostate Cancer*. URL: http://clinicaltrials.gov/show/NCT01686958 (accessed 3 October 2013).

292. ClinicalTrials.gov. *Stereotactic Hypofractionated Radiosurgery for Early Stage Prostate Cancer*. URL: www.clinicaltrials.gov/show/NCT00969202 (accessed 3 October 2013).

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295. Svatek RS, Lee JJ, Roehrborn CG, Lippman SM, Lotan Y. Cost-effectiveness of prostate cancer chemoprevention – a quality of life-years analysis. *Cancer* 2008;**112**:1058–65. http://dx.doi.org/10.1002/cncr.23276

Appendix 1 Search strategy

Ablative therapies for prostate cancer: clinical effectiveness

Database: EMBASE (1974 to week 13, 2013), Ovid MEDLINE(R) (1946 to March week 3, 2013), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations (29 March 2013)

Ovid multifile search URL: https://shibboleth.ovid.com/

Search strategy

1. Prostatic Neoplasms/ use mesz
2. exp prostate cancer/ use oemez
3. (prostat$ adj3 (neoplasm$ or cancer or carcinoma or tumo?r$ or malignan$)).tw.
4. or/1-3
5. ablation techniques/ use mesz
6. ablation therapy/ use oemez
7. (ablation or ablative).ti.
8. brachytherapy/
9. interstitial radiation/ use oemez
10. brachytherap$.tw.
11. (seed$ adj3 implant$).tw.
12. ((interstitial or intracavit$ or implant$ or surface) adj3 radio$).tw
13. cryosurgery/
14. (cryotherap$ or cryoablat$ or cryosurg$).tw.
15. exp High-Intensity Focused Ultrasound Ablation/ use mesz
16. high intensity focused ultrasound/ use oemez
17. (hifu or "high intensity focused ultrasound").tw.
18. Photochemotherapy/ use mesz
19. photodynamic therapy/ use oemez
20. (photodynamic adj3 (therap$ or treat$)).tw.
21. (photosensitiv$ or phototherm$).tw.
22. exp Light Coagulation/
23. (laser adj3 (photocoagulat$ or coagulat$ or therap$ or treat$)).tw.
24. laser surgery/
25. laser coagulation/ use oemez
26. (laser adj3 (ablat$ or interstitial tumo?r)).tw.
27. radiofrequency interstitial tumo?r ablat$.tw.
28. rita.tw.
29. catheter ablation/
30. ((focal or focus$) adj3 (therap$ or treat$)).tw.
31. hemi?ablat$.tw.
32. or/5-31
33. 4 and 32
34. (external beam adj3 (radiotherapy or radiation)).tw.
35. ebrt.tw.
36. Radiotherapy, Conformal/ use mesz
37. external beam radiotherapy/ use oemez
38. ((active or expectant or conservative) adj3 (management or surveillance or treatment)).tw.
39. watchful waiting.tw.
40. Watchful Waiting/

41. conservative treatment/ use oemez
42. or/34-41
43. 4 and 42
44. exp clinical trial/ use oemez
45. randomized controlled trial.pt.
46. controlled clinical trial.pt.
47. randomization/ use oemez
48. randomi?ed.ab.
49. randomly.ab.
50. trial.ab.
51. groups.ab.
52. or/44-51
53. (exp animals/ or nonhuman/) not humans/
54. 52 not 53
55. 33 and 54
56. 43 and 54
57. 55 or 56
58. comparative study/ use mesz
59. controlled study/ use oemez
60. (compare$ or compara$).tw. use oemez
61. or/58-60
62. 61 and (33 or 43)
63. 62 not 53
64. 63 not 57
65. limit 64 to english
66. follow-up studies/ use mesz
67. time factors/ use mesz
68. Treatment outcome/ use oemez
69. major clinical study/ use oemez
70. survival rate/
71. (chang$ or evaluat$ or reviewed or baseline).tw.
72. (prospective$ or retrospective$).tw. use mesz
73. (cohort$ or case series).tw. use mesz
74. or/66-73
75. case report/ use oemez
76. case reports.pt.
77. 74 not (75 or 76)
78. 77 not 53
79. 33 and 78
80. 4 and (38 or 39 or 40 or 41)
81. 80 and 78
82. 79 or 81
83. 82 not (57 or 65)
84. limit 83 to english
85. 57 or 65 or 84
86. 85 not conference abstract.pt.
87. 86 not (letter or editorial or review or comment or note or short survey).pt.
88. remove duplicates from 87

Science Citation Index (1970 to 1 April 2013)

Bioscience Information Service (1956 to 1 April 2013)

ISI Web of Knowledge URL: http://wok.mimas.ac.uk/

Search strategy

1 (TS=(prostat* NEAR/3 (neoplasm* or cancer or carcinoma or tumour* or tumor* or malignan*))

2 (TS=(ablation or abalative))

3 (TS=brachytherap*)

4 (TS=(seed NEAR/3 implant*))

5 (TS=((interstitial or intracavit* or implant* or surface) NEAR/3 radio*))

6 (TS=(cryotherap* or cryoablat* or cryosurg*))

7 (TS=(hifu or "high intensity focused ultrasound"))

8 (TS=photochemotherap*)

9 (TS=(photodynamic NEAR/3 (therap* or treat*)))

10 (TS=(photosensitiv* or phototherm*))

11 (TS=light coagulat*)

12 (TS=(laser NEAR/3 (ablat* or interstitial)))

13 (TS=rita)

14 (TS=("radiofrequency interstitial" NEAR/2 ablat*))

15 (TS=catheter ablat*)

16 (TS=((focal or focus*) NEAR/3 (therap* or treat*)))

17 (TS= (hemi ablat* or hemiablat*))

18 (#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #15 or #16 or #17)

19 (#1 and #18)

20 (TS= ("external beam" NEAR/3 (radiotherap* or radiation)))

21 (TS=watchful waiting)

22 (TS=((active or expectant or conservative) NEAR/3 (management or surveillance or treatment)))

23 (#20 or #21 or #22)

24 (#1 and #23)

25 (#19 or #24)

26 (TS=(randomized or randomised))

27 (TS=randomly)

28 (#25 and (#26 or #27))

29 (TS=control group*)

30 (TS=control arm*)

31 (TS=comparative)

32 (TS=trial)

33 (#25 and (#29 or #30 or #31 or #32)) AND Language=(English)

34 (#19 not (#28 or #33)) AND Language=(English)

35 (#34 and su=oncology) AND Language=(English)

36 (#35 OR #33 OR #28) AND Document Types=(Article)

The Cochrane Library issue 3, 2013 (CENTRAL, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database, NHS EED)

URL: www3.interscience.wiley.com/

Search strategy

#1 MeSH descriptor Prostatic Neoplasms, this term only

#2 (prostat* NEAR/3 (neoplasm* or cancer or carcinoma or tumor* or tumour* or malignan*)):ti,ab,kw

#3 (#1 OR #2)

#4 MeSH descriptor Ablation Techniques, this term only

#5 MeSH descriptor Brachytherapy, this term only

#6 MeSH descriptor Cryosurgery, this term only

#7 MeSH descriptor High-Intensity Focused Ultrasound Ablation explode all trees

#8 MeSH descriptor Photochemotherapy, this term only

#9 MeSH descriptor Light Coagulation explode all trees

#10 MeSH descriptor Laser Therapy, this term only

#11 MeSH descriptor Catheter Ablation, this term only

#12 MeSH descriptor Radiotherapy, Conformal, this term only

#13 MeSH descriptor Watchful Waiting, this term only

#14 (ablation or ablative):ti,ab,kw

#15 (brachytherap*):ti,ab,kw or (seed* NEAR/3 implant*):ti,ab,kw or (cryotherap*):ti,ab,kw or (cryosurg*):ti,ab,kw or (cryoablat*):ti,ab,kw

#16 (radio* NEAR/3 (interstitial or intracavit* or implant* or surface)):ti,ab,kw 225 edit delete

#17 (hifu):ti,ab,kw or "high intensity focused ultrasound":

#18 (photosensitiv*):ti,ab,kw or (phototherm*):ti,ab,kw or (photodynamic NEAR/3 (therap* or treat*)):ti,ab,kw

#19 (rita):ti,ab,kw or "radiofrequency interstitial":ti,ab,kw

#20 (hemiablat*):ti,ab,kw or (hemi ablat*):ti,ab,kw or (focal NEAR/3 (therap* or treat*)):ti,ab,kw or (focus* NEAR/3 (therap* or treat*)):ti,ab,kw

#21 (laser near/3 (ablat* or interstitial or therap*)):ti,ab,kw or (laser near/3 (photocoagulat* or coagulat* or treat*)):ti,ab,kw

#22 "external beam" near/3 (radiotherap* or radiation):ti,ab,kw or (ebrt):ti,ab,kw

#23 (watchful waiting):ti,ab,kw or (active near/3 (management or surveillance or treatment)):ti,ab,kw or (expectant near/3 (management or surveillance or treatment)):ti,ab,kw or (conservative near/3 (management or surveillance or treatment)):ti,ab,kw

#24 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23)

#25 (#3 AND #24)

Scopus (1 April 2013)

URL: www.scopus.com/home.url

Search strategy

("prostate cancer")) AND ((TITLE-ABS-KEY(prostatectomy OR radation OR surveillance OR salvage) AND DOCTYPE(ip)) OR (TITLE-ABS-KEY(ablation OR brachytherapy OR cryotherapy OR hifu OR laser OR pdt) AND DOCTYPE(ip))) AND (LIMIT-TO(PUBYEAR, 2013) OR LIMIT-TO(PUBYEAR, 2012)) AND (LIMIT-TO (LANGUAGE, "English"))

Health Technology Assessment/Database of Abstracts of Reviews of Effects (September 2012)

Centre for Reviews and Dissemination URL: http://nhscrd.york.ac.uk/welcome.htm

Search strategy

1. MeSH DESCRIPTOR Prostatic Neoplasms
2. MeSH DESCRIPTOR Ablation Techniques
3. MeSH DESCRIPTOR cryosurgery EXPLODE ALL TREES
4. MeSH DESCRIPTOR High-Intensity Focused Ultrasound Ablation EXPLODE ALL TREES
5. MeSH DESCRIPTOR brachytherapy

6. MeSH DESCRIPTOR photochemotherapy EXPLODE ALL
7. MeSH DESCRIPTOR light coagulation EXPLODE ALL TREES
8. MeSH DESCRIPTOR Laser Therapy
9. MeSH DESCRIPTOR Catheter Ablation
10. MeSH DESCRIPTOR Radiotherapy, Conformal
11. MeSH DESCRIPTOR Watchful Waiting
12. (ebrt) OR (hifu) OR (rita)
13. (external beam) OR (hemiablat &or hemi ablat*) OR (ablat*)
14. (focal) OR (focus*)
15. (expectant) OR (conservative) OR (active)
16. (photosentitiv*) OR (phototherm*) OR (photodynamic)
17. (radiofrequency) OR (radiotherapy)
18. #2 OR #3 OR #4 OR #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
19. #1 AND #18

ClinicalTrials.gov (September 2012)

URL: http://clinicaltrials.gov/ct/gui/c/r

Search strategy

Condition=prostatic neoplasms

Interventions=brachytherapy or cryotherapy or cryoablation or cryosurgery or ablation or focal or focus* or hifu or high intensity focussed ultrasound or photo* or laser or coagulation

Current Controlled Trials (September 2012)

URL: www.controlled-trials.com/

Search strategy

Prostat% cancer

International Clinical Trials Registry Platform (ICTRP) (September 2012)

World Health Organization URL: www.who.int/ictrp/en/

Search strategy

Condition=prostat* cancer

Intervention= brachy* or cryo* or ablation or focal or focus* or hifu or photo* or coagulation

Additional searches for salvage prostatectomy after external beam radiotherapy

EMBASE (1980 to week 13, 2013), Ovid MEDLINE(R) (1946 to March week 3, 2013), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations (29 March 2013)

Ovid multifile search URL: https://shibboleth.ovid.com/

Search strategy

1. exp prostatic neoplasms/su use mesz
2. exp prostate cancer/su use emez
3. or/1-2

4. prostatic neoplasms/ use mesz
5. exp prostate cancer/ use emez
6. (cancer adj3 (prostate or prostatic)).tw.
7. (carcinoma adj3 (prostate or prostatic)).tw.
8. (neoplas$ adj3 (prostate or prostatic)).tw.
9. (malignan$ adj3 (prostate or prostatic)).tw.
10. or/4-9
11. prostatectomy/
12. (radical adj5 prostatectom$).tw.
13. surgical procedures,operative/ use mesz
14. surgery/ use emez
15. su.fs.
16. (surgery or surgical or surgeon$).tw.
17. (resect $ or operation$ or operate$).tw.
18. or/11-17
19. 10 and 18
20. 3 or 19
21. salvage therapy/
22. (salvage adj5 prostat$).tw.
23. 21 or 22
24. 20 and 23
25. Neoplasm Recurrence, Local/su use mesz
26. Tumor Recurrence/su use emez
27. 10 and (25 or 26)
28. 24 or 27
29. exp clinical trial/ use emez
30. randomized controlled trial.pt.
31. controlled clinical trial.pt.
32. randomization/ use emez
33. randomi?ed.ab.
34. placebo.ab.
35. drug therapy.fs.
36. randomly.ab.
37. trial.ab.
38. groups.ab.
39. or/29-38
40. comparative study/ use mesz
41. follow-up studies/ use mesz
42. time factors/ use mesz
43. Treatment outcome/ use emez
44. major clinical study/ use emez
45. controlled study/ use emez
46. clinical trial/ use emez
47. (preoperat$ or pre operat$).mp. use mesz
48. (chang$ or evaluat$ or reviewed or baseline).tw.
49. (prospective$ or retrospective$).tw. use mesz
50. (cohort$ or case series).tw. use mesz
51. (compare$ or compara$).tw. use emez
52. case report/ use emez
53. case reports.pt.
54. or/39-51 (1)
55. 54 not (52 or 53)
56. 28 and 55

57. (exp animals/ or nonhuman/) not humans/
58. 56 not 57
59. 58 not (conference abstract or letter or editorial or review or comment or note or short
60. limit 59 to english language
61. remove duplicates from 60

The Cochrane Library issue 3, 2013 (CENTRAL, CDSR, DARE, HTA Database, NHS EED)

URL: www3.interscience.wiley.com/

Search strategy

#1 MeSH descriptor: [Prostatic Neoplasms]

#2 ((prostate or prostatic) near/3 cancer):ti,ab,kw

#3 ((prostate or prostatic) near/3 carcinoma):ti,ab,kw

#4 ((prostate or prostatic) near/3 neoplas*):ti,ab,kw

#5 ((prostate or prostatic) near/3 malignan*):ti,ab,kw

#6 #1 or #2 or #3 or #4 or #5 4014

#7 MeSH descriptor: [Prostatectomy] explode all trees

#8 (radical near/5 prostatectom$) .:ti,ab,kw

#9 #7 or #8

#10 #6 and #9

#11 MeSH descriptor: [Salvage Therapy] explode all trees

#12 salvage near/5 prostat*

#13 #11 or #12

#14 #10 and #13

Ablation therapies for prostate cancer: quality of life

EMBASE (1980 to week 13, 2013), Ovid MEDLINE(R) (1946 to March week 3, 2013), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations (1 April 2013)

Ovid multifile search URL: https://shibboleth.ovid.com/

Search strategy

1. quality of life/
2. quality adjusted life year/
3. "Value of Life"/ use mesz
4. health status indicators/ use mesz

5. health status/ use emez
6. sickness impact profile/ use mesz
7. disability evaluation/ use mesz
8. disability/ use emez
9. activities of daily living/ use mesz
10. exp daily life activity/ use emez
11. cost utility analysis/ use emez
12. rating scale/
13. questionnaires/
14. (quality adj1 life).tw.
15. quality adjusted life.tw.
16. disability adjusted life.tw.
17. (qaly? or qald? or qale? or qtime? or daly?).tw.
18. (euroqol or euro qol or eq5d or eq 5d).tw.
19. (hql or hqol or h qol or hrqol or hr qol).tw.
20. (hye or hyes).tw
21. health$ year$ equivalent$.tw.
22. (hui or hui1 or hui2 or hui3).tw.
23. (health adj3 (utilit$ or disutili$)).tw.
24. (health adj3 (state or status)).tw.
25. (sf36 or sf 36 or short form 36 or shortform 36).tw.
26. (sf6 or sf 6 or short form 6 or shortform 6).tw.
27. (sf12 or sf 12 or short form 12 or shortform 12).tw.
28. (sf16 or sf 16 or short form 16 or shortform 16).tw.
29. (sf20 or sf 20 or short form 20 or shortform 20).tw.
30. willingness to pay.tw
31. standard gamble.tw.
32. trade off.tw.
33. conjoint analys?s.tw.
34. discrete choice.tw.
35. or/1-34
36. (case report or editorial or letter).pt.
37. case report/
38. Prostatic Neoplasms/ use mesz
39. exp prostate cancer/ use emez
40. (prostat$ adj3 (neoplasm$ or cancer or carcinoma or tumo?r$ or malignan$)).tw. (186141)
41. or/38-40
42. ablation techniques/ use mesz
43. ablation therapy/ use emez
44. (ablation or ablative).ti.
45. brachytherapy/
46. interstitial radiation/ use emez
47. brachytherap$.tw.
48. (seed$ adj3 implant$).tw.
49. ((interstitial or intracavit$ or implant$ or surface) adj3 radio$).tw.
50. cryosurgery/
51. (cryotherap$ or cryoablat$ or cryosurg$).tw.
52. exp High-Intensity Focused Ultrasound Ablation/ use mesz
53. high intensity focused ultrasound/ use emez
54. (hifu or "high intensity focused ultrasound").tw.
55. Photochemotherapy/ use mesz
56. photodynamic therapy/ use emez
57. (photodynamic adj3 (therap$ or treat$)).tw.

58. (photosensitiv$ or phototherm$).tw.
59. exp Light Coagulation/
60. (laser adj3 (photocoagulat$ or coagulat$ or therap$ or treat$)).tw.
61. laser surgery/
62. laser coagulation/ use emez
63. (laser adj3 (ablat$ or interstitial tumo?r)).tw.
64. radiofrequency interstitial tumo?r ablat$.tw.
65. rita.tw.
66. catheter ablation/
67. ((focal or focus$) adj3 (therap$ or treat$)).tw.
68. hemi?ablat$.tw.
69. or/42-68
70. 41 and 69
71. (external beam adj3 (radiotherapy or radiation)).tw.
72. ebrt.tw
73. Radiotherapy, Conformal/ use mesz
74. external beam radiotherapy/ use emez
75. ((active or expectant or conservative) adj3 (management or surveillance or treatment)).tw.
76. watchful waiting.tw
77. Watchful Waiting/
78. conservative treatment/ use emez
79. or/71-78
80. 41 and 79
81. 70 or 80
82. 35 and 81
83. 82 not (36 or 37)
84. remove duplicates from 83
85. limit 84 to english language

Science Citation Index (1995 to 2 April 2013)

ISI Web of Knowledge URL: http://wok.mimas.ac.uk/

Search strategy

1 (TS=(prostat* NEAR/3 (neoplasm* or cancer or carcinoma or tumour* or tumor* or malignan*)))

2 (TS=(ablation or abalative))

3 (TS=brachytherap*)

4 (TS=(seed NEAR/3 implant*))

5 (TS=((interstitial or intracavit* or implant* or surface) NEAR/3 radio*))

6 (TS=(cryotherap* or cryoablat* or cryosurg*))

7 (TS=(hifu or "high intensity focused ultrasound"))

8 (TS=photochemotherap*)

9 (TS=(photodynamic NEAR/3 (therap* or treat*)))

10 (TS=(photosensitiv* or phototherm*))

11 (TS=light coagulat*)

12 (TS=(laser NEAR/3 (ablat* or interstitial)))

13 (TS=rita)

14 (TS=("radiofrequency interstitial" NEAR/2 ablat*))

15 (TS=catheter ablat*)

16 (TS=((focal or focus*) NEAR/3 (therap* or treat*)))

17 (TS= (hemi ablat* or hemiablat*))

18 (#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #15 or #16 or #17)

19 (#1 and #18)

20 (TS= ("external beam" NEAR/3 (radiotherap* or radiation)))

21 (TS=watchful waiting)

22 (TS=((active or expectant or conservative) NEAR/3 (management or surveillance or treatment)))

23 (#20 or #21 or #22)

24 (#1 and #23)

25 (#19 or #24)

26 (TS=quality of life)

27 (TS=quality adjusted life)

28 (TS=disability adjusted life)

29 (TS= (qaly* OR qald* OR qale* OR qtime* OR daly))

30 (TS=(hql OR hqol OR h qol OR hrqol OR hr qol))

31 (TS=(euroqol* OR euro qol* OR eq5d OR eq 5d))

32 (TS=health* year* equivalent*)

33 (TS=(hye OR hyes OR hui OR hui1 OR hui2 OR hui3))

34 (TS=(health utilit* OR disutilit*)

35 (TS=willingness to pay)

36 (TS= conjoint analys*)

37 (TS=trade off)

38 (TS=discrete choice.)

39 (TS=standard gamble)

40 (#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)

#41 #25 AND #40 AND Language=(English) AND Document Types=(Article)

Cost-effectiveness Analysis Registry, September 2012

URL: https://research.tufts-nemc.org/cear4/default.asp

Search strategy

Prostate cancer or prostatic cancer

Ablation therapies for prostate cancer: economic evaluations

NHS Economic Evaluation Database, September 2012

Centre for Reviews and Dissemination URL: http://nhscrd.york.ac.uk/welcome.htm

Search strategy

1. MeSH DESCRIPTOR Prostatic Neoplasms
2. MeSH DESCRIPTOR Ablation Techniques
3. MeSH DESCRIPTOR cryosurgery EXPLODE ALL TREES
4. MeSH DESCRIPTOR High-Intensity Focused Ultrasound Ablation EXPLODE ALL TREES
5. MeSH DESCRIPTOR brachytherapy
6. MeSH DESCRIPTOR photochemotherapy EXPLODE ALL
7. MeSH DESCRIPTOR light coagulation EXPLODE ALL TREES
8. MeSH DESCRIPTOR Laser Therapy
9. MeSH DESCRIPTOR Catheter Ablation
10. MeSH DESCRIPTOR Radiotherapy, Conformal
11. MeSH DESCRIPTOR Watchful Waiting
12. (ebrt) OR (hifu) OR (rita)
13. (external beam) OR (hemiablat &or hemi ablat*) OR (ablat*)
14. (focal) OR (focus*)
15. (expectant) OR (conservative) OR (active)
16. (photosentitiv*) OR (phototherm*) OR (photodynamic)
17. (radiofrequency) OR (radiotherapy)
18. #2 OR #3 OR #4 OR #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
19. #1 AND #18

IDEAS, September 2012

Research Papers in Economics (RePEc) URL: http://ideas.repec.org/

Search strategy

(prostate | prostatic) + cancer

Websites consulted

Agency for Healthcare Research and Quality (URL: www.ahrq.gov/).

American Society of Clinical Oncology (URL: www.asco.org).

American Urological Association (URL: www.auanet.org/).

Australian Safety and Efficacy Register of New Interventional Procedures (URL: www.surgeons.org/for-health-professionals/audits-and-surgical-research/asernip-s).

Belgian Health Care Knowledge Centre (KCE) (URL: https://kce.fgov.be/).

BAUS (URL: www.baus.org.uk/).

Canadian Agency for Drugs and Technologies in Health (URL: www.cadth.ca/).

Cancer Research UK (URL: http://info.cancerresearchuk.org/cancerstats/).

European Association of Urology (URL: www.uroweb.org/).

French National Authority for Health (HAS) (URL: www.has-sante.fr/).

Health Information and Quality Authority (URL: www.hiqa.ie/).

Institute for Clinical and Economic Review (URL: www.icer-review.org/).

Institute for Quality and Efficiency in Health Care (URL: www.iqwig.de/).

Medical Services Advisory Committee, Australia (URL: http://www.msac.gov.au/).

National Comprehensive Cancer Network (URL: www.nccn.org/index.asp).

National Institute for Health and Care Excellence (URL: www.nice.org.uk/).

NHS Quality Improvement Scotland (URL: www.healthcareimprovementscotland.org/).

Appendix 2 Data extraction form

Data Extraction Form

Ablative therapy for people with localised prostate cancer: systematic review and economic modelling evaluation

Reviewer ID: Data extraction date:

Study ID (Author, year): Language if non-English:
Publication status: full-text papers / conference abstract / personal communication / other unpublished reports (specify)
Study IDs of any linked reports:
Reporting Institution:
Hospital(s):
Study design
Aim of the study:
Study design: ☐ RCT ☐ Non-randomised comparative study ☐ Registry report ☐ Case series (ablative only)
Prospective/ Retrospective/ Unclear/ Not reported
For non-RCTs and case series, was patients recruitment consecutive: Yes /No / not reported
Intervention :
Comparator :
For comparative studies, patients in the groups were recruited during the same period/different period/not reported

Number of study centres: Single centre / multicentre n= / not reported Setting: hospital / other: Country:
Study start – end dates: Duration of study:
Length of follow-up:
Source of funding:

Patients			
Inclusion criteria:			
Exclusion criteria:			
Baseline Patient Characteristics			
	Intervention:	**Comparator:**	**Total**
Number of patients enrolled			
Number randomised (RCTs only)			
Withdrew/lost to follow-up, with reasons			
Number analysed			
Age (Mean/median, SD/range)			
BMI (Mean/median, SD/range)			
Co-morbidities, including previous abdominal or pelvic surgery, previous pelvic radiotherapy, n/N (%):			
Disease severity			
PSA level, ng/ml, n, mean(SD) / median (range); if categorical, specify n, mean(SD) / median (range) for each category			

Clinical stage T1, n T2, n T3, n T4, n Staging method: (e.g. digital rectal examination, MRI)			
Biopsy Gleason Score ≤ 6, n 7, n 8-10, n			
Prostate size, ml, mean (SD) / median (range)			
Erectile dysfunction, n/N (%), specify measure and whether validated or not:			

Intervention(s)
Definition of focal therapy Yes ☐ No ☐ If yes, Tissues preservation ☐ Subtotal ☐ Partial ☐ Nerve sparing prostate ablation ☐ Posterior hockey stick ☐ Hyperfocal ☐ Hemiablation ☐ Targeted focal therapy ☐ Anterior hockey stick ablation ☐ Zonal ablation ☐ Other..... **Cryotherapy** Name, Manufacturer and Model of the equipment:

HIFU Name, Manufacturer and Model of the equipment:
PDT Name, Manufacturer and Model of the equipment:
RITA Name, Manufacturer and Model of the equipment:
Laser ablation Name, Manufacturer and Model of the equipment:
Brachytherapy Radiation source: Iodine ☐ Palladium ☐ Caesium ☐ Low dose rate (permanent seeds) ☐ High dose rate (temporary seeds) ☐ Dose:

Comparator
Prostatectomy Yes ☐ No ☐ If yes, Open n/N (%): Laparoscopic n/N (%): Robot-assisted n/N (%): Type of prostatectomy not specified ☐
Active surveillance Number of assessments: Definition of failure:
EBRT Name, Manufacturer and Model of the equipment: Dose:

Efficacy outcomes			
	Timing	**Intervention:**	**Comparator:**
Disease free survival, n/N (%)			
Overall survival n/N (%)			
Biochemical disease-free status	-	-	-
PSA control n/N (%)			
PSA level ng/ml			
Positive biopsy on follow up n/N (%)			
Re-intervention rates n/N (%)			
Functional outcomes			
n/N (%), mean (SD)/median (range) score	**Timing**	**Intervention:**	**Comparator:**
Sexual (penile erection) function (validated score or as defined by trialists) ☐ International Index of Erectile Dysfunction ☐ Other measure:			
Urinary continence (validated score, or as defined by trialists) ☐ ≤1 thin pad per day ☐ Other measure:			
Faecal continence (validated score, or as defined by trialists) ☐ ICIQ-BS ☐ Other measure:			

Other complications:			

Adverse effects			
	Timing	**Intervention:**	**Comparator:**
Urethral sloughing n/N (%)			
Recto-urethral fistula formation n/N (%)			
Urethral stricture formation n/N (%)			
Acute urinary retention n/N (%)			
Dysuria n/N (%)			
Pelvic pain n/N (%)			
Rectal injury n/N (%)			
Perioperative death n/N (%)			
Others			
Quality of life outcomes			
Mean (SD)/median (range) score (per category if applicable)	**Timing**	**Intervention:**	**Comparator:**
☐ Generic QoL measure: ☐ Disease specific QoL measure: ☐ Other validated measure:			

Procedural outcomes		
	Intervention:	**Comparator:**
Procedure time (min), reported as mean/median		
Nature of anaesthetic (e.g. general, local)		
Length of hospital stay (days), reported as mean/median		

Procedures done in the centre each year, mean (SD) / median (range)		
Surgeon competence (as reported by the trialists)		
Abandonment n/N (%)		
Conclusion as reported by the authors of the study		
Additional information and comments		

Appendix 3 Cochrane risk-of-bias form for randomised controlled trials

Ablative therapy for people with localised prostate cancer: systematic review and economic modelling evaluation

Study ID	Reviewer ID	Date
Domain	Supporting quote	Reviewer's judgement
Selection bias		
Random sequence generation[i] Allocation concealment[ii]		
Performance bias		
Blinding of participants and personnel[iii] *Outcome 1:*		
Blinding of participants and personnel[iii] *Outcome 2:*		
Blinding of participants and personnel[iii] *Outcome 3:*		
Blinding of participants and personnel[iii] *Outcome 4:*		
Detection bias		
Blinding of outcome assessment[iv] *Outcome 1:*		
Blinding of outcome assessment[iv] *Outcome 2:*		
Blinding of outcome assessment[iv] *Outcome 3:*		
Blinding of outcome assessment[iv] *Outcome 4:*		
Attrition bias		
Incomplete outcome data[v] *Outcome 1:*		
Incomplete outcome data[v] *Outcome 2:*		
Incomplete outcome data[v] *Outcome 3:*		

Study ID	Reviewer ID	Date
Incomplete outcome data[v] *Outcome 4:*		
Reporting bias		
Selective reporting[vi]		
Other bias		
Other sources of bias[vii]		

i Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether or not it should produce comparable groups.
ii Describe the method used to conceal the allocation sequence in sufficient detail to determine whether or not intervention allocations could have been foreseen in advance of, or during, enrolment.
iii Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. *Provide any information relating to whether or not the intended blinding was effective.*
iv Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. *Provide any information relating to whether or not the intended blinding was effective.*
v Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether or not attrition and exclusions were reported, the *numbers in each intervention group* (compared with total randomised participants), *reasons for attrition/exclusions* where reported, and *any reinclusions in analyses performed by the review authors*.
vi State how the possibility of selective outcome reporting was examined by the review authors, and what was found.
vii State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.

Appendix 4 Cochrane risk-of-bias form for non-randomised controlled studies

Cochrane risk-of-bias table (non-randomised studies)

Ablative therapy for people with localised prostate cancer: systematic review and economic modelling evaluation

Assessor initial: Date evaluated:

Study ID:

Item			Judgement[a]	Description (quote from paper, or describe key information)
1. Sequence generation				
2. Allocation concealment				
3a. Confounding	Outcome 1 (Efficacy)	**Confounders balanced[b,c]**		
	PSA score balanced at baseline			
	Difference between risk group (D'Amico definition)			
3b. Confounding	Outcome 2 (Functional outcomes)	**Confounders balanced[b,c]**		
Erectile function	Pre-op status			
	Age			
Urinary function	Pre-op status			
	Age			
Bowel function	Pre-op status			
	Age			
3c. Confounding	Outcome 3 (Quality of life)	**Confounders balanced[c,d]**		
	Age			
4a. Blinding?	Outcome 1 (Efficacy outcomes)			
4b. Blinding?	Outcome 2 (Erectile function)			
	Outcome 2 (Urinary function)			

Item		Judgement[a]	Description (quote from paper, or describe key information)
	Outcome 2 (Bowel function)		
4d. Blinding?	Outcome 3 (Quality of life)		
5a. Incomplete outcome data addressed?	Outcome 1 (Efficacy outcomes)		
5b. Incomplete outcome data addressed?	Outcome 2 (Erectile function)		
	Outcome 2 (Urinary function)		
	Outcome 2 (Bowel function)		
5c. Incomplete outcome data addressed?	Outcome 3 (Quality of life)		
6a. Free of selective reporting?	Outcome 1 (Efficacy outcomes)		
6b. Free of selective reporting?	Outcome 2 (Erectile function)		
	Outcome 2 (Urinary function)		
	Outcome 2 (Bowel function)		
6c. Free of selective reporting?	Outcome 3 (Quality of life)		
7. Free of other bias?			
8. A priori protocol?[e]			
9. A priori analysis plan?[f]			

a Some items on *low/high risk/unclear scale* (single-line border), some on *yes/no/unclear scale* (dashed border). For all items, record 'unclear' if inadequate reporting prevents a judgement being made.
b Confounders listed by order of importance (high to low importance) based on list of confounders considered important at the outset and defined in the protocol for the review.

Low risk:
2 balanced = low risk
1 balanced, 1 unclear = low risk

High risk:
2 unbalanced = high risk
1 unbalanced, 1 unclear = high risk

Unclear:
2 unclear = unclear

c Note, if confounders are unbalanced but adjusted for in the analysis, the imbalance is no longer a serious concern for risk of bias.
d For quality of life outcomes where only one confounder was considered relevant, the following decision rules were applied:

Low risk:
1 balanced = low risk

High risk:
1 unbalanced = high risk

Unclear:
1 unclear = unclear

e Did the researchers write a protocol defining the study population, intervention and comparator, primary and other outcomes, data collection methods, etc., *in advance of* starting the study?
f Did the researchers have an analysis plan defining the primary and other outcomes, statistical methods, subgroup analyses, etc., *in advance of* starting the study?

General decision rules

Where a paper does not report details of confounders/other source of bias this should be judged as unclear.

Where a paper does not report considered outcome this should be judged as not applicable.

Allocation concealment should be judged as high risk of bias if groups are allocated by factors such as surgeon decision, patient preference. Allocation by hospital/institution = low risk. Where no details are given, judge as unclear.

Absence of blinding is likely to have low risk of bias for perioperative and efficacy outcomes.

Free of other bias: default is low risk unless there is a fundamental flaw with the study (e.g. inadequate follow-up time for dysfunction outcomes, data not presented for learning curve effects if these are likely to influence outcomes).

Judging overall direction of bias for individual outcomes: if confounding is judged unbalanced, outcome should be judged as high risk of bias.

Further guidance:

Refer to tables 13.2.a and b in Reeves BC, Deeks J, Higgins JP, Wells GA on behalf of the Cochrane Non-Randomised Studies Methods Group. Chapter 13: Including non-randomized studies. In Higgins JP, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* (updated March 2011). Cochrane; 2011. URL: www.cochrane-handbook.org (accessed March 2011).

Appendix 5 Quality assessment form for case series

Checklist of quality assessment of non-randomised studies

Ablative therapy for people with localised prostate cancer: systematic review and economic modelling evaluation

Assessor initial: Date evaluated:

Study ID:

Criteria	Yes	No	Unclear	Comments
1. Were participants a representative sample selected from a relevant patient population, e.g. randomly selected from those seeking treatment despite age, duration of disease, primary or secondary disease, and severity of disease?				
2. Were the inclusion/exclusion criteria of participants clearly described?				
3. Were participants entering the study at a similar point in their disease progression, i.e. severity of disease?				
4. Was selection of patients consecutive?				
5. Was data collection undertaken prospectively?				
6. *Were the groups comparable on demographic characteristics and clinical features?*	N/A	N/A	N/A	N/A
7. Was the intervention (and comparison) clearly defined?				
8. Was the intervention undertaken by someone experienced at performing the procedure?[1]				
9. Were the staff, place and facilities where the patients were treated appropriate for performing the procedure? (e.g. access to back-up facilities in hospital or special clinic)				
10. Were any of the important outcomes considered?				
11. Were objective (valid and reliable) outcome measures used?				
12. Was the assessment of main outcomes blind?	N/A	N/A	N/A	N/A
13. Was follow-up long enough (≥ 1 year) to detect important effects on outcomes of interest?				
14. Was information provided on non-respondents, dropouts?[2]				
15. Were the withdrawals/dropouts similar in characteristics to those who completed the study and therefore unlikely to cause bias?[3]				

APPENDIX 5

Criteria	Yes	No	Unclear	Comments
16. Was length of follow-up similar between comparison groups?	N/A	N/A	N/A	N/A
17. Were the important prognostic factors identified, e.g. age, disease severity, pre-operative status?[4]				
18. Were the analyses adjusted for confounding factors?	N/A	N/A	N/A	N/A

N/A, not applicable.

Note

1. 'Yes' if the practitioner received training on conducting the procedure before or conducted same kind of procedure before, i.e. no learning curve.
2. 'No' if participants were from those whose follow-up records were available (retrospective).
3. 'Yes' if no withdrawal/dropout; 'no' if dropout rate $\geq$ 30% or differential dropout, e.g. those having most severe disease died during follow-up but the death was not due to treatment; no description of those lost.
4. 'Yes' if two or more than two factors were identified.

The same form was adapted to assess the quality of case series by excluding questions 6, 12, 16 and 18.

Appendix 6 List of included studies

Primary review: included studies

Additional studies listed are linked to the relevant named study, and data were extracted from all of them.

Randomised controlled trials (four studies)

Crook 2011

Crook JM, Gomez-Iturriaga A, Wallace K, Ma C, Fung S, Alibhai S, *et al.* Comparison of health-related quality of life 5 years after spirit: surgical prostatectomy versus interstitial radiation intervention trial. *J Clin Oncol* 2011;**29**:362–8.

Donnelly 2010

Donnelly BJ, Saliken JC, Brasher PMA, Ernst SD, Rewcastle JC, Lau H, *et al.* A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer. *Cancer* 2010;**116**:323–30.

Robinson JW, Donnelly BJ, Siever JE, Saliken JC, Ernst SD, Rewcastle JC, *et al.* A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer: quality of life outcomes. *Cancer* 2009;**115**:4695–704.

Giberti 2009

Giberti C, Chiono L, Gallo F, Schenone M, Gastaldi E. Radical retropubic prostatectomy versus brachytherapy for low-risk prostatic cancer: a prospective study. *World J Urol* 2009;**27**:607–12.

Paulson 1982

Paulson DF, Lin GH, Hinshaw W, Stephani S. Radical surgery versus radiotherapy for adenocarcinoma of the prostate. *J Urol* 1982;**128**:502–4.

Paulson DF. Management of patients with prostatic adenocarcinoma. *Aktuelle Urol* 1982;**31**:91–5.

Non-randomised comparative studies involving brachytherapy (39 studies)

Alemozaffar 2011

Alemozaffar M, Regan MM, Cooperberg MR, Wei JT, Michalski JM, Sandler HM, *et al.* Prediction of erectile function following treatment for prostate cancer. *JAMA* 2011;**306**:1205–14.

Arvold 2011

Arvold ND, Chen MH, Moul JW, Moran BJ, Dosoretz DE, Baez LL, *et al.* Risk of death from prostate cancer after radical prostatectomy or brachytherapy in men with low or intermediate risk disease. *J Urol* 2011;**186**:91–6.

Barret 2013

Barret E, Ahallal Y, Sanchez-Salas R, Galiano M, Cosset JM, Validire P, *et al.* Morbidity of focal therapy in the treatment of localized prostate cancer. *Eur Urol* 2013;**63**:618–22.

Beyer 2000

Beyer DC, Brachman DG. Failure free survival following brachytherapy alone for prostate cancer: comparison with external beam radiotherapy. *Radiother Oncol* 2000;**57**:263–7.

Boettcher 2012
Boettcher M, Haselhuhn A, Jakse G, Brehmer B, Kirschner-Hermanns R. Overactive bladder syndrome: an underestimated long-term problem after treatment of patients with localized prostate cancer? *BJU Int* 2012;**109**:1824–30.

Borchers 2004
Borchers H, Kirschner-Hermanns R, Brehmer B, Tietze L, Reineke T, Pinkawa M, *et al.* Permanent 125I-seed brachytherapy or radical prostatectomy: a prospective comparison considering oncological and quality of life results. *BJU Int* 2004;**94**:805–11.

Bradley 2004
Bradley EB, Bissonette EA, Theodorescu D. Determinants of long-term quality of life and voiding function of patients treated with radical prostatectomy or permanent brachytherapy for prostate cancer. *BJU Int* 2004;**94**:1003–9.

Buron 2007
Buron C, Le Vu B, Cosset JM, Pommier P, Peiffert D, Delannes M, *et al.* Brachytherapy versus prostatectomy in localized prostate cancer: results of a French multicenter prospective medico-economic study. *Int J Radiat Oncol Biol Phys* 2007;**67**:812–22.

Chen 2009
Chen RC, Clark JA, Talcott JA. Individualizing quality-of-life outcomes reporting: how localized prostate cancer treatments affect patients with different levels of baseline urinary, bowel, and sexual function. *J Clin Oncol* 2009;**27**:3916–22.

Coen 2012
Coen JJ, Zietman AL, Rossi CJ, Grocela JA, Efstathiou JA, Yan Y, *et al.* Comparison of high-dose proton radiotherapy and brachytherapy in localized prostate cancer: a case-matched analysis. *Int J Radiat Oncol Biol Phys* 2012;**82**:e25–31.

Crook 2011
Crook JM, Gomez-Iturriaga A, Wallace K, Ma C, Fung S, Alibhai S, *et al.* Comparison of health-related quality of life 5 years after spirit: surgical prostatectomy versus interstitial radiation intervention trial. *J Clin Oncol* 2011;**29**:362–8.

D'Amico 1998
D'Amico AV, Whittington R, Bruce M, Schultz D, Blank K, Broderick GA, *et al.* Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998;**280**:969–74.

D'Amico 2003
D'Amico AV, Tempany CM, Schultz D, Cormack RA, Hurwitz M, Beard C, *et al.* Comparing PSA outcome after radical prostatectomy or magnetic resonance imaging-guided partial prostatic irradiation in select patients with clinically localized adenocarcinoma of the prostate. *Urology* 2003;**62**:1063–7.

Eade 2008
Eade TN, Horwitz EM, Ruth K, Buyyounouski MK, D'Ambrosio DJ, Feigenberg SJ, *et al.* A comparison of acute and chronic toxicity for men with low-risk prostate cancer treated with intensity-modulated radiation therapy or 125I permanent implant. *Int J Radiat Oncol Biol Phys* 2008;**71**:338–45.

Elliott 2007
Elliott SP, Meng MV, Elkin EP, McAninch JW, DuChane J, Carroll PR. Incidence of urethral stricture after primary treatment for prostate cancer: data from CaPSURE. *J Urol* 2007;**178**:529–34.

Ferrer 2008

Ferrer M, Suarez JF, Guedea F, Fernandez P, Macias V, Marino A, *et al.* Health-related quality of life 2 years after treatment with radical prostatectomy, prostate brachytherapy, or external beam radiotherapy in patients with clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;**72**:421–32.

Guedea F, Ferrer M, Pera J, Aguilo F, Boladeras A, Suarez JF, *et al.* Quality of life two years after radical prostatectomy, prostate brachytherapy or external beam radiotherapy for clinically localised prostate cancer: the Catalan Institute of Oncology/Bellvitge Hospital experience. *Clin Transl Oncol* 2009;**11**:470–8.

Pardo Y, Guedea F, Aguilo F, Fernandez P, Macias V, Marino A, *et al.* Quality-of-life impact of primary treatments for localized prostate cancer in patients without hormonal treatment. *J Clin Oncol* 2010;**28**:4687–96.

Frank 2007

Frank SJ, Pisters LL, Davis J, Lee AK, Bassett R, Kuban DA. An assessment of quality of life following radical prostatectomy, high dose external beam radiation therapy and brachytherapy iodine implantation as monotherapies for localized prostate cancer. *J Urol* 2007;**177**:2151–6.

Goldner 2012a

Goldner G, Potter R, Battermann JJ, Schmid MP, Kirisits C, Sljivic S, *et al.* Comparison of seed brachytherapy or external beam radiotherapy (70 Gy or 74 Gy) in 919 low-risk prostate cancer patients. *Strahlenther Onkol* 2012;**188**:305–10.

Goldner 2012b

Goldner G, Potter R, Battermann JJ, Kirisits C, Schmid MP, Sljivic S, *et al.* Comparison between external beam radiotherapy (70 Gy/74 Gy) and permanent interstitial brachytherapy in 890 intermediate risk prostate cancer patients. *Radiother Oncol* 2012;**103**:223–7.

Kibel 2012

Kibel AS, Ciezki JP, Klein EA, Reddy CA, Lubahn JD, Haslag-Minoff J, *et al.* Survival among men with clinically localized prostate cancer treated with radical prostatectomy or radiation therapy in the prostate specific antigen era. *J Urol* 2012;**187**:1259–65.

Ciezki JP, Klein EA, Angermeier K, Ulchaker J, Chehade N, Altman A, *et al.* A retrospective comparison of androgen deprivation (AD) vs. no AD among low-risk and intermediate-risk prostate cancer patients treated with brachytherapy, external beam radiotherapy, or radical prostatectomy. *Int J Radiat Oncol Biol Phys* 2004;**60**:1347–50.

Burdick MJ, Reddy CA, Ulchaker J, Angermeier K, Altman A, Chehade N, *et al.* Comparison of biochemical relapse-free survival between primary Gleason score 3 and primary Gleason score 4 for biopsy Gleason score 7 prostate cancer. *Int J Radiat Oncol Biol Phys* 2009;**73**:1439–45.

Vassil AD, Murphy ES, Reddy CA, Angermeier KW, Altman A, Chehade N, *et al.* Five year biochemical recurrence free survival for intermediate risk prostate cancer after radical prostatectomy, external beam radiation therapy or permanent seed implantation. *Urology* 2010;**76**:1251–7.

Nepple KG, Stephenson AJ, Kallogjeri D, Michalski J, Grubb RL, III, Strope SA, *et al.* Mortality after prostate cancer treatment with radical prostatectomy, external-beam radiation therapy, or brachytherapy in men without comorbidity. *Eur Urol* 2013;**64**:372–8.

Kirschner-Hermanns 2008
Kirschner-Hermanns R, Brehmer B, Borchers H, Kahle C, Eble MJ, Reineke T, *et al.* Do patients with urodynamically proven infravesical obstruction and detrusor overactivity have a higher risk for long-term bothersome symptoms after brachytherapy in comparison to patients treated with radical prostatectomy for localized prostate cancer? *Curr Urol* 2008;**2**:135–41.

Kobuke 2009
Kobuke M, Saika T, Nakanishi Y, Ebara S, Manabe D, Uesugi T, *et al.* Prospective longitudinal comparative study of health-related quality of life in patients treated with radical prostatectomy or permanent brachytherapy for prostate cancer. *Acta Med Okayama* 2009;**63**:129–35.

Kupelian 2004
Kupelian PA, Potters L, Khuntia D, Ciezki JP, Reddy CA, Reuther AM, *et al.* Radical prostatectomy, external beam radiotherapy > 72 Gy, external beam radiotherapy <= 72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1–T2 prostate cancer. *Int J Radiat Oncol Biol Phys* 2004;**58**:25–33.

Lee 2001
Lee WR, Hall MC, McQuellon RP, Case LD, McCullough DL. A prospective quality-of-life study in men with clinically localized prostate carcinoma treated with radical prostatectomy, external beam radiotherapy, or interstitial brachytherapy. *Int J Radiat Oncol Biol Phys* 2001;**51**:614–23.

Litwin 2004
Litwin MS, Sadetsky N, Pasta DJ, Lubeck DP. Bowel function and bother after treatment for early stage prostate cancer: a longitudinal quality of life analysis from CaPSURE. *J Urol* 2004;**172**:515–19.

Malcolm 2010
Malcolm JB, Fabrizio MD, Barone BB, Given RW, Lance RS, Lynch DF, *et al.* Quality of life after open or robotic prostatectomy, cryoablation or brachytherapy for localized prostate cancer. *J Urol* 2010;**183**:1822–9.

Mohamed 2012
Mohamed NE, Bovbjerg DH, Montgomery GH, Hall SJ, Diefenbach MA. Pretreatment depressive symptoms and treatment modality predict post-treatment disease-specific quality of life among patients with localized prostate cancer. *Urol Oncol* 2012;**30**:804–12.

Pe 2009
Pe ML, Trabulsi EJ, Kedika R, Pequignot E, Dicker AP, Gomella LG, *et al.* Effect of percentage of positive prostate biopsy cores on biochemical outcome in low-risk PCa treated with brachytherapy or 3D-CRT. *Urology* 2009;**73**:1328–34.

Pickles 2010
Pickles T, Keyes M, Morris WJ. Brachytherapy or conformal external radiotherapy for prostate cancer: a single-institution matched-pair analysis. *Int J Radiat Oncol Biol Phys* 2010;**76**:43–9.

Pinkawa 2009
Pinkawa M, Asadpour B, Piroth MD, Gagel B, Nussen S, Kehl M, *et al.* Health-related quality of life after permanent I-125 brachytherapy and conformal external beam radiotherapy for prostate cancer – a matched-pair comparison. *Radiother Oncol* 2009;**91**:225–31.

Reeve 2012
Reeve BB, Stover AM, Jensen RE, Chen RC, Taylor KL, Clauser SB, *et al.* Impact of diagnosis and treatment of clinically localized prostate cancer on health-related quality of life for older Americans: a population-based study. *Cancer* 2012;**118**:5679–87.

Shah 2012
Shah C, Jones PM, Wallace M, Kestin LL, Ghilezan M, Fakhouri M, *et al.* Differences in disease presentation, treatment outcomes, and toxicities in African American patients treated with radiation therapy for prostate cancer. *Am J Clin Oncol* 2012;**35**:566–71.

Mohammed N, Kestin L, Ghilezan M, Krauss D, Vicini F, Brabbins D, *et al.* Comparison of acute and late toxicities for three modern high-dose radiation treatment techniques for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2012;**82**:204–12.

Vicini FA, Shah C, Kestin L, Ghilezan M, Krauss D, Ye H, *et al.* Identifying differences between biochemical failure and cure: incidence rates and predictors. *Int J Radiat Oncol Biol Phys* 2011;**81**:E369–75.

Smith 2009
Smith DP, King MT, Egger S, Berry MP, Stricker PD, Cozzi P, *et al.* Quality of life three years after diagnosis of localised prostate cancer: population based cohort study. *BMJ* 2009;**339**:b4817.

Talcott 2003
Talcott JA, Manola J, Clark JA, Kaplan I, Beard CJ, Mitchell SP, *et al.* Time course and predictors of symptoms after primary prostate cancer therapy. *J Clin Oncol* 2003;**21**:3979–86.

Tsui 2005
Tsui G, Gillan C, Pond G, Catton C, Crook J. Posttreatment complications of early-stage prostate cancer patients: brachytherapy versus three-dimensional conformal radiation therapy. *Cancer J* 2005;**11**:122–32.

Williams 2012
Williams SB, Lei Y, Nguyen PL, Gu X, Lipsitz SR, Yu HY, *et al.* Comparative effectiveness of cryotherapy vs. brachytherapy for localised prostate cancer. *BJU Int* 2012;**110**:e92–8.

Wong 2009
Wong WW, Vora SA, Schild SE, Ezzell GA, Andrews PE, Ferrigni RG, *et al.* Radiation dose escalation for localized prostate cancer: intensity-modulated radiotherapy versus permanent transperineal brachytherapy. *Cancer* 2009;**115**:5596–606.

Zelefsy 1999
Zelefsky MJ, Wallner KE, Ling CC, Raben A, Hollister T, Wolfe T, *et al.* Comparison of the 5-year outcome and morbidity of three-dimensional conformal radiotherapy versus transperineal permanent iodine-125 implantation for early-stage prostatic cancer. *J Clin Oncol* 1999;**17**:517–22.

Zelefsy 2011
Zelefsky MJ, Yamada Y, Pei X, Hunt M, Cohen G, Zhang Z, *et al.* Comparison of tumor control and toxicity outcomes of high-dose intensity-modulated radiotherapy and brachytherapy for patients with favorable risk prostate cancer. *Urology* 2011;**77**:986–93.

Case series: cryotherapy (14 studies)

Bahn 2002
Bahn DK, Lee F, Badalament R, Kumar A, Greski J, Chernick M. Targeted cryoablation of the prostate: 7-year outcomes in the primary treatment of prostate cancer. *Urology* 2002;**60**:3–11.

Caso 2012
Caso JR, Tsivian M, Mouraviev V, Kimura M, Polascik TJ. Complications and postoperative events after cryosurgery for prostate cancer. *BJU Int* 2012;**109**:840–5.

Caso JR, Tsivian M, Mouraviev V, Polascik TJ. Predicting biopsy-proven prostate cancer recurrence following cryosurgery. *Urol Oncol* 2012;**30**:391–5.

Polascik TJ, Nosnik I, Mayes JM, Mouraviev V. Short-term cancer control after primary cryosurgical ablation for clinically localized prostate cancer using third-generation cryotechnology. *Urology* 2007;**70**:117–21.

Cytron 2003
Cytron S, Paz A, Kravchick S, Shumalinski D, Moore J, De Reijke T. Active rectal wall protection using direct transperineal cryo-needles for histologically proven prostate adenocarcinomas. *Eur Urol* 2003;**44**:315–21.

Donnelly 2002
Donnelly BJ, Saliken JC, Ernst DS, Ali-Ridha N, Brasher PMA, Robinson JW, *et al.* Prospective trial of cryosurgical ablation of the prostate: five-year results. *Urology* 2002;**60**:645–9.

Robinson JW, Saliken JC, Donnelly BJ, Barnes P, Guyn L. Quality-of-life outcomes for men treated with cryosurgery for localized prostate carcinoma. *Cancer* 1999;**86**:1793–801.

Saliken JC, Donnelly BJ, Brasher P, Ali-Ridha N, Ernst S, Robinson J. Outcome and safety of transrectal US-guided percutaneous cryotherapy for localized prostate cancer. *J Vasc Intervent Radiol* 1999;**10**:199–208.

Robinson JW, Donnelly BJ, Saliken JC, Weber BA, Ernst S, Rewcastle JC. Quality of life and sexuality of men with prostate cancer 3 years after cryosurgery. *Urology* 2002;**60**:12–18.

Ellis 2007
Ellis DS, Manny J, Rewcastle JC. Focal cryosurgery followed by penile rehabilitation as primary treatment for localized prostate cancer: initial results. *Urology* 2007;**70**:S9–15.

Hale 2013
Hale Z, Miyake M, Palacios DA, Rosser CJ. Focal cryosurgical ablation of the prostate: a single institute's perspective. *BMC Urol* 2013;**13**:2.

Han 2003
Han K-R, Cohen JK, Miller RJ, Pantuck AJ, Freitas DG, Cuevas CA, *et al.* Treatment of organ confined prostate cancer with third generation cryosurgery: preliminary multicenter experience. *J Urol* 2003;**170**:1126–30.

Hubosky 2007
Hubosky SG, Fabrizio MD, Schellhammer PF, Barone BB, Tepera CM, Given RW. Single center experience with third-generation cryosurgery for management of organ-confined prostate cancer: critical evaluation of short-term outcomes, complications, and patient quality of life. *J Endourol* 2007;**21**:1521–31.

Lian 2011
Lian H, Guo H, Gan W, Li X, Yan X, Wang W, *et al.* Cryosurgery as primary treatment for localized prostate cancer. *Int Urol Nephrol* 2011;**43**:1089–94.

Mack 1997
Mack D, Jungwirth A, Adam U, Kunit G, Miller K, Dietze O, *et al.* Long-term follow-up after open perineal cryotherapy in patients with locally confined prostate cancer. *Eur Urol* 1997;**32**:129–32.

Onik 2008
Onik G. Rationale for a 'male lumpectomy', a prostate cancer targeted approach using cryoablation: results in 21 patients with at least 2 years of follow-up. *Cardiovasc Intervent Radiol* 2008;**31**:98–106.

Truesdale 2010
Truesdale MD, Cheetham PJ, Hruby GW, Wenske S, Conforto AK, Cooper AB, *et al.* An evaluation of patient selection criteria on predicting progression-free survival after primary focal unilateral nerve-sparing cryoablation for prostate cancer: recommendations for follow up. *Cancer J* 2010;**16**:544–9.

Lambert EH, Bolte K, Masson P, Katz AE. Focal cryosurgery: encouraging health outcomes for unifocal prostate cancer. *Urology* 2007;**69**:1117–20.

Ward 2012
Ward JF, Jones JS. Focal cryotherapy for localized prostate cancer: a report from the national Cryo On-Line Database (COLD) Registry. *BJU Int* 2012;**109**:1648–54.

Wong 1997
Wong WS, Chinn DO, Chinn M, Chinn J, Tom WL. Cryosurgery as a treatment for prostate carcinoma. Results and complications. *Cancer* 1997;**79**:963–74.

Case series: laser therapy (one study)

Lindner 2009
Lindner U, Weersink RA, Haider MA, Gertner MR, Davidson SRH, Atri M, *et al.* Image guided photothermal focal therapy for localized prostate cancer: phase I trial. *J Urol* 2009;**182**:1371–7.

Case series: high-intensity focused ultrasound (20 studies)

Ahmed 2011
Ahmed HU, Freeman A, Kirkham A, Sahu M, Scott R, Allen C, *et al.* Focal therapy for localized prostate cancer: a phase I/II trial. *J Urol* 2011;**185**:1246–54.

Ahmed 2012
Ahmed HU, Hindley RG, Dickinson L, Freeman A, Kirkham AP, Sahu M, *et al.* Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study. *Lancet Oncol* 2012;**13**:622–32.

Blana 2009
Blana A, Brown SCW, Chaussy C, Conti GN, Eastham JA, Ganzer R, *et al.* High-intensity focused ultrasound for prostate cancer: comparative definitions of biochemical failure. *BJU Int* 2009;**104**:1058–62.

Blana 2012
Blana A, Robertson CN, Brown SCW, Chaussy C, Crouzet S, Gelet A, *et al.* Complete high-intensity focused ultrasound in prostate cancer: outcome from the @-Registry. *Prostate Cancer Prostatic Dis* 2012;**15**:256–9.

Chaussy 2003
Chaussy C, Thuroff S. The status of high-intensity focused ultrasound in the treatment of localized prostate cancer and the impact of a combined resection. *Curr Urol Rep* 2003;**4**:248–52.

Colombel 2006
Colombel M, Poissonnier L, Martin X, Gelet A. Clinical results of the prostate HIFU project. *Eur Urol Suppl* 2006;**5**:491–4.

El Fegoun 2011
El Fegoun AB, Barret E, Prapotnich D, Soon S, Cathelineau X, Rozet F, *et al.* Focal therapy with high-intensity focused ultrasound for prostate cancer in the elderly. A feasibility study with 10 years follow-up. *Int Braz J Urol* 2011;**37**:213–19.

Ganzer 2008
Ganzer R, Rogenhofer S, Walter B, Lunz JC, Schostak M, Wieland WF, *et al.* PSA nadir is a significant predictor of treatment failure after high-intensity focussed ultrasound (HIFU) treatment of localised prostate cancer. *Eur Urol* 2008;**53**:547–53.

Ganzer 2011
Ganzer R, Robertson CN, Ward JF, Brown SCW, Conti GN, Murat FJ, *et al.* Correlation of prostate-specific antigen nadir and biochemical failure after high-intensity focused ultrasound of localized prostate cancer based on the Stuttgart failure criteria – analysis from the @-Registry. *BJU Int* 2011;**108**:E196–201.

Illing 2006
lling RO, Leslie TA, Kennedy JE, Calleary JG, Ogden CW, Emberton M. Visually directed high-intensity focused ultrasound for organ-confined prostate cancer: a proposed standard for the conduct of therapy. *BJU Int* 2006;**98**:1187–92.

Inoue 2011
Inoue Y, Goto K, Hayashi T, Hayashi M. Transrectal high-intensity focused ultrasound for treatment of localized prostate cancer. *Int J Urol* 2011;**18**:358–63.

Koch 2007
Koch MO, Gardner T, Cheng L, Fedewa RJ, Seip R, Sangvhi NT. Phase I/II trial of high intensity focused ultrasound for the treatment of previously untreated localized prostate cancer. *J Urol* 2007;**178**:2366–71.

Maestroni 2008
Maestroni U, Ziveri M, Azzolini N, Dinale F, Ziglioli F, Campaniello G, *et al.* High intensity focused ultrasound (HIFU): a useful alternative choice in prostate cancer treatment. Preliminary results. *Acta Biomed* 2008;**79**:211–16.

Mearini 2009
Mearini L, D'Urso L, Collura D, Zucchi A, Costantini E, Formiconi A, *et al.* Visually directed transrectal high intensity focused ultrasound for the treatment of prostate cancer: a preliminary report on the Italian experience. *J Urol* 2009;**181**:105–12.

Misrai 2008
Misrai V, Roupret M, Chartier-Kastler E, Comperat E, Renard-Penna R, Haertig A, *et al.* Oncologic control provided by HIFU therapy as single treatment in men with clinically localized prostate cancer. *World J Urol* 2008;**26**:481–5.

Pinthus 2012
Pinthus JH, Farrokhyar F, Hassouna MM, Woods E, Whelan K, Shayegan B, *et al.* Single-session primary high-intensity focused ultrasonography treatment for localized prostate cancer: biochemical outcomes using third generation-based technology. *BJU Int* 2012;**110**:1142–8.

Poissonnier 2007
Poissonnier L, Chapelon JY, Rouviere O, Curiel L, Bouvier R, Martin X, *et al.* Control of prostate cancer by transrectal HIFU in 227 patients. *Eur Urol* 2007;**51**:381–7.

Sumitomo 2010
Sumitomo M, Asakuma J, Sato A, Ito K, Nagakura K, Asano T. Transurethral resection of the prostate immediately after high-intensity focused ultrasound treatment for prostate cancer. *Int J Urol* 2010;**17**:924–30.

Uchida 2005
Uchida T, Baba S, Irie A, Soh S, Masumori N, Tsukamoto T, *et al.* Transrectal high-intensity focused ultrasound in the treatment of localized prostate cancer: a multicenter study. *Hinyokika Kiyo* 2005;**51**:651–8.

Uchida 2009
Uchida T, Shoji S, Nakano M, Hongo S, Nitta M, Murota A, *et al.* Transrectal high-intensity focused ultrasound for the treatment of localized prostate cancer: eight-year experience. *Int J Urol* 2009;**16**:881–6.

Uchida T, Ohkusa H, Nagata Y, Hyodo T, Satoh T, Irie A. Treatment of localized prostate cancer using high-intensity focused ultrasound. *BJU Int* 2006;**97**:56–61.

Uchida T, Sanghvi NT, Gardner TA, Koch MO, Ishii D, Minei S, *et al.* Transrectal high-intensity focused ultrasound for treatment of patients with stage T1b-2n0m0 localized prostate cancer: a preliminary report. *Urology* 2002;**59**:394–8.

Uchida T, Ohkusa H, Yamashita H, Shoji S, Nagata Y, Hyodo T, *et al.* Five years experience of transrectal high-intensity focused ultrasound using the Sonablate device in the treatment of localized prostate cancer. *Int J Urol* 2006;**13**:228–33.

Uchida T, Illing RO, Cathcart PJ, Emberton M. To what extent does the prostate-specific antigen nadir predict subsequent treatment failure after transrectal high-intensity focused ultrasound therapy for presumed localized adenocarcinoma of the prostate? *BJU Int* 2006;**98**:537–9.

Shoji S, Nakano M, Nagata Y, Usui Y, Terachi T, Uchida T. Quality of life following high-intensity focused ultrasound for the treatment of localized prostate cancer: a prospective study. *Int J Urol* 2010;**17**:715–19.

Active surveillance (10 studies)

Bellardita 2013
Bellardita L, Rancati T, Alvisi MF, Villani D, Magnani T, Marenghi C, *et al.* Predictors of health-related quality of life and adjustment to prostate cancer during active surveillance. *Eur Urol* 2013;**64**:30–6.

Bul 2013
Bul M, Zhu X, Valdagni R, Pickles T, Kakehi Y, Rannikko A, *et al.* Active surveillance for low-risk prostate cancer worldwide: the PRIAS Study. *Eur Urol* 2013;**63**:597–603.

van den Bergh RC, Vasarainen H, van der Poel HG, Vis-Maters JJ, Rietbergen JB, Pickles T, *et al.* Short-term outcomes of the prospective multicentre 'Prostate Cancer Research International: Active Surveillance' study. *BJU Int* 2010;**105**:956–62.

Godtman 2013
Godtman RA, Holmberg E, Khatami A, Stranne J, Hugosson J. Outcome following active surveillance of men with screen-detected prostate cancer. Results from the Goteborg randomised population-based prostate cancer screening trial. *Eur Urol* 2013;**63**:101–7.

Hardie 2005
Hardie C, Parker C, Norman A, Eeles R, Horwich A, Huddart R, *et al.* Early outcomes of active surveillance for localized prostate cancer. *BJU Int* 2005;**95**:956–60.

Hilton 2012
Hilton JF, Blaschko SD, Whitson JM, Cowan JE, Carroll PR. The impact of serial prostate biopsies on sexual function in men on active surveillance for prostate cancer. *J Urol* 2012;**188**:1252–8.

Klotz 2010
Klotz L, Zhang L, Lam A, Nam R, Mamedov A, Loblaw A. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. *J Clin Oncol* 2010;**28**:126–31.

Klotz LH. Active surveillance for good risk prostate cancer: rationale, method, and results. *Can J Urol* 2005;**12**(Suppl. 2):21–4.

Loblaw A, Zhang L, Lam A, Nam R, Mamedov A, Vesprini D, *et al.* Comparing prostate specific antigen triggers for intervention in men with stable prostate cancer on active surveillance. *J Urol* 2010;**184**:1942–6.

Klotz L. Active surveillance: the Canadian experience with an 'inclusive approach'. *J Natl Cancer Inst Monogr* 2012;**45**:234–41.

Selvadurai 2013
Selvadurai ED, Singhera M, Thomas K, Mohammed K, Woode-Amissah R, Horwich A, *et al.* Medium-term outcomes of active surveillance for localised prostate cancer. *Eur Urol* 2013;**64**:981–7.

van As NJ, Norman AR, Thomas K, Khoo VS, Thompson A, Huddart RA, *et al.* Predicting the probability of deferred radical treatment for localised prostate cancer managed by active surveillance. *Eur Urol* 2008;**54**:1297–305.

Tosoian 2011
Tosoian JJ, Trock BJ, Landis P, Feng Z, Epstein JI, Partin AW, *et al.* Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. *J Clin Oncol* 2011;**29**:2185–90.

van den Bergh 2012
van den Bergh RC, Korfage IJ, Roobol MJ, Bangma CH, de Koning HJ, Steyerberg EW, *et al.* Sexual function with localized prostate cancer: active surveillance vs radical therapy. *BJU Int* 2012;**110**:1032–9.

Vasarainen 2012
Vasarainen H, Lokman U, Ruutu M, Taari K, Rannikko A. Prostate cancer active surveillance and health-related quality of life: results of the Finnish arm of the prospective trial. *BJU Int* 2012;**109**:1614–19.

Salvage review: included studies (nine studies)

Chin 2001
Chin JL, Pautler SE, Mouraviev V, Touma N, Moore K, Downey DB. Results of salvage cryoablation of the prostate after radiation: identifying predictors of treatment failure and complications. *J Urol* 2001;**165**:1937–41.

Colombel 2006
Colombel M, Poissonnier L, Martin X, Gelet A. Clinical results of the prostate HIFU project. *Eur Urol Suppl* 2006;**5**:491–4.

Darras 2006
Darras J, Joniau S, Van Poppel H. Salvage radical prostatectomy for radiorecurrent prostate cancer: indications and results. *Eur J Surg Oncol* 2006;**32**:964–9.

Gheiler 1998
Gheiler EL, Tefilli MV, Tiguert R, Grignon D, Cher ML, Sakr W, *et al.* Predictors for maximal outcome in patients undergoing salvage surgery for radio-recurrent prostate cancer. *Urology* 1998;**51**:789–95.

Neerhut 1988
Neerhut GJ, Wheeler T, Cantini M, Scardino PT. Salvage radical prostatectomy for radiorecurrent adenocarcinoma of the prostate. *J Urol* 1988;**140**:544–9.

Robinson 2006
Robinson JW, Donnelly BJ, Coupland K, Siever JE, Saliken JC, Scott C, *et al.* Quality of life 2 years after salvage cryosurgery for the treatment of local recurrence of prostate cancer after radiotherapy. *Urol Oncol* 2006;**24**:472–86.

Seabra 2009
Seabra D, Faria E, Dauster B, Rodrigues G, Fava G. Critical analysis of salvage radical prostatectomy in the management of radioresistant prostate cancer. *Int Braz J Urol* 2009;**35**:43–8.

Tefilli 1998
Tefilli MV, Gheiler EL, Tiguert R, Barroso U Jr, Barton CD, Wood DP Jr, *et al.* Quality of life in patients undergoing salvage procedures for locally recurrent prostate cancer. *J Surg Oncol* 1998;**69**:156–61.

Van Der Poel 2008
Van Der Poel HG, Moonen L, Horenblas S. Sequential treatment for recurrent localized prostate cancer. *J Surg Oncol* 2008;**97**:377–82.

TABLE 72 Linked reports

Primary report	Linked report(s)
Bul 2013[111]	van den Bergh 2010[197]
Caso 2012a[114]	Caso 2012b,[115] Polascik 2007[175]
Donnelly 2010[125]	Robinson 2009[179]
Donnelly 2002[124]	Robinson 2002,[178] Saliken 1999,[180] Robinson 1999[177]
Ferrer 2008[130]	Pardo 2010,[167] Guedea 2009[137]
Kibel 2012[144]	Nepple 2013,[165] Vassil 2010,[200] Burdick 2009,[112] Ciezki 2004[118]
Klotz 2010[146]	Klotz 2012,[147] Loblaw 2010,[157] Klotz 2005[148]
Paulson 1982a[168]	Paulson 1982b[169]
Selvadurai 2013[181]	van As 2008[196]
Shah 2012[182]	Mohammed 2012,[164] Vicini 2011[201]
Truesdale 2010[188]	Lambert 2007[152]
Uchida 2009[195]	Shoji 2010,[183] Uchida 2006a,[192] Uchida 2006b,[193] Uchida 2006c,[194] Uchida 2002[190]

Appendix 7 List of excluded studies

Inadequate sample size (*n* = 10)

Anselmo G, Mobilio G, Cosciani C. Indications and results of cryosurgery in 47 high risk patients with prostatic hypertrophy or carcinoma. *Endoscopy* 1975;**7**:146–50.

Bochner BH, Figueroa AJ, Skinner EC, Lieskovsky G, Petrovich Z, Boyd SD, *et al.* Salvage radical cystoprostatectomy and orthotopic urinary diversion following radiation failure. *J Urol* 1998;**160**:29–33.

Hacker A, Kohrmann KU, Back W, Kraut O, Marlinghaus E, Alken P, *et al.* Extracorporeal application of high-intensity focused ultrasound for prostatic tissue ablation. *BJU Int* 2005;**96**:71–6.

Haddad RL, Hossack TA, Woo HH. Results of low threshold to biopsy following high-intensity focused ultrasound for localized prostate cancer. *Urol Ann* 2012;**4**:84–8.

Hansen RI, Donde R. Cryoprostatectomy. A follow-up study with special reference to long-term results. *Scand J Urol Nephrol* 1972;**6**:99–102.

Kumar SM. Photoselective vaporization of the prostate: a volume reduction analysis in patients with lower urinary tract symptoms secondary to benign prostatic hyperplasia and carcinoma of the prostate. *J Urol* 2005;**173**:511–13.

Nunez-Mora C, Garcia-Mediero JM, Cabrera-Castillo PM. Radical laparoscopic salvage prostatectomy: medium-term functional and oncological results. *J Endourol* 2009;**23**:1301–5.

Rosenberg GS, Basralian KG. Active hydrodissection might optimize cryosurgical ablation of the prostate. *Urology* 2010;**76**:988–91.

Stein A, Smith RB, DeKernion JB. Salvage radical prostatectomy after failure of curative radiotherapy for adenocarcinoma of prostate. *Urology* 1992;**40**:197–200.

Vallancien G, Gupta R, Cathelineau X, Baumert H, Rozet F. Initial results of salvage laparoscopic radical prostatectomy after radiation failure. *J Urol* 2003;**170**:1838–40.

Ineligible population (*n* = 136)

Ahmed HU, Cathcart P, Mccartan N, Kirkham A, Allen C, Freeman A, *et al.* Focal salvage therapy for localized prostate cancer recurrence after external beam radiotherapy: a pilot study. *Cancer* 2012;**118**:4148–55.

Ahmed H, Cathcart P, Chalasani V, Williams A, Mccartan N, Freeman A, *et al.* Whole-gland salvage high-intensity focused ultrasound therapy for localized prostate cancer recurrence after external beam radiation therapy. *Cancer* 2012;**118**:3071–8.

Ahmed HU, Zacharakis E, Dudderidge T, Armitage JN, Scott R, Calleary J, *et al.* High-intensity-focused ultrasound in the treatment of primary prostate cancer: the first UK series. *Br J Cancer* 2009;**101**:19–26.

Aus G, Pileblad E, Hugosson J. Cryosurgical ablation of the prostate: 5-year follow-up of a prospective study. *Eur Urology* 2002;**42**:133–8.

Bahn DK, Lee F, Solomon MH, Gontina H, Klionsky DL, Lee FT. Prostate cancer: US-guided percutaneous cryoablation. Work in progress. *Radiology* 1995;**194**:551–6.

Bahn DK, Silverman P, Lee S, Badalament R, Bahn ED, Rewcastle JC. In treating localized prostate cancer the efficacy of cryoablation is independent of DNA ploidy type. *Technol Cancer Res Treat* 2004;**3**:253–7.

Beerlage HP, Thuroff S, Debruyne FMJ, Chaussy C, de la Rosette JJ. Transrectal high-intensity focused ultrasound using the Ablatherm device in the treatment of localized prostate carcinoma. *Urology* 1999;**54**:273–7.

Berge V, Baco E, Karlsen SJ. A prospective study of salvage high-intensity focused ultrasound for locally radiorecurrent prostate cancer: early results. *Scand J Urol Nephrol* 2010;**44**:223–7.

Bergman J, Kwan L, Litwin MS. Improving decisions for men with prostate cancer: translational outcomes research. *J Urol* 2010;**183**:2186–92.

Bianco FJ Jr, Scardino PT, Stephenson AJ, Diblasio CJ, Fearn PA, Eastham JA. Long-term oncologic results of salvage radical prostatectomy for locally recurrent prostate cancer after radiotherapy. *Int J Radiat Oncol Biol Phys* 2005;**62**:448–53.

Blana A, Rogenhofer S, Ganzer R, Lunz JC, Schostak M, Wieland WF, *et al.* Eight years' experience with high-intensity focused ultrasonography for treatment of localized prostate cancer. *Urology* 2008;**72**:1329–33.

Blana A, Murat FJ, Walter B, Thuroff S, Wieland WF, Chaussy C, *et al.* First analysis of the long-term results with transrectal HIFU in patients with localised prostate cancer. *Eur Urology* 2008;**53**:1194–203.

Blana A, Walter B, Rogenhofer S, Wieland WF. High-intensity focused ultrasound for the treatment of localized prostate cancer: 5-year experience. *Urology* 2004;**63**:297–300.

Bonney WW, Fallon B, Gerber WL, Hawtrey CE, Loening SA, Narayana AS, *et al.* Cryosurgery in prostatic cancer: elimination of local lesion. *Urology* 1983;**22**:8–15.

Bonney WW, Fallon B, Gerber WL. Cryosurgery in prostatic cancer: survival. *Urology* 1982;**19**:37–42.

Bouchier-Hayes DM, Van Appledorn S, Bugeja P, Crowe H, Challacombe B, Costello AJ. A randomized trial of photoselective vaporization of the prostate using the 80-W potassium-titanyl-phosphate laser vs. transurethral prostatectomy, with a 1-year follow-up. *BJU Int* 2010;**105**:964–9.

Brassell SA, Elsamanoudi SI, Cullen J, Williams ME, McLeod DG. Health-related quality of life for men with prostate cancer – an evaluation of outcomes 12–24 months after treatment. *Urol Oncol* 2013;**31**:1504–10.

Callea A, Piccinni R, Zizzi V, Sblendorio D, Berardi B, Tempesta A, *et al.* High-intensity focused ultrasound (HIFU) in prostate cancer: a single centre experience in patients with low, intermediate or high-risk of progression. *Arch Ital Urol Androl* 2010;**82**:253–5.

Carter HB, Kettermann A, Warlick C, Metter EJ, Landis P, Walsh PC, *et al.* Expectant management of prostate cancer with curative intent: an update of the Johns Hopkins experience. *J Urol* 2007;**178**:2359–64.

Chaussy C, Thuroff S. High-intensity focused ultrasound in prostate cancer: results after 3 years. *Mol Urol* 2000;**4**:179–82.

Chaussy C, Thuroff S. Results and side effects of high-intensity focused ultrasound in localized prostate cancer. *J Endourol* 2001;**15**:437–40.

Chaussy CG, Thuroff S. High-intensive focused ultrasound in localized prostate cancer. *J Endourol* 2000;**14**:293–9.

Cheng L, Sebo TJ, Slezak J, Pisansky TM, Bergstralh EJ, Neumann RM, *et al.* Predictors of survival for prostate carcinoma patients treated with salvage radical prostatectomy after radiation therapy. *Cancer* 1998;**83**:2164–71.

Chin JL, Downey DB, Mulligan M, Fenster A. Three-dimensional transrectal ultrasound guided cryoablation for localized prostate cancer in nonsurgical candidates: a feasibility study and report of early results. *J Urol* 1998;**159**:910–14.

Chin JL, Ng CK, Touma NJ, Pus NJ, Hardie R, Abdelhady M, *et al.* Randomized trial comparing cryoablation and external beam radiotherapy for T2C-T3B prostate cancer. *Prostate Cancer Prostatic Dis* 2008;**11**:40–5.

Chin JL, Al-Zahrani AA, Autran-Gomez AM, Williams AK, Bauman G. Extended followup oncologic outcome of randomized trial between cryoablation and external beam therapy for locally advanced prostate cancer (T2c-T3b). *J Urol* 2012;**188**:1170–5.

Christoffersen JC, Hvidt V. Prostatic desiccation used in poor-risk patients with benign and malignant prostatic obstruction. *Eur Urol* 1976;**2**:229–33.

Cohen JK, Miller J, Rooker GM, Shuman BA. Cryosurgical ablation of the prostate: two-year prostate-specific antigen and biopsy results. *Urology* 1996;**47**:395–401.

Cohen JK, Miller J, Ahmed S, Lotz MJ, Baust J. Ten-year biochemical disease control for patients with prostate cancer treated with cryosurgery as primary therapy. *Urology* 2008;**71**:515–18.

Coogan CL, McKiel CF. Percutaneous cryoablation of the prostate: preliminary results after 95 procedures. *J Urol* 1995;**154**:1813–17.

Cox RL, Crawford ED. Complications of cryosurgical ablation of the prostate to treat localized adenocarcinoma of the prostate. *Urology* 1995;**45**:932–5.

Cresswell J, Asterling S, Chaudhary M, Sheikh N, Greene D. Third-generation cryotherapy for prostate cancer in the UK: a prospective study of the early outcomes in primary and recurrent disease. *BJU Int* 2006;**97**:969–74.

Cross DS, Ritter M, Reding DJ. Historical prostate cancer screening and treatment outcomes from a single institution. *Clin Med Res* 2012;**10**:97–105.

Crouzet S, Rebillard X, Chevallier D, Rischmann P, Pasticier G, Garcia G, *et al.* Multicentric oncologic outcomes of high-intensity focused ultrasound for localized prostate cancer in 803 patients. *Eur Urol* 2010;**58**:559–66.

de la Taille A, Hayek O, Benson MC, Bagiella E, Olsson CA, Fatal M, *et al.* Salvage cryotherapy for recurrent prostate cancer after radiation therapy: the Columbia experience. *Urology* 2000;**55**:79–84.

Derakhshani P, Neubauer S, Braun M, Zumbe J, Heidenreich A, Engelmann U. Cryoablation of localized prostate cancer. Experience in 48 cases, PSA and biopsy results. *Eur Urology* 1998;**34**:181–7.

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Appendix 8 Characteristics of included studies

TABLE 73 Characteristics of the included studies (primary review)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Ahmed 2011[98] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** UK **Recruitment/treatment dates:** July 2006–October 2008 **Study design:** case series **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** 12 months **Source of funding:** Medical Research Council; Pelican Cancer Foundation; Prostate Research Campaign UK; Prostate Cancer Research Centre at University College London and St. Peter's Trust; UK National Institute for Health Research, University College London Hospitals/University College London Comprehensive Biomedical Research Centre **Systematic reviewer:** TEA	**Inclusion criteria:** people with low- to intermediate-risk unilateral disease (Gleason 4 + 3 or less, PSA 15 ng/ml or less, cT2bN0M0 or less) diagnosed by TRUS-guided biopsies, who had no prior treatment, or people who had mp-MRI and TPM to protocol standards outside the trial **Exclusion criteria:** bilateral disease, erectile dysfunction refractory to PDE5-I **Staging method:** TRUS-guided biopsy	**HIFU:** hemiablation with a transrectal HIFU device up to the midline as defined by the urethra, and in case of midline disease, the zone of ablation was extended 5 mm over midline **Extent of ablation:** focal	**Efficacy:** cancer control **Functional:** sexual function, incontinence **Adverse events:** mild to moderate dysuria, intermittent haematuria, presphincteric stricture **QoL:** physical well-being, social/family well-being, emotional well-being, functional well-being

Patient characteristics	HIFU
Number of patients enrolled	20
Low risk, *n* (%)	5 (25)
Intermediate risk, *n* (%)	15 (75)
Age (years)	
Mean (SD)	60.4 (5.4)
Range	50–70
PSA level (ng/ml)	
Mean (SD)	7.3 (2.8)
Range	3.4–11.8
Biopsy Gleason score	3 (15%) demonstrated the absence of Gleason pattern 4 and 5

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Ahmed 2012[99] **Language:** English **Publication type:** full-text paper **Number of study centres:** 2 **Setting:** hospital **Country:** UK **Recruitment/treatment dates:** 27 June 2007–30 June 2010 **Study design:** case series **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** 12 months **Source of funding:** Medical Research Council (UK); Pelican Cancer Foundation; St Peters Trust **Systematic reviewer:** SJ	**Inclusion criteria:** this study included people with low- to high-risk disease (PSA ≤ 15 ng/ml, Gleason score of ≤ 4 + 3, stage ≤ T2), aged 45–80 years with a life expectancy of 5 years or more, a prostate volume of 40 ml or less or maximum anterior–posterior length of 40 mm, who had undergone multiparametric MRI and transperineal template (5 mm-spaced) biopsies in the 6 months before recruitment **Exclusion criteria:** people who had androgen suppression within the previous 6 months, previous radiation therapy or chemotherapy for prostate cancer, latex allergies, previous rectal surgery preventing insertion of transrectal probe, intraprostatic calcifications making HIFU of focal areas of cancer difficult, previous transurethral resection of the prostate or laser prostatectomy in 5 years before recruitment, previous HIFU, cryosurgery, or thermal or microwave therapy to the prostate at any point before recruitment. Patients unable to have MRI scanning were also excluded **Staging method:** N/R	**HIFU:** people underwent focal ablation with a transrectal HIFU device (Sonablate® 500). Study researchers standardised the process of focal therapy by setting three broad guidelines. First, a maximum of 60% of the prostate could be ablated. Second, the edge of the ablation zone had to be at least 10 mm from a neurovascular bundle. The ablation zone had to be at least 5 mm from both neurovascular bundles if disease was bilateral. Third, untreated areas could not have any histological evidence of prostate cancer; high-grade prostate intraepithelial neoplasia and atypical small acinar proliferation were permitted **Extent of ablation:** focal	**Efficacy:** PSA levels, positive biopsy **Functional outcomes:** erectile, dysfunction, urinary incontinence **QoL:** FACT-G, FACT-P **Adverse events:** urinary retention, dysuria, intermittent haematuria, urinary debris, UTI

Patient characteristics	HIFU
Number of patients enrolled	41
Age (years)	
Median (IQR)	63 (58–66)
PSA level (ng/ml)	
Median (IQR)	6.6 (5.4–7.7)
Clinical stage, *n* (%)	
T1c	37 (90)
T2a	4 (10)
Biopsy Gleason score, *n* (%)	
6	13 (32)
7	28 (68)
Prostate volume (ml)	
Median (IQR)	35 (29–45.5)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Alemozaffar 2011[100] **Language:** English **Publication type:** full-text paper **Number of study centres:** 9 **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** 2003–6 **Study design:** NRCS **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** 2 years **Source of funding:** NIH grants **Systematic reviewer:** TEA	**Inclusion criteria:** people with previously untreated clinical stage T1–T2 prostate cancer who had elected prostatectomy, EBRT or BT as primary treatment **Exclusion criteria:** N/R **Staging method:** N/R	**BT:** N/R **EBRT:** N/R **RP:** N/R	**Functional:** erectile dysfunction

Patient characteristics	BT	EBRT	RP
Number of patients analysed (total enrolled = 1201)	262	241	524

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Arvold 2011[101] **Language:** English **Publication type:** full-text paper **Number of study centres:** 21 **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** BT: May 1991–July 2007 RP: January 1988–October 2008 **Study design:** NRCS **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** median 4.2 years Low risk, median (IQR): BT 3.6 (1.8–5.9) years; RP 6.1 (2.9–9.9) years Intermediate risk, median (IQR): BT 4.1 (2.0–6.7) years; RP 7.2 (2.8–11.9) years **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** low-risk (T1c or T2a, PSA ≤ 10 ng/ml and Gleason score of ≤ 6) and intermediate-risk patients (T2b or T2c, PSA > 10–20 ng/ml or Gleason score of 7). All patients had at least 10-year life expectancy. RP patients who received adjuvant AST or EBRT within 6 months of RP were included because pathological findings can inform postoperative treatment **Exclusion criteria:** people receiving AST or supplemental EBRT in addition to BT, or those who received neoadjuvant AST before RP	**BT:** patients with low-risk disease had BT monotherapy, and in case of significant risk of extraprostatic extension, supplemental EBRT was administered. Neoadjuvant HT was used for favourable-risk disease to downsize the gland and eliminate pubic arch interference during the administration of BT **RP:** typically included pelvic lymph node dissection. Adjuvant EBRT or AST was at the discretion of the treating physician within 6 months postoperatively	**Efficacy:** death from prostate cancer, prostate cancer-specific mortality, reintervention rate

Patient characteristics	BT	RP
Number of patients enrolled	5902	2937
Low risk, *n* (%)	3851 (65)	1909 (65)
Intermediate risk, *n* (%)	2051 (35)	1028 (35)
Age (years)		
Low risk, median (IQR)	68.8 (62.7–73.5)	61.4 (56.3–66.6)
Intermediate risk, median (IQR)	71.2 (65.4–75.5)	62.9 (57.5–68.1)
PSA level		
Low risk		
≤ 4 ng/ml, *n* (%)	507 (13)	460 (24)
> 4–10 ng/ml, *n* (%)	3344 (87)	1449 (76)
Median ng/ml (IQR)	6.0 (4.8–7.5)	5.3 (4.1–6.9)
Intermediate risk		
≤ 4 ng/ml, *n* (%)	122 (6)	119 (12)
> 4–10 ng/ml, *n* (%)	877 (43)	460 (45)
> 10–20 ng/ml, *n* (%)	1052 (51)	449 (44)
Median ng/ml (IQR)	10.1 (6.3–12.1)	8.4 (5.3–12.6)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics			Intervention characteristics	Outcomes
	Patient characteristics	**BT**	**RP**		
	Clinical stage, *n* (%)				
	Low risk				
	T1c	2998 (78)	1671 (88)		
	T2a	853 (22)	238 (13)		
	Intermediate risk				
	T1c	1278 (62)	756 (74)		
	T2a	434 (21)	153 (15)		
	T2b	188 (9)	75 (7)		
	T2c	151 (7)	44 (4)		
	Biopsy Gleason score, *n* (%)				
	Low risk				
	< 6	557 (15)	387 (20)		
	6	3294 (86)	1522 (80)		
	Intermediate risk				
	≤ 6	977 (48)	406 (40)		
	7	1074 (52)	622 (61)		

Study details	Participant characteristics			Intervention characteristics	Outcomes
	Patient characteristics	**BT**	**RP**		
	Comorbidity,[a] *n* (%)				
	Low risk				
	Score 0	1989 (52)	1009 (53)		
	Score 1	1862 (48)	900 (47)		
	Intermediate risk				
	Score 0	1080 (53)	578 (56)		
	Score 1	971 (47)	450 (44)		
	a Comorbidity score 1: history of coronary artery disease, congestive heart failure or myocardial infarction at the time of local therapy.				
	Staging method: N/R				

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Bahn 2002[102] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** March 1993–September 2001 **Study design:** case series study **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** mean 5.43 years; median 5.72 years **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** localised or locally advanced disease (T1–T3) **Exclusion criteria:** N/R **Staging method:** N/R	**CRYO:** liquid nitrogen cryomachine (first 350 patients), argon-based cryomachine; machines were used with cryoprobes (Endocare Inc., Irvine, CA). 91.5% had LHRH combined with an antiandrogen agent 3 months to 1 year before treatment to downsize the gland	**Efficacy:** freedom from biochemical relapse, positive prostate biopsy, reintervention rate **Functional:** impotence, urinary continence **Adverse events:** rectourethral fistula, TURP for postcryoablation morbidity

Patient characteristics	CRYO
Number of patients enrolled	590
Age (years)	
Mean	70.76
Median	71.13
PSA level, *n* (%)	
< 4 ng/ml	97 (16.4)
4–10 ng/ml	348 (59.0)
> 10 ng/ml	145 (24.6)
Clinical stage, *n* (%)	
T1	11 (1.9)
T2	461 (78.1)
T3	104 (17.6)
T4	12 (2.0)
Missing	2 (0.3)
Biopsy Gleason score, *n* (%)	
3–6	241 (40.8)
7	310 (52.5)
8–9	35 (5.9)
Missing	4 (0.7)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Barret 2013[103] **Language:** English **Publication type:** full-text paper **Number of study centres:** single **Setting:** hospital **Country:** France **Recruitment/treatment dates:** 2009–11 **Study design:** NRCS **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** median 9 months (IQR 6–15 months) **Source of funding:** none **Systematic reviewer:** SJ	**Inclusion criteria:** patients who had low-risk prostate cancer according to the D'Amico criteria (PSA < 10 ng/ml, Gleason sum ≤ 6, clinical stage T2a or below) and unilateral disease, and fewer than three positive biopsies **Exclusion criteria:** exclusion criteria included clinically bilateral cancer, Gleason score of ≥ 7, extracapsular extension proven on biopsy or suspected on multiparametric MRI, and having received ADT by referring physicians	**BT:** twelve patients (11%) had focal BT. The technique is derived from the whole-gland procedure performed by our team. Radioactive seeds ('free' iodine-125 seeds) are placed throughout the BT template grid in the cancer area under ultrasound guidance. People with prostate volume > 50 ml, prior TURP or obstructive symptoms are often not candidates for BT Extent of ablation: focal **CRYO:** focal cryoablation used argon gas and cryoablation needles (Galil Medical, Inc., St Paul, MN) were inserted under ultrasound guidance in the prostate lobe, where cancer had been proven by biopsy, to perform a hemiablation with a double freeze–thaw cycle (each hemicycle – i.e. freeze or thaw – lasted 10 minutes). Temperature sensors were inserted at two locations: the Denonvilliers fascia and the cancer area as shown by the TVS. The therapeutic goals were to achieve cryoablation of the cancer area under TRUS control and to reach a temperature of –40 °C or lower in the target area while minimising cold exposure to the rectum and external sphincter. Cryotherapy is used for smaller prostates and peripheral tumours Extent of ablation: focal	**Efficacy:** PSA levels **Functional outcomes:** urinary function, erectile function **Adverse events:** rectourethral fistula, urethral stricture, urinary retention, pelvic pain, gross haematuria

Patient characteristics	Total
Number of patients enrolled	106
BT	12
CRYO	50
HIFU	21
Vascular-targeted PDT	23
Age (years)	
Median (IQR)	66.5 (61–73)
PSA level (ng/ml)	
Median (IQR)	6.1 (5–8.1)
Clinical stage, *n* (%)	
T1c	91 (86)
T2a	15 (14)
Biopsy Gleason score, *n* (%)	
6	106 (100)
Urinary function (I-PSS score)	
Median (IQR)	6 (3–10)
Erectile function (IIEF-5 score)	
Median (IQR)	20 (15–23)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
	Staging method: N/R	**HIFU:** twenty-one patients (20%) had prostate hemiablation using HIFU delivered by the Ablatherm® system (EDAP TMS, Vaulx-en-Velin, France). The treatment area was heated for 4.5 seconds and then cooled for 5 seconds under real-time ultrasound control. There is also a limit on the prostate size for HIFU Extent of ablation: focal **Vascular-targeted PDT:** Tookad® vascular-targeted PDT was used. Under ultrasound guidance, laser probes were inserted transperineally in the cancer area using a BT-type grid. WST11 (padeliporfin; palladium bacteriopheophorbide monolysotaurine) was then injected intravenously over 10 minutes, and the vascular-targeted PDT was set for a 20-minute illumination period. Vascular-targeted PDT is used for larger prostates, but patients taking anticoagulants cannot stop the treatment as the procedure is based on vascular mechanisms Extent of ablation: focal	

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Bellardita 2013[104] **Language:** English **Publication type:** full-text paper **Number of study centres:** single **Setting:** hospital **Country:** Italy **Recruitment/treatment dates:** September 2007–March 2012 **Study design:** case series **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** 10 months **Source of funding:** none **Systematic reviewer:** SJ	**Inclusion criteria:** patients eligible for the PRIAS study if they had a diagnosis of prostate adenocarcinoma with a PSA level ≤ 10.0 ng/ml; PSA density (PSA/prostate volume) < 0.2 ng/ml per ml; non-palpable or localised disease; no more than two positive prostate needle biopsy cores; and Gleason score of 3 + 3 = 6. These patients were invited to take part in the ancillary PRIAS QoL study and patients who agreed were included **Exclusion criteria:** N/R **Staging method:** N/R	**AS:** baseline and 10-months QoL questionnaires were assessed	**QoL:** FACT-G, FACT-P, mini mental adjustment for cancer

Patient characteristics	AS
Number of patients enrolled	154
Number of patients analysed	103
Age (years)	
Mean (SD)/median (IQR)	67 (7)/68 (63–73)
PSA level (ng/ml)	
Mean (SD)/median (IQR)	5 (1.87)/5 (4.2–6.4)
Clinical stage, *n* (%)	
T1c	96 (93)
T2a	7 (7)
Biopsy Gleason score, *n* (%)	
≤ 6	103 (100)
IIEF-5 score, mean (SD)	19.9 (9.6)
I-PSS score, mean (SD)	9.9 (6.3)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Beyer 2000[105] **Language:** English **Publication type:** full-text papers **Number of study centres:** single **Setting:** Arizona Oncology Services (BT outpatient clinic) **Country:** USA **Recruitment/treatment dates:** December 1988–December 1998 **Study design:** NRCS **Prospective/retrospective data collection:** unclear (Arizona Oncology Service database) **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** more than 8 years (median follow-up for all patients 45 months) Median follow-up (range): BT 41.3 (1–114.7) months; EBRT 51.3 (1–116.2) months **Source of funding:** N/R **Systematic reviewer:** SJ	**Inclusion criteria:** patients who underwent EBRT alone or BT alone for localised prostate cancer with T1/T2 Nx-N0 M0 disease at Arizona Oncology Services. None of the patients received prior or concurrent hormonal treatment **Exclusion criteria:** patients not meeting these guidelines were excluded from analysis	**BT:** BT was transperineal, ultrasound-guided treatment using either I-125 (663 patients, 95%) or Pd-103 (32 patients, 5%) after loaded needle with Mick Applicator (Eckert & Ziegler, Mick Radio-Nuclear Instruments, Inc., Mount Vernon, NY) **EBRT:** the median total dose for EBRT patients was 66.6 Gy (range 14.4–72.0 Gy), which was delivered using 4–15-MV photons Bilateral arc rotation was performed in 86% of cases, with the rest of the patients receiving either four-field pelvic treatment or combination (9%)	**Efficacy:** failure-free survival **QoL:** N/R

Patient characteristics	BT	EBRT
Number of patients enrolled	695	1527
Median age (years)	74	74
PSA level, *n* (%)		
0–4 ng/ml	128 (19)	132 (9)
> 4–10 ng/ml	345 (50)	565 (37)
> 10–20 ng/ml	144 (21)	481 (32)
> 20 ng/ml	73 (10)	332 (22)
Unknown	5 (< 1)	18 (1)
Clinical stage, *n* (%)		
T1	117 (17)	290 (19)
T1a	19 (3)	40 (3)
T1b	38 (5)	131 (9)
T1c	60 (9)	119 (8)
T2	578 (83)	1238 (81)
T2a	328 (47)	451 (30)
T2b	164 (24)	645 (42)
T2c	86 (12)	142 (9)

Study details	Participant characteristics			Intervention characteristics	Outcomes
	Patient characteristics	**BT**	**EBRT**		
	Biopsy Gleason score, *n* (%)				
	2–4	145 (21)	434 (28)		
	5–6	433 (63)	705 (46)		
	7	85 (12)	268 (17)		
	8–10	20 (3)	116 (8)		
	Unknown	12 (2)	5 (< 1)		
	Staging method: DRE				

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Blana 2009[106] **Language:** English **Publication type:** full-text paper **Number of study centres:** 2 **Setting:** registry **Country:** France and Germany **Recruitment/treatment dates:** October 1997–July 2006 **Study design:** case series **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** median 4.7 (range 2–10.9) years **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** primary HIFU for localised prostate cancer (T1–T2), no prior prostate cancer treatment including hormone therapy or radiotherapy **Exclusion criteria:** any form of incomplete ablation, such as nerve-sparing or focal HIFU, less than 2 years' follow-up or less than four PSA measurements after HIFU **Staging method:** N/R	**HIFU:** N/R	**Efficacy:** clinical failure (defined as positive prostate biopsy, initiation of secondary prostate cancer therapy), radiographic evidence of prostate cancer metastases or prostate cancer-related death)

Patient characteristics	HIFU
Number of patients enrolled	285
Age (years)	
Mean (SD)	68.9 (6.0)
Range	49–87
PSA level (ng/ml)	
Mean (SD)	6.6 (3.2)
Clinical stage, *n* (%)	
T1	152 (53.3)
T2a	83 (29.1)
T2b	43 (15.1)
T2c	7 (2.5)
Biopsy Gleason score	
Mean (SD)	5.6 (1.3)
Median	6
Prostate size (ml)	
Mean (SD)	25.9 (12.4)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Blana 2012[107] **Language:** English **Publication type:** full-text paper **Number of study centres:** 9 **Setting:** registry data **Country:** Germany, UK, France, Italy **Recruitment/treatment dates:** February 1993–October 2010 **Study design:** case series **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** yes	**Inclusion criteria:** patients with localised disease (T1–T2) with anteroposterior prostate height of ≤ 24 mm and a treated volume > 120% of the prostate volume **Exclusion criteria:** prior treatment for prostate cancer (non-steroidal antiandrogens, LHRH agonist, radiation therapy or cryotherapy)	**HIFU:** all patients had whole-gland treatment and 205 (57.6%) underwent TURP at the time of HIFU	**Efficacy:** negative biopsy rate, biochemical disease-free survival

Patient characteristics	HIFU
Number of patients enrolled	356
Low risk, *n* (%)	160 (45)
Intermediate risk, *n* (%)	141 (40)
High risk, *n* (%)	52 (15)
Unknown, *n* (%)	3 (1)
Age (years)	
Mean (SD)	69.6 (7.2)
PSA level (ng/ml)	
Median (range)	6.83 (0.12–58.0)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics		Intervention characteristics	Outcomes
Length of follow-up: median 2.8 years **Source of funding:** N/R **Systematic reviewer:** TEA	**Patient characteristics**	**HIFU**		
	Clinical stage, *n* (%)			
	T1c	142 (40)		
	T2a	83 (23)		
	T2b	53 (15)		
	T2c	37 (10)		
	Missing	41 (11.5)		
	Biopsy Gleason score, *n* (%)			
	≤ 6	271 (76)		
	7	80 (23)		
	8–10	5 (1)		
	Prostate size (ml)			
	Median (range)	18.0 (4.0–38.0)		
	Staging method: N/R			

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Boettcher 2012[108] **Language:** English **Publication type:** full-text papers **Number of study centres:** single **Setting:** hospital clinic **Country:** Germany **Recruitment/treatment dates:** November 1999–December 2006 **Study design:** NRCS **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** 6, 12, 24 and 36 months **Source of funding:** funded in part by the Forderverein Zur Kontinenzforchung und Kontinenzaufklarung e.V., Amtsgericht Aachen **Systematic reviewer:** SJ	**Inclusion criteria:** all patients with T1–T2 prostate cancer underwent therapy for localised prostate cancer in the clinic **Exclusion criteria:** N/R **Staging method:** N/R	**BT:** high dose rate, Ir-192; low dose rate, I-125 seeds application Only patients with a prostate volume of < 60 ml, a urinary flow rate of > 10 ml and no significant residual urine were eligible for BT **RP:** 66 patients; of these, 53 patients underwent RPP and 13 went through forms of RRP An extended RP was carried out in patients for whom the preservation of potency was not desirable	**Efficacy:** N/R **QoL:** overactive bladder, syndrome scores

Patient characteristics	BT	RP
Number of patients enrolled	33	66
Age (years)		
Mean (SD)	67.2 (5.4)	63.8 (6.4)
Range	57–75	43–77
PSA level, *n/N* (%)		
≥ 10 ng/ml	13/33 (39.4)	26/66 (39.4)
Clinical stage, *n/N* (%)		
T1	8/24 (33.3)	32/61 (52.4)
T2	16/24 (66.7)	24/61 (39.3)
T3	0/24 (0)	5/61 (8.2)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Borchers 2004[109] **Language:** English **Publication type:** full-text paper **Number of study centres:** N/R **Setting:** hospital clinic **Country:** Germany **Recruitment/treatment dates:** study initiated in 1999 **Study design:** NRCS **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** 6, 12 and 24 months after surgery. Median follow-up 26 months (range 12–60 months) **Source of funding:** N/R **Systematic reviewer:** SJ	**Inclusion criteria:** patients with prostate cancer of T1–T2a N0 M0, and with PSA levels of ≤ 10 ng/ml, a Gleason score of < 7 and a prostate volume of < 60 ml **Exclusion criteria:** no neoadjuvant therapy was allowed **Staging method:** N/R	**BT:** I-125 seeds were implanted. The prescription dose was 145 Gy in accordance with ABS recommendation. The maximum dose to urethra was 250 Gy, and the dose to 10% of the anterior rectal was restricted to 145 Gy The median source strength was 23.7 MBq (range 14.8–26.6 MBq) and the median number of sources was 54 (range 23–79) Only patients with a prostate volume of < 60 ml, a urinary flow rate of > 10 ml and no significant residual urine were eligible for BT **RP:** RPP method was used	**Efficacy:** PSA relapse-free survival **QoL:** EORTC-QLQ-C30 for urinary function, sexual function and HRQoL Kelley questionnaire for stool incontinence

Patient characteristics	BT	RP
Number of patients enrolled	52	42
Age (years)		
Mean (SD)	66.5 (6.0)	65.2 (4.9)
Range	54–75	56–76
PSA level (ng/ml)		
Mean (SD)	6.6 (2.6)	6.6 (2.6)
Median (range)	1.0–10.0	2.5–10.0
Clinical stage, *n* (%)		
T1c	23 (44)	19 (45)
T2a[a]	29 (56)	23 (55)
Biopsy Gleason score, *n* (%)		
2–4	21 (40)	18 (42)
5–6	31 (60)	24 (58)

a Reported as 39 (56%).

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Bradley 2004[110] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** 1 January 1997–1 August 2000 **Study design:** NRCS **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** BT, median 25.5 months; RP, median 18.8 months **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** all were stage T1c–T3. Patients with PSA < 10 ng/ml or Gleason score of < 7 or clinical stage < T2c had BT **Exclusion criteria:** metastatic disease **Staging method:** N/R	**BT:** Pd-103 implant dose of 115 Gy; all had 8 months of hormonal therapy beginning 2–3 months before treatment **RP:** retropubic, bladder neck-sparing approach with or without nerve sparing	**Functional:** continence, pad use **Adverse events:** diarrhoea **QoL:** physical well-being, social/family well-being, functional well-being, emotional well-being

Patient characteristics	BT	RP
Number of patients enrolled	130	77
Age (years)		
Median (IQR)	68.5 (63.1–72.2) (*n* = 102)	60.4 (55.3–63.8) (*n* = 60)
PSA level (ng/ml)		
Median (IQR)	6.5 (5.1–9.5) (*n* = 102)	5.3 (4.6–8.1) (*n* = 60)
Clinical stage, *n*/*N* (%)		
≤ T1	63/99 (64)	46/60 (77)
T2	35/99 (35)	13/60 (22)
≥ T3	1/99 (1)	1/60 (2)
Biopsy Gleason score, *n*/*N* (%)		
≤ 6	74/89 (83)	37/57 (65)
7	15/89 (17)	14/57 (25)
8–10	0/89 (0)	6/57 (11)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Bul 2013[111,197] **Language:** English **Publication type:** full-text paper **Number of study centres:** 100 **Setting:** hospitals **Country:** multinational study (17 countries) **Recruitment/treatment dates:** December 2006–May 2012 **Study design:** case series **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** median follow-up for cohort was 1.6 (IQR 1.0–2.8) years **Source of funding:** the PRIAS study is supported by grants from the Prostate Cancer Research Foundation (SWOP), Rotterdam, and the Dutch Urological Association (project 10222946) **Systematic reviewer:** SJ	**Inclusion criteria:** eligible patients fulfil the PRIAS inclusion criteria for low-risk prostate cancer: clinical stage T1C/T2, PSA ≤ 10 ng/ml, PSA density < 0.2 ng/ml per ml, one or two positive biopsy cores and Gleason score of ≤ 6 **Exclusion criteria:** N/R **Staging method:** N/R	**AS:** the follow-up protocol scheduled PSA measurements every 3 months for the first 2 years and PSA measurements every 6 months thereafter. Repeat biopsies were scheduled after 1, 4 and 7 years; in case of a PSA doubling time between 3 and 10 years, yearly repeat biopsies were advised. Volume-dependent biopsies were recommended according to protocol	**Efficacy:** overall survival, disease-specific survival

Patient characteristics	AS
Number of patients enrolled	2494
Age (years)	
Median (IQR)	65.8 (61.0–70.4)
PSA level (ng/ml)	
Median (IQR)	5.6 (4.4–7.0)
Clinical stage, *n* (%)	
T1	2122 (85.1)
T2a	324 (87.1)
T2b	34 (9.1)
T2c	14 (3.8)
Biopsy Gleason score, *n* (%)	
≤ 6	2494 (100)
Prostate size (ml)	
Median (IQR)	44 (35–57)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Buron 2007[113] **Language:** English **Publication type:** full-text paper **Number of study centres:** 11 **Setting:** hospital **Country:** France **Recruitment/treatment dates:** March 2001–June 2002 **Study design:** case series **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** BT, mean 28.5 (SD 2.9) months; RP, mean 25.0 (SD 2.6) months **Source of funding:** French Ministry of Health **Systematic reviewer:** TEA	**Inclusion criteria:** T1/T2 N0 M0 localised cancer, PSA < 20 ng/ml, biopsy Gleason score of < 8 **Exclusion criteria:** N/R	**BT:** permanent I-125 seeds at a dose of 145 Gy were implanted. 43.5% received neoadjuvant hormone therapy **RP:** 109/127 patients (86%) had retropubic approach, whereas others had laparoscopic approach. 6.3% received neoadjuvant hormonal therapy	**Functional:** ED, urinary incontinence, faecal incontinence **QoL:** global health status **Adverse events:** urinary pain

Patient characteristics	BT	RP
Number of patients enrolled	308	127
Age (years)		
Mean (SD)	65.2 (6.3)	62.7 (6.0)
PSA level (ng/ml)		
Mean (SD)	7.5 (2.7)	8.9 (4.0)
Clinical stage, *n* (%)		
T1	200 (64.9)	67 (52.8)
T2	108 (35.1)	60 (47.2)
Biopsy Gleason score		
Mean (SD)	5.5 (1.1)	5.5 (1.1)
Prostate size (ml)		
Mean (SD)	37.3 (13.0)	38.8 (16.9)
Comorbidity, *n* (%)		
Hypertension	103 (33.3)	38 (29.7)

Staging method: N/R

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Caso 2012[114,115] **Language:** English **Publication type:** full-text paper **Number of study centres:** N/R **Setting:** hospital/outpatient **Country:** USA **Recruitment/treatment dates:** data were collected 2002–10 **Study design:** case series **Prospective/retrospective data collection:** prospectively maintained database **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** median 25.7 (range 9.4–43.2) months **Source of funding:** co-author Thomas Polascik is supported by research funds from Galil Medical **Systematic reviewer:** SJ	**Inclusion criteria:** unclear Hormonal ablation was used in some people with prostate volumes estimated at > 40 g and was stopped immediately **Exclusion criteria:** patients who received neoadjuvant radiotherapy as part of salvage therapy or clinical trial	**CRYO:** all patients were treated using third-generation technology. Neurovascular preservation was attempted in certain potent people before surgery by placing an active cryoneedle outside the prostate and keeping the area warm with helium Briefly, 17-gauge cryoneedles (SeedNet™; Galil Medical, Plymouth Meeting, PA) were introduced into the prostate under TRUS guidance through a BT grid A cystoscopy was performed afterwards, with subsequent placement of a urethral warming catheter. Two freeze–thaw cycles were performed with real-time temperature and TRUS monitoring. Afterwards, patients were followed up with 3-month PSA values, which were spaced out after 1 year if stable	**Efficacy:** deaths recorded **Functional outcomes:** ED, persistent incontinence

Patient characteristics	CRYO
Number of patients enrolled	106
Age (years)	
Median (range)	69.6 (63.1–73.9)
PSA level (ng/ml)	
Median (range)	5.1 (4.2–8.5)
Clinical stage, *n* (%)	
T1	80 (75.5)
T2	26 (24.5)
Biopsy Gleason score, *n* (%)	
≤ 6	63 (59.4)
7	33 (31.1)
≥ 8	10 (9.4)
Comorbidity: preoperative LUTS, *n* (%)	
Yes	55 (52)
No	51 (48)
Erectile dysfunction: preoperative impotence, *n* (%)	
Yes	71 (67)
No	35 (33)

Staging method: DRE, bone scan, CT or endorectal coil MRI

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Polascik 2007[175] (secondary to Caso 2012[114,115])	**Inclusion criteria:** people with biopsy-proven prostate cancer underwent primary cryosurgery for clinically localised prostate cancer. Patients with prostates larger than 40 cm^3 underwent hormonal ablation for 3–6 months	**CRYO:** all patients underwent a dual freeze–thaw cycle using third-generation cryotechnology with ultrathin 17-gauge cryoneedles (SeedNet)	**Efficacy:** PSA level (ng/ml), overall survival
Language: English	**Exclusion criteria:** patients who had previously undergone surgery, radiotherapy or cryoablation for prostate cancer were excluded	**Procedure:** the patient was placed in a modified lithotomy position after induction with general anaesthesia	**Functional outcomes:** urinary incontinence, ED/impotence
Publication type: full-text paper			
Number of study centres: single			
Setting: outpatient and some inpatient (hospital)			
Country: USA			
Recruitment/treatment dates: from January 2002 to 2005			
Study design: case series			
Prospective/retrospective data collection: N/R			
Patients recruited consecutively (Y/N): N/R			
Length of follow-up: median 18 (range 3–43) months			
Source of funding: N/R			
Systematic reviewer: SJ			

Patient characteristics	CRYO
Number of patients enrolled	50
Age (years)	
Median (range)	68 (50–83)
PSA level (ng/ml)	
Median (range)	5.1 (0.2–17)
Clinical stage, *n* (%)	
T1c	39 (78)
T2a	10 (20)
T2b	1 (2)
Biopsy Gleason score, *n* (%)	
≤ 6	36 (72)
7	9 (18)
8	5 (10)
Prostate size (ml)	
Median (range)	26 (7–69)
Erectile dysfunction, *n* (%)	44 (88)
Incontinence, *n/N* (%)	1/50 (2)

Staging method: N/R

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Chaussy 2003[116] **Language:** English **Publication type:** full-text paper **Number of study centres:** single **Setting:** hospital **Country:** Germany **Recruitment/treatment dates:** N/R **Study design:** case series **Prospective/retrospective data collection:** N/R **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** HIFU group, mean 18.7 (± 12.1) months (range 3.0–46.3 months); TURP and HIFU group, mean 10.9 (± 6.2) months (range 2.9–26.9 months)	**Inclusion criteria:** selection criteria for HIFU treatment were localised prostate cancer, no previous treatment for prostate cancer and PSA ≤ 15 ng/ml at diagnosis **Exclusion criteria:** patients who received hormones before the HIFU treatment for more than 6 months were excluded from analysis	**HIFU, HIFU + TURP:** treatments were performed using the Ablatherm device. HIFU energy is delivered through an endorectal probe that includes an imaging and a firing transducer. The high-energy ultrasonic waves propagate through the rectal wall and are focused on the prostate, generating intense heat and causing the coagulation of prostate tissue within the focal area. Each shot creates a lesion that spans from the anterior to the posterior prostate capsula. The transducer movements allow for the accurate positioning of the focal point. They also help define the appropriate lesion depth to match the prostate shape. Contiguous shots are delivered repeatedly to obtain a complete treatment of the gland and preserve the rectal wall and the surrounding tissues	**Efficacy:** PSA stability rate **QoL:** I-PSS **Functional outcomes:** potency status, stress incontinence **Adverse events:** urinary tract infections

Patient characteristics	HIFU	HIFU + TURP	Total
Number of patients enrolled	96	175	271
Age (years)			
Mean (SD)	65.8 (7.6)	68.4 (6.8)	
PSA level (ng/ml)			
Mean (SD)	8.6 (3.2)	8.0 (3.4)	
Clinical stage, *n*/*N* (%)[a]			
T1	N/R	N/R	
T2	N/R	N/R	
Low risk, *n* (%)	37 (38.5)	71 (40.6)	108 (39.8)
Intermediate risk, *n* (%)	55 (57.3)	95 (54.3)	150 (55.3)
High risk, *n* (%)	4 (4.2)	9 (5.1)	13 (4.8)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Source of funding: N/R **Systematic reviewer:** SJ	**Staging method:** N/R	The TURP procedure is performed first, mainly resecting the anterior and lateral parts of the prostate. Immediately following the TURP, the HIFU treatment is performed 271 patients received a total of 303 HIFU sessions owing to a 11.4% retreatment rate: 25% in the HIFU group and 4% in the TURP and HIFU group	

Patient characteristics	HIFU	HIFU + TURP	Total
Biopsy Gleason score, *n*/*N* (%)			
≤ 6	67/96 (69.8)	130/175 (74.3)	197/271 (72.7)
7	25/96 (26)	38/175 (21.7)	3/271 (23.3)
8–10	4/96 (4.2)	7/175 (4)	11/271 (4)
Prostate size (ml)			
Mean (SD)	21.7 (6.8)	20.5 (9.8)	

a All patients were clinical stage T1 or T2.

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Chen 2009[117] **Language:** English **Publication type:** full-text paper **Number of study centres:** 4 **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** 1994–2000 **Study design:** case series **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** 36 months	**Inclusion criteria:** patients with untreated localised prostate cancer **Exclusion criteria:** N/R	**BT:** N/R **EBRT:** N/R **RP:** N/R	**Functional outcomes:** sexual dysfunction, UI, bowel problems, urinary obstruction/irritation

Patient characteristics	BT	EBRT	RP
Number of patients analysed (total enrolled = 522)	92	190	127
Low risk, *n* (%)	52 (57)	66 (35)	43 (34)
Intermediate risk, *n* (%)	20 (22)	60 (32)	43 (34)
High risk, *n* (%)	20 (22)	64 (34)	41 (33)
Age (years)			
Median (range)	64 (47–77)	69 (51–82)	60 (46–74)
PSA level, *n* (%)			
≤ 10 ng/ml	85 (92)	127 (67)	105 (83)
10–20 ng/ml	7 (8)	44 (23)	18 (14)
> 20 ng/ml	0 (0)	19 (10)	4 (3)

Study details	Participant characteristics				Intervention characteristics	Outcomes
Source of funding: James A Talcott **Systematic reviewer:** TEA	**Patient characteristics**	**BT**	**EBRT**	**RP**		
	Clinical stage, *n* (%)					
	T1	73 (79)	142 (75)	97 (76)		
	T2	19 (21)	48 (25)	30 (24)		
	Biopsy Gleason score, *n* (%)					
	4–6	72 (78)	91 (48)	64 (51)		
	7	19 (21)	66 (35)	50 (39)		
	8–10	1 (1)	33 (18)	13 (10)		
	Comorbidity: index of coexistent disease, *n* (%)					
	0	32 (35)	46 (24)	48 (38)		
	1	59 (64)	135 (71)	79 (62)		
	2 or 3	1 (1)	9 (5)	0 (0)		
	Staging method: N/R					

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Coen 2012[119] **Language:** English **Publication type:** full-text paper **Number of study centres:** 2 **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** EBRT 1996–9; BT 1997–2002 **Study design:** case series **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** no **Length of follow-up:** BT, median 7.4 (range 3.1–11.3) years; EBRT, median 8.6 (range 1.2–12.3) years	**Inclusion criteria:** stage 1b–2b; serum PSA < 15 ng/ml; no evidence of metastatic disease as assessed by whole-body scan (if PSA ≥ 10 ng/ml, tumour stage T2b or Gleason ≥ 7) and abdominal and pelvic CT Matching criteria applied on BT patients: the implant was performed between 1997 and 2002, at least 3 years of follow-up, no external radiation or ADT was used as a component of the primary therapy, T1 or T2, Gleason ≤ 7, PSA ≤ 15 ng/ml, no age restriction, both I-125 and Pd-103 were allowed **Exclusion criteria:** no exclusion from entry into the study on the basis of tumour histology (Gleason score); however, patients with a Gleason score of > 7 were excluded from this case-matched analysis	**BT:** delivered using either I-125 (145 Gy) or Pd-103 (115 Gy). No patient received neoadjuvant, concurrent or adjuvant hormonal therapy **EBRT:** a dose of 50.4 Gy was delivered using three-dimensional conformal photon radiation to the prostate and seminal vesicles; patients received a photon boost delivered to the prostate alone before the photon component of the therapy. No patient received neoadjuvant, concurrent or adjuvant hormonal therapy	**Efficacy:** biochemical failure

Patient characteristics	BT	EBRT
Number of patients enrolled	144	144
Age (years) ($n = 141$)		
Median (range)	65 (48–78)	67 (47–76)
PSA level, *n/N* (%)		
≤ 4 ng/ml	28/141 (20)	17/141 (12)
4–10 ng/ml	107/141 (76)	112/141 (79)
10–15 ng/ml	6/141 (4)	12/141 (9)

Study details	Participant characteristics			Intervention characteristics	Outcomes
Source of funding: N/R	**Patient characteristics**	**BT**	**EBRT**		
Systematic reviewer: TEA	Median PSA level, ng/ml (range)	5.6 (0.6–12.1)	6.1 (0.7–13.8)		
	Clinical stage, *n*/*N* (%)				
	T1c	104/141 (74)	104/141 (74)		
	T2a	36/141 (26)	36/141 (26)		
	T2b	1/141 (1)	1/141 (1)		
	Biopsy Gleason score, *n*/*N* (%)				
	6	125/141 (89)	125/141 (89)		
	7	16/141 (11)	16/141 (11)		
	Staging method: N/R				

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Colombel 2006[120] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** France **Recruitment/treatment dates:** N/R **Study design:** case series **Prospective/retrospective data collection:** N/R **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** 5 years **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** N/R **Exclusion criteria:** N/R **Staging method:** N/R	**HIFU:** performed using the Ablatherm device, transurethral resection of the transitional zone before HIFU, no nerve-sparing intent	**Efficacy:** PSA nadir, negative biopsy, treatment success, disease-free survival **Functional:** potency, UI **Adverse events:** bladder neck stenosis

Patient characteristics	HIFU
Number of patients enrolled	242
Age (years)	
Mean (SD)	71.0 (5.5)
PSA level (ng/ml)	
Mean (SD)	9.22 (5.5)
Clinical stage, *n* (%)	
T1c	118 (49)
T2	124 (51)
Prostate size (ml)	
Mean (SD)	24 (10)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Crook 2011[121] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** Canada **Recruitment/treatment dates:** May 2002–April 2004 **Study design:** RCT and NRCS **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Randomisation method:** N/R **Length of follow-up:** mean 5.3 years, median 5.2 years, range 3.2–6.5 years **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** people with favourable-risk prostate cancer (Gleason score of ≤ 6, PSA < 10 ng/ml, stage T1–T2a) **Exclusion criteria:** N/R **Staging method:** N/R	**BT:** N/R **RP:** N/R	**QoL:** prostate cancer-specific EPIC domains (UI, urinary irritation/ obstruction, sexual function and bowel function)

Patient characteristics	BT	RP
Number of patients enrolled	94	62
Total enrolled = 190 (34 of the total enrolled were randomly assigned but the number assigned per group was unclear)		
Number analysed		
Non-randomised participants	86	50
Randomised participants	16	16
Total analysed	102	66
Age (years)		
Mean (SD)	61.4 (6.2)	59.4 (5.9)
PSA level (ng/ml)		
Median (SD)	5.5 (2.1)	5.3 (2.8)
Medications for heart disease, diabetes and hypertension, *n* (%)	51 (50)	27 (40.9)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Cytron 2003[122] **Language:** English **Publication type:** full-text paper **Number of study centres:** N/R **Setting:** hospital **Country:** Israel **Recruitment/treatment dates:** N/R **Study design:** case series **Prospective/retrospective data collection:** N/R **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** 18 (mean 13.2) months **Source of funding:** N/R **Systematic reviewer:** SJ	**Inclusion criteria:** patients with locally confined prostate cancer diagnosed by prostate biopsy All of these patients were categorised into two groups: favourable group (PSA ≤ 10 ng/ml, Gleason score of ≤ 6, TNM ≤ T2a) and unfavourable group (PSA > 10 ng/ml, Gleason score of > 6, TNM > T2a) **Exclusion criteria:** N/R **Staging method:** N/R	**CRYO:** the method used consists of insertion of an array of ultrathin SeedNet needles This evaluated the feasibility of a new method of active rectal wall protection during cryoablation of the prostate. Fourteen ultrathin, 17-gauge probes (cryoneedles) were percutaneously introduced into the prostate under TRUS guidance. The peripheral region of the prostate and the area between the prostate and rectal wall were real-time monitored for temperature changes. Two cryoneedles were placed between the prostate and rectal wall for active warming using the thawing mode when the temperatures dropped to approximately 0 °C, and rectal lumen washing with hot water (+40 °C) when the temperature reading dropped further to –8 °C or –10 °C	**Efficacy:** PSA level

Patient characteristics	CRYO
Number of patients enrolled	22
PSA level (ng/ml)	
Mean (SD)	11.8 (7.68)
Median (range)	9.5 (5.1–36)
Clinical stage, *n* (%)	
T1c	14 (63.6)
T2a	4 (18.2)
T2b	4 (18.2)
Biopsy Gleason score, *n* (%)	
≤ 6	12 (54.5)
7	7 (31.8)
8–10	3 (13.8)
Prostate size (ml)	
Mean (SD)	37.2 (12.5)
Median (range)	34.6 (18–66.2)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: D'Amico 1998[36] **Language:** English **Publication type:** full-text paper **Number of study centres:** 2 **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** January 1989–October 1997 **Study design:** NRCS **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** BT, median 41 (range 3–72) months; RP, median 38 (range 8–100) months; EBRT, median 38 (range 8–75) months **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** clinically localised prostate cancer **Exclusion criteria:** N/R	**BT:** Pd-103 seeds at a dosage of 115 Gy **EBRT:** low-risk patients had 66 Gy (66–70 Gy) in 2-Gy fractions delivered to the prostate only with a margin of 1.5 cm. Other patients were irradiated with a median dose of 45 Gy (45–50.4 Gy) in 1.8-Gy fractions to the prostate and seminal vesicles and a 1.5-cm margin **RP:** retropubic approach with bilateral pelvic lymph node sampling	**Efficacy:** PSA failure-free survival

Patient characteristics	BT	EBRT	RP
Number of patients enrolled	218	766	888
Low risk, *n* (%)	123 (56)	225 (29)	402 (45)
Intermediate risk, *n* (%)	53 (24)	232 (30)	247 (28)
High risk, *n* (%)	42 (19)	309 (40)	239 (27)
PSA level, *n* (%)			
> 0–4 ng/ml	21 (10)	77 (10)	85 (10)
4.1–10 ng/ml	148 (68)	329 (43)	510 (57)
10.1–20 ng/ml	40 (18)	198 (26)	210 (24)
> 20 ng/ml	9 (4)	162 (21)	83 (9)
Clinical stage, *n* (%)			
T1c	72 (33)	222 (29)	256 (29)
T2a	103 (47)	246 (32)	388 (44)
T2b	12 (6)	141 (18)	93 (10)
T2c	31 (14)	157 (20)	151 (17)
Biopsy Gleason score, *n* (%)			
2–4	16 (7)	109 (14)	164 (18)
5–6	157 (72)	376 (49)	517 (58)
7	39 (18)	192 (25)	133 (15)
8–10	6 (3)	89 (12)	74 (8)

Staging method: DRE

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: D'Amico 2003[123] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** 1997–2000 **Study design:** NRCS **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** BT median 3.95 years; RP median 4.2 years	**Inclusion criteria:** clinical stage T1c, PSA level < 10 ng/ml and biopsy Gleason score of 3 + 4 or less and no perineural invasion on biopsy **Exclusion criteria:** patients who had previous TURP, daytime urinary frequency more frequent than every 2 hours and/or nocturia exceeding 4 hours that was refractory to α_{1A}-blocker were not eligible for BT	**BT:** the target volume receiving 100% of the prescribed dose was at least 100%. No patient received neoadjuvant or adjuvant androgen suppression or radiotherapy **RP:** no patient received neoadjuvant or adjuvant androgen suppression or radiotherapy	**Efficacy:** PSA failure-free survival, prostate cancer-related death, PSA control, PSA nadir

Patient characteristics	BT	RP
Number of patients enrolled	227	406
Age, *n* (%)		
< 60 years	72 (32)	194 (48)
60–64 years	75 (33)	97 (24)
65–69 years	39 (17)	85 (21)
≥ 70 years	41 (18)	28 (7)
Median age, years (range)	62 (49–79)	60 (44–75)
PSA level, *n* (%)		
< 4 ng/ml	43 (19)	37 (9)
4–9.9 ng/ml	184 (81)	369 (91)

Study details	Participant characteristics			Intervention characteristics	Outcomes
Source of funding: research grant **Systematic reviewer:** TEA	**Patient characteristics**	**BT**	**RP**		
	Clinical stage, *n* (%)				
	T1c	227 (100)	406 (100)		
	Biopsy Gleason score, *n* (%)				
	≤ 5	18 (8)	81 (20)		
	6	184 (81)	264 (65)		
	3 + 4	25 (11)	61 (15)		
	Prostate size, *n* (%)				
	< 20 ml	14 (6)	4 (1)		
	20–44.9 ml	132 (58)	106 (26)		
	45–59.9 ml	45 (20)	154 (38)		
	60–99.9 ml	34 (15)	122 (30)		
	≥ 100 ml	2 (1)	20 (5)		
	Staging method: N/R				

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Donnelly 2002[124] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** Canada **Recruitment/treatment dates:** December 1994–February 1998 **Study design:** case series **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** median 60.8 (range 35–85) months	**Inclusion criteria:** see Saliken 1999[180] **Exclusion criteria:** see Saliken 1999[180] **Patient characteristics** / **CRYO** Number of patients enrolled: 76 Age (years) Mean (range): 65 (51–77) PSA level, *n* (%) < 10 ng/ml: 47 (62) > 10 ng/ml: 29 (38) Mean PSA level, ng/ml (range): 9.7 (1.5–30) Clinical stage, *n* (%) T2a: 43 (56) T2b: 24 (32) T2c: 0 (0) T3a: 6 (8) T3b: 3 (4)	**CRYO:** see Saliken 1999[180]	**Efficacy:** 5-year cancer-specific survival, overall survival, biochemical disease-free status, positive biopsy, reintervention rate **Functional:** impotence, incontinence **Adverse events:** urethral sloughing requiring TURP, testicular abscess

Study details	Participant characteristics		Intervention characteristics	Outcomes
Source of funding: Alberta Cancer Board **Systematic reviewer:** TEA	**Patient characteristics**	**CRYO**		
	Biopsy Gleason score, *n* (%)			
	5	4 (5)		
	6	30 (39)		
	7	29 (38)		
	8	8 (11)		
	9	5 (7)		
	Mean biopsy Gleason score	7		
	Median biopsy Gleason score	6		
	Comorbidity, *n* (%)	See Saliken 1999[180] for comorbidity data available at baseline for the first 71 patients		
	Staging method: see Saliken 1999[180]			

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Robinson 2002[178] (secondary to Donnelly 2002[124]) **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** Canada **Recruitment/treatment dates:** December 1994–February 1998 **Study design:** case series **Prospective/retrospective data collection:** prospective	**Inclusion criteria:** see Saliken 1999[180] **Exclusion criteria:** see Saliken 1999[180]	**CRYO:** see Saliken 1999[180]	**QoL:** physical well-being, social/family well-being, functional well-being, emotional well-being, relationship with doctor, additional concerns, appetite, maintain body weight, not bothered by aches and pains, not experiencing aches and pains, pain does not hinder activities, satisfied with comfort, bowel movement, no difficulty urinating, no increased urinary frequency, activities not limited by urination, satisfied with sex life, feel like an individual, able to have erection

Patient characteristics	CRYO
Number of patients enrolled	76
Age (years)	
< 60	17 (22)
60–69	39 (51)
70–77	20 (26)
PSA level, ng/ml	
1.5–10	46 (60)
11–20	25 (33)
21–30	5 (7)

Study details	Participant characteristics		Intervention characteristics	Outcomes
Patients recruited consecutively (Y/N): yes **Length of follow-up:** 3 years **Source of funding:** Alberta Cancer Board **Systematic reviewer:** TEA	**Patient characteristics**	**CRYO**		
	Clinical stage, *n* (%)			
	T2a	28 (37)		
	T2b	15 (20)		
	T2c	24 (32)		
	T3a	4 (5)		
	T3b	5 (7)		
	Biopsy Gleason score, *n* (%)			
	< 5	0 (0)		
	5–7	63 (83)		
	8–10	13 (17)		
	Comorbidity, *n* (%)	See Saliken 1999[180] for comorbidity data available at baseline for the first 71 patients		
	Staging method: see Saliken 1999[180]			

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Robinson 1999[177] (secondary to Donnelly 2002[124]) **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** Canada **Recruitment/treatment dates:** December 1994–February 1998 **Study design:** case series **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** yes	**Inclusion criteria:** see Saliken 1999[180] **Exclusion criteria:** see Saliken 1999[180]	**CRYO:** see Saliken 1999[180]	**QoL:** physical well-being, social/family well-being, functional well-being, emotional well-being, relationship with doctor, additional concerns, appetite, weight loss, aches and pain, certain areas of pain, pain hinders activities, satisfied with comfort, trouble moving bowels, difficulty urinating, urinate more frequently, urinating limits activities, satisfied with sex life, feel like an individual, able to have erection

Patient characteristics	CRYO
Number of patients enrolled	70
Age, *n*/*N* (%)	
< 60 years	15/69 (22)
60–69 years	32/69 (46)
70–77 years	22/69 (32)
Mean age, years (range)	66 (51–77)
PSA level, *n*/*N* (%)	
1.5–10 ng/ml	46/69 (67)
11–20 ng/ml	21/69 (30)
21–30 ng/ml	2/69 (3)

Study details	Participant characteristics		Intervention characteristics	Outcomes
Length of follow-up: 1 year **Source of funding:** Alberta Cancer Board **Systematic reviewer:** TEA	**Patient characteristics**	**CRYO**		
	Mean PSA level, ng/ml (range)	9.7 (1.5–30)		
	Clinical stage, *n*/*N* (%)			
	T2a	26/69 (38)		
	T2b	13/69 (19)		
	T2c	22/69 (32)		
	T3a	3/69 (4)		
	T3b	5/69 (7)		
	Biopsy Gleason score, *n*/*N* (%)			
	< 5	0/69 (0)		
	5–7	56/69 (81)		
	8–10	13/69 (19)		
	Mean biopsy Gleason score	6.6		
	Comorbidity, *n* (%)	See Saliken 1999[180]		
	Staging method: see Saliken 1999[180]			

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Saliken 1999[180] (secondary to Donnelly 2002[124]) **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** Canada **Recruitment/treatment dates:** December 1994–February 1997 **Study design:** case series **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** 10–36 months **Source of funding:** Alberta Cancer Board	**Inclusion criteria:** localised biopsy-proven adenocarcinoma of the prostate, Karnofscky score of ≥ 70, PSA ≤ 30 ng/ml, clinical stage T1–T3, N0, M0. Prior to inclusion in the study, a laparoscopic pelvic lymph node dissection was carried out if the patient's risk of lymph node involvement exceeded 5% as calculated by the formula of Roach **Exclusion criteria:** T4, any evidence of metastases, a gland size > 60 g, any previous treatment for prostate cancer, coagulopathy, urinary tract infection, an inability to give informed consent	**CRYO:** multiprobe supercooled liquid nitrogen-based cryogenic system; after patient 30, neoadjuvant hormonal therapy was initiated for gland downsizing (glands > 30 g). 26 patients received 3 months of neoadjuvant hormonal therapy	**Efficacy:** biochemical disease-free status, positive biopsy, reintervention rate **Functional outcomes:** incontinence **Adverse events:** urinary retention requiring TURP, testicular abscess

Patient characteristics	CRYO
Number of patients enrolled	71
Age (years)	
Mean (range)	65 (51–77)
PSA level (ng/ml)	
Mean (range)	9.7 (1.5–30)
Clinical stage, *n* (%)	
T2a	28 (39)
T2b	13 (18)
T2c	22 (31)
T3a	3 (4)
T3b	5 (7)

Study details	Participant characteristics		Intervention characteristics	Outcomes
Systematic reviewer: TEA	**Patient characteristics**	**CRYO**		
	Biopsy Gleason score, *n* (%)			
	5	5 (7)		
	6	31 (31)		
	7	22 (31)		
	8	8 (11)		
	9	5 (7)		
	Mean, median biopsy Gleason score	7, 6		
	Comorbidity, *n* (%)			
	Bladder dysfunction with large postvoid residual volumes	1 (1.4)		
	Chronic and clinically severe arteriopathy	1 (1.4)		
	Staging method: clinical evaluation, bone scan, TRUS scan and biopsy results			

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Donnelly 2010[125] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** Canada **Recruitment/treatment dates:** December 1997–February 2003 **Study design:** RCT **Prospective/retrospective data collection:** prospective **Randomisation method:** N/R **Length of follow-up:** median 100 (range 53–128) months **Source of funding:** National Cancer Institute of Canada, Alberta Cancer Board **Systematic reviewer:** TEA	**Inclusion criteria:** see Robinson 2009[179] **Exclusion criteria:** see Robinson 2009[179]	**CRYO:** see Robinson 2009[179] **EBRT:** see Robinson 2009[179]	**Functional:** urgency/frequency, incontinence, gastrointestinal incontinence, urgency/frequency/ diarrhoea, bowel function, sexual function, urinary function **QoL:** physical function, role function, emotional function, cognitive function, social function, health function, fatigue score, nausea and vomiting, pain score **Adverse events:** proctitis, gastrointestinal pain and bleeding, anorectal toxicity, genitourinary pain and bleeding, retention

Patient characteristics	CRYO	EBRT
Number of patients randomised	122	122
Age (years)		
Median (range)	69.4 (52.8–81.4)	68.6 (53.2–78.6)
PSA level (ng/ml)		
Median (IQR, range)	8.1 (5.7–10.9, 0.7–19.9)	9.0 (6.6–12.5, 2.5–23.3)
Clinical stage, *n* (%)		
T2a	22 (18.0)	20 (16.4)
T2b	28 (23.0)	23 (18.9)
T2c	49 (40.2)	57 (46.7)
T3a	17 (13.9)	18 (14.8)
T3b, c	6 (4.0)	4 (3.3)
Biopsy Gleason score, *n* (%)		
4–5	5 (4.1)	2 (1.6)
6	37 (30.3)	42 (34.4)
7	69 (56.6)	65 (53.3)
8–10	11 (9.0)	13 (10.7)

Staging method: see Robinson 2009[179]

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Robinson 2009[179] (secondary to Donnelly 2010[125]) **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** Canada **Recruitment/treatment dates:** December 1997–February 2003 **Study design:** RCT **Prospective/retrospective data collection:** prospective **Randomisation method:** N/R **Length of follow-up:** median 100 (range 53–128) months **Source of funding:** National Cancer Institute of Canada, Alberta Cancer Board **Systematic reviewer:** TEA	**Inclusion criteria:** histologically proven prostate adenocarcinoma, T2 or T3 with no evidence of lymph node or distant metastases, pretreatment PSA ≤ 20 ng/ml, gland volume ≤ 60 cm^3 **Exclusion criteria:** clinically bulky T3 tumour, prior pelvic radiation, previous ADT at any point, TURP within the previous 3 months	**CRYO:** multiprobe supercooled liquid nitrogen-based cryogenic system was used. All patients received neoadjuvant antiandrogen therapy **EBRT:** 68 Gy, 70 Gy and 73.5 Gy (reflecting the changing standards of practice) were administered. All patients received neoadjuvant antiandrogen therapy	**Efficacy:** biochemical failure, non-prostate cancer death, positive biopsy rate **Adverse events:** shortness of breath, insomnia, appetite loss, constipation, diarrhoea

Patient characteristics	CRYO	EBRT
Number of patients randomised	122	122
Age (years)		
Median (range)	69.4 (52.8–81.4)	68.6 (53.2–78.6)
PSA level (ng/ml)		
Median (IQR, range)	8.1 (5.7–10.9, 0.7–19.9)	9.0 (6.6–12.5, 2.5–23.3)
Clinical stage, *n* (%)		
T2a	22 (18.0)	20 (16.4)
T2b	28 (23.0)	23 (18.9)
T2c	49 (40.2)	57 (46.7)
T3a	17 (13.9)	18 (14.8)
T3b, c	6 (4.0)	4 (3.3)
Biopsy Gleason score, *n* (%)		
4–5	5 (4.1)	2 (1.6)
6	37 (30.3)	42 (34.4)
7	69 (56.6)	65 (53.3)
8–10	11 (9.0)	13 (10.7)

Staging method: physical examination, TRUS-guided 10-core biopsy, lymph node dissection for patients with Gleason ≥ 8

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Eade 2008[126] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** BT, May 1998–August 2004; IMRT, August 2001–June 2004 **Study design:** NRCS **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** IMRT, median 43 (range 17–61) months; BT, median 48 (range 16–99) months **Source of funding:** N/R	**Inclusion criteria:** clinical stage T1C–T2B, PSA ≤ 10 ng/ml and Gleason score of ≤ 6, treated with either IMRT or BT (caution was exercised when considering implants in patients with diabetes or previous TURP) **Exclusion criteria:** any neoadjuvant ADT, treatment with a combination of EBRT and seed implant or follow-up of less than 15 months	**I-125 transperineal permanent prostate seed implant (BT):** the prescribed minimum radiation dose was 145 Gy; 2/158 (1.3%) had prior TURP **IMRT (EBRT):** the prescription dose was 74–78 Gy, delivered with 6-MV or higher photons in daily fractions of 2.0 Gy; 17/216 (1.3%) had prior TURP	**Efficacy:** freedom from biochemical failure **Adverse events:** acute and late gastrointestinal and genitourinary toxicities

Patient characteristics	BT	EBRT
Number of patients enrolled	158	216
Age (years)		
Median (range)	64.7 (42.0–78.3)	67.6 (26.7–80.6)
PSA level, *n* (%)		
< 5 ng/ml	71 (45)	97 (45)
5–8 ng/ml	69 (44)	103 (48)
8–10 ng/ml	18 (11)	16 (7)
Median PSA level, ng/ml (range)	5.2 (0.5–9.8)	5.2 (0.4–9.6)
Clinical stage, *n* (%)		
T1c	132 (84)	169 (78)
T2a	26 (17)	33 (15)
T2b	0 (0)	14 (7)

Study details	Participant characteristics			Intervention characteristics	Outcomes
Systematic reviewer: TEA	**Patient characteristics**	**BT**	**EBRT**		
	Biopsy Gleason score, *n* (%)				
	5	6 (4)	8 (4)		
	6	152 (96)	208 (96)		
	Prostate size (ml)				
	Median (range)	38.1 (22–66.8) (*n* = 158)	47.8 (12.9–160) (*n* = 199)		
	Comorbidity, *n* (%)				
	Diabetes	18 (11)	36 (17)		
	Staging method: N/R				

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: El Fegoun 2011[127] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** France **Recruitment/treatment dates:** June 1997–March 2000 **Study design:** case series **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** median 10.6 (range 7.5–11.1) years **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** PSA ≤ 10 ng/ml, ≤ 3 positive biopsies with only one lobe involved, clinical stage ≤ T2a, Gleason score of ≤ 7 with no predominant pattern 4, absent lymphadenopathy on CT scan, negative bone scan **Exclusion criteria:** previous definitive treatment for prostate cancer or hormonal therapy **Staging method:** CT scan, bone scan	**HIFU:** focal therapy (hemiablation) with a first-generation Ablatherm® device using a 2.5- and 3-MHz transducer; five patients had TURP prior to HIFU **Extent of ablation:** focal	**Efficacy:** treatment failure, negative biopsy, death from non-cancer related causes, recurrence-free survival, overall survival **Functional outcomes:** acute urinary retention, UI **Adverse events:** asymptomatic urinary tract infection, epididymo-orchitis, urethral strictures **Procedural outcomes:** procedure time

Patient characteristics	HIFU
Number of patients enrolled	12
Age (years)	
Mean (SD)	70 (4.8)
PSA level (ng/ml)	
Mean (range)	7.3 (2.6–10.0)
Clinical stage, *n* (%)	
T1c	9 (75)
T2a	3 (25)
Prostate volume (g)	
Mean (range)	37 (23–62)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Elliott 2007[128] **Language:** English **Publication type:** full-text paper **Number of study centres:** multicentre (80) **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** 1995–2006 **Study design:** NRCS **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** no (database) **Length of follow-up:** median 2.7 years (range 3 days–10.9 years) **Source of funding:** supported by TAP Pharmaceutical Products, Inc., Lake Forest, IL, and National Institutes of Health/National Cancer Institute, University of California, San Francisco **Systematic reviewer:** SJ	**Inclusion criteria:** CaPSURE registry data included in this study. Primary treatment for prostate cancer in this database included WW, ADT, RP, BT, EBRT, CRYO and any combination of these therapies. Only treatments specific to stricture disease were included **Exclusion criteria:** those with a history of urethral stricture	**BT:** N/R **CRYO:** N/R **EBRT:** N/R **RP:** N/R	**Adverse events:** urethral stricture formation

Patient characteristics	Total
Number of patients enrolled	6597
Cryosurgery	199
BT	799
EBRT	645
RP	3310
WW	378
Other treatments	1265
Missing data	1
Age (years), *n* (%)	
< 60	1655 (25)
60–69	2607 (40)
70 or older	2334 (35)
PSA level (ng/ml), *n* (%)	
4 or less	952 (14)
4.1–10.0	4116 (62)
10.1–20	1029 (16)
> 20	499 (8)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics		Intervention characteristics	Outcomes
	Patient characteristics	**Total**		
	Clinical stage, *n* (%)			
	T1	3463 (53)		
	T2	2997 (45)		
	T3	136 (2)		
	Biopsy Gleason score, *n* (%)			
	2–6	4304 (65)		
	7	1723 (26)		
	8–10	569 (9)		
	Comorbidity (BMI), *n* (%)			
	Not overweight	1328 (28)		
	Overweight	2418 (51)		
	Obese	1036 (22)		
	Staging method: N/R			

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Ellis 2007[129] **Language:** English **Publication type:** full-text publication **Number of study centres:** 3 **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** December 2000–December 2005 **Study design:** case series **Prospective/retrospective data collection:** unclear (retrospective analysis) **Patients recruited consecutively (Y/N):** yes	**Inclusion criteria:** patients with clinical stage T1–T3, N0, M0 with minimally morbid fashion who met one of the following criteria: 1. relatively young but unwilling to undergo any standard treatment option that would put their potency at what they perceived as unacceptable risk (including bilateral nerve-sparing RP) 2. older candidates who potentially engaged in WW and were uncomfortable with the concept of leaving untreated cancer in their bodies **Exclusion criteria:** N/R	**CRYO:** patients were treated with focal cryoablation with argon cryoprobes under ultrasonographic visualisation with temperature monitoring All procedures were performed with the Cryocare® System (Endocare, Inc., Irvine, CA) **Extent of ablation:** focal	**Efficacy:** biochemical disease-free survival **Functional outcomes:** ED – impotence, incontinence

Patient characteristics	CRYO
Number of patients enrolled	60
Age (years)	
Mean/median (SD)	69/69 (7.8)
PSA level (ng/ml)	
Mean (SD)	7.2 (4.7)
< 10, *n* (%)	49 (81.7)
≥ 10, *n* (%)	11 (18.3)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics		Intervention characteristics	Outcomes
Length of follow-up: mean 15.2 (SD 7.4) months (6 weeks, 3, 6, 9 and 12 months, and every 6 months thereafter); median 12 (range 3–36) months **Source of funding:** N/R **Systematic reviewer:** SJ	**Patient characteristics**	**CRYO**		
	Clinical stage, *n* (%)			
	T1c, T2a	56 (92.5)		
	T2b, T2c	4 (7.5)		
	Biopsy Gleason score, *n* (%)			
	≤ 6	47 (78.3)		
	7	12 (20.0)		
	8–10	1 (1.7)		
	Mean biopsy Gleason score (SD)	6.1 (0.7)		
	Median biopsy Gleason score	6		
	Erectile dysfunction, *n*/*N* (%)	15/55 (27.3)		
	Staging method: N/R			

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Ferrer 2008[130,137,167] **Language:** English **Publication type:** full-text paper **Number of study centres:** 10 **Setting:** hospital **Country:** Spain **Recruitment/treatment dates:** April 2003–March 2005 **Study design:** NRCS **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** questionnaires administered before and after treatment at 1, 3, 6, 12 and 24 months Pardo 2010[167]: 36 months follow-up **Source of funding:** sanitary research fund **Systematic reviewer:** SJ	**Inclusion criteria:** clinically localised prostate cancer patients with T1 and T2 and no previous TURP Patients were classified according to D'Amico definition (low risk: T1c or T2a, PSA < 10 ng/ml and Gleason < 6; intermediate risk: T2b, PSA 11–20 ng/ml; high risk: T2c, PSA > 20 ng/ml, Gleason > 7) **Exclusion criteria:** patients excluded if they did not meet the inclusion criteria Pardo 2010[167] excluded patients who received neoadjuvant or adjuvant hormonal therapy **Staging method:** N/R	**BT:** in the BT group, all patients received BT alone with I-125. The prescription dose was 144 Gy to the reference isodose (100%) according to the TG-T43. The median dose of D90 (the minimum dose covering 90% of the prostate volume) and V100% (the percentage volume of prostate receiving at least 100% of the prescribed dose) was 152 Gy and 93% respectively **RP:** all patients included in the surgery group underwent RRP. Nerve-sparing techniques were used at the discretion of the operating surgeon **EBRT:** EBRT was carried out with the three-dimensional conformal technique. Patients were treated in a supine position by immobilising feet and legs. Treatment was delivered in 1.8–2.0-Gy daily fractions, 5 days per week, to a mean dose of 74.03 Gy (SD 4.3 Gy) to the prostate planning targeted volume	**Efficacy:** N/R **QoL:** SF-36, FACT-G, FACT-P, EPIC, AUA symptom index

Patient characteristics	BT	EBRT	RP
Number of patients enrolled	275	205	134
Age (years)			
Mean (SD)	66.9 (6.5)	69.2 (5.5)	64.0 (5.5)
PSA level (ng/ml)			
Mean (SD)	6.9 (2.3)	10.1 (7.9)	7.9 (3.3)
Clinical stage, *n* (%)			
T1	224 (81.5)	106 (51.7)	88 (65.5)
T2	51 (18.5)	95 (46.3)	46 (34.3)
TX (unknown)	0 (0)	4 (2)	0 (0)
Biopsy Gleason score			
Mean (SD)	5.7 (4.4)	6.0 (1.1)	6.8 (6.2)
Prostate size (cm^3)			
Mean (SD)	34.0 (9.8)	45.2 (25.3)	52.4 (27.2)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Frank 2007[131] **Language:** English **Publication type:** full-text paper **Number of study centres:** single **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** 1998–2000 **Study design:** NRCS **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** N/R **Source of funding:** financial interest and/or other relationship with Imtech International, Calypso Medical technologies and Oncura **Systematic reviewer:** SJ	**Inclusion criteria:** only patients treated with a monotherapy treatment approach were included in the analysis. Patients who received hormonal therapy as part of treatment were included in the protocol database **Exclusion criteria:** in this study, patients who received any form of combination therapy and/or hormone therapy were excluded **Staging method:** N/R	**BT:** 145-Gy I-125 using a modified peripheral loading technique via TRUS-guided transperineal approach **RP:** nerve-sparing RP was performed in some cases at surgeon's discretion **EBRT:** consisted of 78 Gy to the prostate with dose prescribed to the isocentre using 3D-CRT	**Efficacy:** N/R **QoL:** EPIC survey to assess disease-specific QoL

Patient characteristics	BT	EBRT	RP
Number of patients	74	135	234
Median age (years)	64	68	61
Clinical stage T1–T2, *n*/*N* (%)	74/74 (100)	131/135 (97)	227/233 (97.4)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Ganzer 2008[132] **Language:** English **Publication type:** full-text paper **Number of study centres:** N/R **Setting:** hospital **Country:** Germany **Recruitment/treatment dates:** December 1997–July 2003 **Study design:** case series **Prospective/retrospective data collection:** retrospectively evaluated **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** median 4.9 (range 3–8.6) years **Source of funding:** no extra institutional funding **Systematic reviewer:** SJ	**Inclusion criteria:** patients with localised prostate cancer, clinical stage T1/T2, serum PSA level 20 ng/ml, Gleason score of 7 and no previous hormonal therapy **Exclusion criteria:** those lost to follow-up were excluded from the study	**HIFU:** before October 2000, patients were treated with the second-generation Ablatherm® prototypes and thereafter with the Ablatherm-Maxis1 (EDAP, Lyon, France) device Treatment in all patients was performed under spinal anaesthesia with a suprapubic tube in place and the patient lying fixated on his right side	**Efficacy:** treatment failure, disease-free survival

Patient characteristics	HIFU
Number of patients enrolled	103
Age (years)	
Mean (SD)	65.7 (6.8)
PSA level (ng/ml)	
Mean (SD)	7.6 (3.6)
Clinical stage, *n* (%)	
T1a	7 (6.8)
T1b	8 (7.8)
T1c	12 (11.7)
T2a	56 (54.4)
T2b	20 (19.4)
Median biopsy Gleason score (range)	5 (2–7)
Prostate size (ml)	
Mean (SD)	24 (7.9)

Staging method: prostate biopsy (DRE and TURP)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Ganzer 2011[133] **Language:** English **Publication type:** full-text paper **Number of study centres:** 4 **Setting:** hospital **Country:** France, Germany and Italy **Recruitment/treatment dates:** February 1993–July 2009 **Study design:** case series **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** mean 5.9 (SD 2.2) years; median 5.0 (range 3–15) years **Source of funding:** EDAP **Systematic reviewer:** TEA	**Inclusion criteria:** T1–T2 disease, no previous hormone therapy, Gleason score of ≤ 7, PSA ≤ 20 ng/ml minimum follow-up of 3 years **Exclusion criteria:** previous hormonal therapy, less than 3 years' follow-up, high-risk disease **Staging method:** N/R	**HIFU:** all were treated with Ablatherm® HIFU; 431/769 (56%) had TURP before HIFU	**Efficacy:** PSA nadir, time to PSA nadir, biochemical disease-free survival, negative biopsy rate

Patient characteristics	HIFU
Number of patients enrolled	804
Low risk, *n* (%)	344 (42.8)
Intermediate risk, *n* (%)	389 (48.4)
High risk, *n* (%)	71 (8.8)
PSA level (ng/ml)	
Mean (SD)	7.7 (3.9)
Clinical stage, *n* (%)	
T1	395 (49.1)
T2	409 (50.9)
Gleason score (*n* = 800)	
Median (range)	6 (2–7)
Prostate size (ml) (*n* = 740)	
Mean (SD)	23.9 (10.4)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Giberti 2009[49] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** Italy **Recruitment/treatment dates:** May 1999–October 2002 **Study design:** RCT **Prospective/retrospective data collection:** prospective **Randomisation method:** computerised block randomisation list **Length of follow-up:** mean 68.2 (range 60–102) months **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** Caucasian patients, T1c or T2a, PSA ≤ 10 ng/ml, Gleason score of ≤ 6, age 51–74 years **Exclusion criteria:** previous pelvic irradiation, large median lobes, uroflow-Qmax < 10 ml/second, history of multiple pelvic surgeries, previous TURP, prostate volume > 60 ml, positive seminal-vesicles biopsy **Staging method:** physical examination and TRUS-guided needle biopsy	**BT:** seeds of I-125 were implanted through a transperineal, template-guided, peripheral-loading, real-time technique at D90 > 140 Gy **RP:** bilateral nerve-sparing RRP (Walsh's principles) and standard lymph node dissection were performed	**Efficacy:** biochemical failure, positive biopsy **Functional outcomes:** ED, urinary disorders, bowel symptoms **QoL:** physical, role, emotional, cognitive and social functions, global health/QoL, fatigue, nausea/vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial problems

Patient characteristics	BT	RP
Number of patients randomised	100	100
Age (years)		
Mean (range)	65.6 (56–74)	65.2 (56–74)
PSA level (ng/ml)		
Mean (range)	7.5 (2.9–9.3)	7.8 (3.5–10.0)
Clinical stage, *n* (%)		
T1	59 (59)	64 (64)
T2	41 (41)	36 (36)
Mean biopsy Gleason score	5.7	5.9
Prostate size (ml)		
Mean (range)	41.7 (21–60)	43.9 (19–56)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Godtman 2013[134] **Language:** English **Publication type:** full-text paper **Number of study centres:** single **Setting:** hospital **Country:** Sweden **Recruitment/treatment dates:** 1 January 1995–31 December 2010 **Study design:** case series **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** median 6 (0.08–15.1) years **Source of funding:** grants received from the Swedish Cancer Society, Märta and Gustaf Ågren's Research Foundation and Percy Falk's Foundation for Prostate and Breast Cancer Research **Systematic reviewer:** SJ	**Inclusion criteria:** among people aged 50–64 years who were living in Göteborg as of 31 December 1994, 10,000 were randomised to a screening group and 10,000 to a control group. People in the screening group were invited every second year for a PSA test until they reached the upper age limit for invitation (averaging 69 years of age). All people with elevated PSA (the cut-off varied between 2.5 and 3.4 ng/ml) were referred for prostate biopsy After the diagnosis of prostate cancer, a treatment strategy was chosen at the discretion of the treating physician and patient. In the majority of cases, the reason for choosing AS was a presumed low-risk prostate cancer, although AS could also be on the patient's initiative or because of comorbidities **Exclusion criteria:** two patients emigrated and one individual refused clinical follow-up and treatment **Staging method:** bone scan, MRI or CT scan	**AS:** patients were followed at intervals of 3–6 months with PSA measurements and clinical follow-up. All patients with a diagnostic biopsy containing < 2 mm cancer were recommended for early rebiopsy. Further rebiopsies were not regulated in any protocol but were recommended at signs of PSA or T stage progression; patients with stable disease were also recommended for rebiopsy, typically every second to third year, but this referral depended on initial biopsy outcome, patient age, comorbidity and preferences. Assessment by means of bone scan, MRI or CT scans for lymph node metastases or distant metastases was not performed unless the patient had symptoms or clinical features (PSA > 20 ng/ml or Gleason score of > 7) indicating a risk of metastasised disease	**Efficacy:** overall survival, death from prostate cancer, non-prostate cancer-related death during follow-up **QoL:** N/R

Patient characteristics	AS
Number of patients enrolled	439
Age (years)	
Median (range)	65.4 (51.2–70.4)
Risk group classification, *n* (%)	
Very low-risk criteria (T1c, not N1 or M1; Gleason score of ≤ 6; PSA density < 0.15 ng/ml; fewer than three cores with cancer; and ≤ 50% cancer in any core)	224 (51.0)
Low-risk criteria (T1, not N1 or M1; Gleason score of ≤ 6; and PSA < 10 ng/ml but not meeting the very low risk criteria)	117 (26.7)
Intermediate-risk criteria (T1–2, not N1 or M1; Gleason score of ≤ 7; and/or PSA < 20 ng/ml and not meeting the very low risk or low risk criteria)	92 (21.0)
High-risk criteria (T1–4, not N1 or M1; Gleason score of ≥ 8; and/or PSA < 100 ng/ml and not meeting the other risk groups' criteria)	6 (1.4)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Goldner 2012a[135] **Language:** English **Publication type:** full-text paper **Number of study centres:** 2 **Setting:** hospital **Country:** the Netherlands and Austria **Recruitment/treatment dates:** 1998–2008 **Study design:** NRCS **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** median 45 months (BT), 81 months (EBRT, 70 Gy), 40 months (EBRT, 74 Gy) **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** T stage T1–T2a and/or Gleason score of ≤ 6 (= low grading) and/or maximal initial PSA ≤ 10 ng/ml **Exclusion criteria:** N/R **Staging method:** N/R	**BT:** I-125 at dose of 144 Gy and 6-month hormonal therapy before BT for gland downsizing when gland size ≥ 50 ml **EBRT**: 2 Gy per fraction five times/week up to a total dose of 70 Gy (1998–2003) or 74 Gy (2003–8) and additional hormonal therapy was left at the urologist's discretion, as was common at that time	**Efficacy:** actuarial bNED rate

Patient characteristics	BT	EBRT (70 Gy)	EBRT (74 Gy)
Number of patients enrolled	667	82	170
Mean age (years)	64	71	71
PSA level, *n* (%)			
< 4 ng/ml	70 (11)	10 (11) (*N* = 81)	21 (12)
4–10 ng/ml	597 (89)	71 (89) (*N* = 81)	149 (88)
Median PSA level (ng/ml)	6.6	6.3 (*n* = 81)	6.5
Clinical stage, *n* (%)			
T1a/b	7 (1)	12 (16)	21 (12)
T1c	490 (73)	40 (48)	103 (61)
T2a	170 (25)	30 (36)	46 (27)
Biopsy Gleason score, *n* (%)			
< 6	268 (40) (*N* = 666)	35 (42)	35 (20)
6 or grading 1 (patients with unknown Gleason score were classified as grading 1 or low grade)	398 (60) (*N* = 666)	47 (58)	135 (80)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Goldner 2012b[136] **Language:** English **Publication type:** full-text paper **Number of study centres:** 2 **Setting:** hospital **Country:** the Netherlands and Austria **Recruitment/treatment dates:** 1998–2008 **Study design:** NRCS **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** median 45 months (BT), 54 months (EBRT) **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** T stage T2b–T2c and/or Gleason score of 7 and/or maximal initial PSA > 10–20 ng/ml **Exclusion criteria:** N/R **Staging method:** N/R	**BT:** I-125 at dose of 144 Gy and 6-month hormonal therapy before BT for gland downsizing when gland size ≥ 50 ml **EBRT:** 2 Gy per fraction five times/week up to a total dose of 70 Gy (1998–03) or 74 Gy (2003–2008) and additional hormonal therapy was left to the discretion of the urologist	**Efficacy:** actuarial biochemical no evidence of disease rate

Patient characteristics	BT	EBRT
Number of patients enrolled	601	289
Mean age (years)	66.6	71.1
PSA level, *n* (%)		
≤ 10 ng/ml	172 (29)	126 (44)
> 10–20 ng/ml	429 (71)	163 (56)
Median PSA level (ng/ml)	11.7	10.5
Clinical stage, *n* (%)		
T1	357 (59)	126 (44)
T2a	165 (27)	52 (18)
T2b, T2c	78 (13)	86 (30)
T2	1 (< 1)	25 (9)
Biopsy Gleason score, *n* (%)		
2–6	314 (52)	148 (51)
7	234 (39)	104 (36)
Unknown	53 (9)	37 (13)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Hale 2013[138] **Language:** English **Publication type:** full-text paper **Number of study centres:** single **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** January 2006–March 2012 **Study design:** case series **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** no **Length of follow-up:** mean 19.1 (range 2–52) months **Source of funding:** N/R **Systematic reviewer:** SJ	**Inclusion criteria:** low-risk prostate cancer patients [i.e. serum PSA ≤ 10.0 ng/ml, Gleason score of < 7, < cT2b ($n = 23$)] and intermediate-risk prostate cancer patients [i.e. serum PSA 10–20 ng/ml ($n = 2$) or Gleason score of 7 ($n = 1$)] **Exclusion criteria:** N/R **Staging method:** DRE	**CRYO:** focal nerve-sparing cryoablation was performed by one surgeon in an outpatient setting. Twenty-four patients underwent hemiablative cryosurgery, while two with bilateral disease underwent subtotal cryosurgery with an attempt to spare the prostatic tissue that resides next to the cavernosal nerve. Endocare's Cryocare® CS system with variable probes along with a urethral warmer was utilised (median three probes) on all cases **Extent of ablation:** focal	**Efficacy:** biochemical failure **Functional outcomes:** impotence, UI **Adverse events:** urethral sloughing, rectourethral fistula formation, acute urinary retention, urinary tract infection, rash

Patient characteristics	CRYO
Number of patients enrolled	26
Age (years)	
Median (range)	65 (55–74)
PSA level, *n* (%)	
≤ 10 ng/ml	24 (92)
10–20 ng/ml	2 (8)
Clinical stage, *n* (%)	
T1c	26 (100)
Biopsy Gleason score, *n* (%)	
6	25 (96)
7	1 (4)
Preoperative urinary continence, *n* (%)	26 (100)
Median preoperative SHIM score (range)	20 (16–25)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Han 2003[139] **Language:** English **Publication type:** full-text paper **Number of study centres:** 8 **Setting:** hospital **Country:** USA and Israel **Recruitment/treatment dates:** 2000–2002 **Study design:** case series **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** 12 months **Source of funding:** N/R **Systematic reviewer:** SJ	**Inclusion criteria:** patients who underwent cryoablation of the prostate gland between 2000 and 2002 at eight institutions. All these patients had biopsy-proven prostate cancer **Exclusion criteria:** N/R Baseline characteristics results were combined with those of 18 (15%) salvage patients	**CRYO:** third-generation cryotherapy technique was used All patients used 17-gauge cryoneedle (Galil Medical, Westbury, NY) and a BT template	**Efficacy:** biochemically free of disease **Functional outcomes:** ED/impotence, incontinence **Adverse effects:** urethral sloughing, pelvic pain, penile tingling/numbness, scrotal swelling

Patient characteristics	CRYO
Number of patients enrolled	122
Age (years)	
Mean/median (range)	69.7/70 (53–85)
PSA level, *n* (%)	
≤ 10 ng/ml	91 (74.6)
> 10 ng/ml	31 (25.4)
Clinical stage, *n* (%)	
T1	53 (43.8)
T2	63 (52.1)
T3	5 (4.1)
Missing data	1 (0.8)
Biopsy Gleason score, *n* (%)	
≤ 6	75 (61.5)
7	29 (23.8)
8–10	18 (14.7)
Prostate size (ml)	
Mean (SD)	28.5 (9.5)
Median	28.05

Staging method: DRE and TRUS imaging

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Hardie 2005[140] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** UK **Recruitment/treatment dates:** April 1993–February 2002 **Study design:** case series **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** median 42 (range 1–116) months **Source of funding:** NHS Executive, Institute of Cancer Research, Bob Champion Cancer Trust, Cancer Research UK Section of Radiotherapy and NCRI South of England Prostate Cancer Collaborative **Systematic reviewer:** TEA	**Inclusion criteria:** histologically confirmed prostate adenocarcinoma, fitness for radical treatment, clinical stage T1/T2, N0/X, M0/X, PSA ≤ 20 ng/ml, Gleason score of ≤ 7 **Exclusion criteria:** N/R **Staging method:** bone scan, CT/MRI of the pelvis (not used routinely for patients with Gleason score of < 7 and PSA < 10 ng/ml)	**AS:** serial PSA and DRE every 3–6 months for 2 years, then every 6 months. Repeat biopsies were performed only when clinically necessary. The rate of PSA rise and clinician and patient judgement informed the need for radical treatment	**Efficacy:** prostate cancer-related death, death from other causes, number treated

Patient characteristics	AS
Number of patients enrolled	80
Age (years)	
Median (range)	70.5 (59–81)
PSA level, *n* (%)	
< 4 ng/ml	17 (21)
4–10 ng/ml	42 (52)
> 10–20 ng/ml	20 (25)
> 20 ng/ml	1 (1)
Clinical stage, *n* (%)	
T1a/b	14 (17)
T1c	39 (49)
T2a	23 (29)
T2b	4 (5)
T3	0
Biopsy Gleason score, *n* (%)	
< 6	73 (91)
7	7 (9)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Hilton 2012[141] **Language:** English **Publication type:** full-text paper **Number of study centres:** single **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** 2003–10 **Study design:** case series **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** median 3.2 (range 1.9–5.1) years **Source of funding:** supported by University of California, San Francisco Special Program of Research Excellence Grant P50-CA89520 from the National Institutes of Health/National Cancer Institute **Systematic reviewer:** SJ	**Inclusion criteria:** people with biopsy-proven prostate cancer diagnosed between 2003 and 2010 who are under AS. These candidates typically have diagnostic PSA < 10 ng/ml, clinical stage cT1 or cT2, BX Gleason grade 2–6 and 33% or fewer biopsy cores positive with 50% or less tumour in any single core Study reviewed the medical records of eligible people to identify all biopsies and all ED evaluations (SHIM questionnaires). Qualifying biopsies were any that preceded cancer treatment. Qualifying ED evaluations were those before any biopsy exposure and at least 31 days after the most recent biopsy (to ignore acute transient effects) and the most recent ED evaluation (to exclude redundant outcomes) **Exclusion criteria:** N/R	**AS:** in AS patients underwent a total of 1531 biopsies from May 1988 to July 2011, of which 8% were prediagnostic, 33% were at diagnosis and 59% were postdiagnostic	**Functional outcomes:** erectile function

Patient characteristics	AS	
Number of patients enrolled	501	
	Study completers	Non-completers
Age (years)		
Median (IQR)	61 (57–66)	64 (58–70)
PSA level (ng/ml)		
Median (IQR)	5.2 (4.0–7.0)	5.8 (3.8–8.5)
Clinical stage, *n* (%)		
T1	296 (69.3)	55 (74.3)
T2	129 (30.2)	18 (24.3)
Missing	2 (0.5)	1 (1.4)
Biopsy Gleason score, *n* (%)		
4–5	4 (0.9)	2 (2.7)
6	393 (92)	66 (89.2)
7–8	29 (6.8)	6 (8.1)
Missing	1 (0.2)	

Staging method: N/R

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Hubosky 2007[52] **Language:** English **Publication type:** full-text paper **Number of study centres:** single **Setting:** hospital **Country:** USA **Recruitment/treatment dates**: March 2003–February 2006 **Study design:** case series **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** mean 12.7, median 11 (range 1–32) months **Source of funding:** N/R **Systematic reviewer:** SJ	**Inclusion criteria:** patients who underwent cryoablation therapy as primary treatment of localised prostate cancer using third-generation techniques **Exclusion criteria:** patients who were diagnosed with ductal carcinoma of the prostate, patients with < 1 month follow-up with no postoperative PSA data, patients who were maintained on immediate postoperative adjuvant hormonal ablation and salvage cryoablation cases **Staging method:** DRE, CT and bone scan	**CRYO:** third-generation cryoablation was performed by a single surgeon using the Cryocare® CS system. This machine has eight cryoprobe ports and an internal temperature monitoring system that can integrate temperature measurements from thermosensors	**Efficacy:** biochemical disease-free status **Adverse events:** urethral sloughing, rectourethral fistula, prolonged retention, prostatic cavitation/ persistent urinary tract infection, penile/perineal pain

Patient characteristics	CRYO
Number of patients enrolled and followed up for all outcomes	89
Number of patients analysed for the primary outcome PSA nadir	81
Age (years) ($n = 81$)	
Mean (range)	71.5 (52–84)
PSA level (ng/ml) ($n = 81$)	
Mean (range)	11.83 (2–69.3)
Clinical stage, n (%) ($n = 81$)	
T1	61 (75)
T2a	8 (9.8)
T2b	9 (11)
T2c	1 (1.2)
T3	2 (2.4)
Biopsy Gleason score, n (%) ($n = 81$)	
≤ 6	42 (51.8)
7	29 (35.8)
8–10	10 (12.3)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Illing 2006[142] **Language:** English **Publication type:** full-text paper **Number of study centres:** unclear (N/R) **Setting:** hospital **Country:** UK **Recruitment/treatment dates:** November 2004–October 2005 **Study design:** case series **Prospective/retrospective data collection:** N/R **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** ≥ 3 months **Source of funding:** Misonix (ongoing financial support) **Systematic reviewer:** SJ	**Inclusion criteria:** patients with prostate cancer stage ≤ T2 (N0, M0), a PSA level of < 15 ng/ml and prostate gland volume of < 40 ml **Exclusion criteria:** patients who had previous hormone therapy, chemotherapy, radiotherapy or surgery for prostate cancer **Staging method:** N/R	**HIFU:** Sonablate® 500 was used. This consists of a power generator, water-cooling system (the 'Sonachill®'), a treatment probe and a probe-positioning system. The probe has two curved rectangular piezoceramic transducers with a driving frequency of 4 MHz and focal lengths of 30 and 40 mm respectively. During treatment, these can be driven at low energy to provide real-time diagnostic ultrasonography imaging or at high energy for therapeutic ablation (in situ intensity 1300–2200 W/cm^2). The probe is covered by a condom through which cold (17–18 °C) de-gassed water circulates, pumped by the Sonachill®. Treatment was under general anaesthesia in all cases. People were placed in the lithotomy position, and the anal sphincter gently dilated Nine people were treated using the algorithm-based HIFU (group 1) and 25 people using the visually directed HIFU (group 2)	**Efficacy:** PSA nadir ≤ 0.2 ng/ml **Adverse effects:** undergoing flexible cystoscopy, urinary tract infection, epididymo-orchitis

Patient characteristics	HIFU
Number of patients enrolled	52
Number of patients analysed	34
Group 1 (algorithm-based HIFU)	9
Group 2 (visually directed HIFU)	25
Age (years), mean (range)	
Group 1 (algorithm-based HIFU)	64 (53–75)
Group 2 (visually directed HIFU)	61 (50–76)
PSA level (ng/ml), mean (range)	
Group 1 (algorithm-based HIFU)	6.58 (4.12–10.60)
Group 2 (visually directed HIFU)	8.00 (3.00–14.80)
Clinical stage, *n* (%)	
T1	20 (59)
Group 1 (algorithm-based HIFU) T1	5 (56)
Group 2 (visually directed HIFU) T1	15 (60)
T2	14 (41)
Group 1 (algorithm-based HIFU) T2	4 (44)
Group 2 (visually directed HIFU) T2	10 (40)
Mean biopsy Gleason score (range)	
Group 1 (algorithm-based HIFU)	6 (6–7)
Group 2 (visually directed HIFU)	6 (5–7)
Prostate size (ml), mean (range)	
Group 1 (algorithm-based HIFU)	30 (24–38)
Group 2 (visually directed HIFU)	30 (17–54)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Inoue 2011[143] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** Japan **Recruitment/treatment dates:** from May 2003 **Study design:** case series **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** median 36 (range 12–84) months **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** stage T1 or T2, N0, M0 **Exclusion criteria:** N/R	**HIFU:** therapy was administered using Sonablate® 500 and Sonablate® 500 version 4. Thirty-one patients received hormonal therapy for > 6 months before HIFU. Sixteen had TURP before HIFU for BPH and two for reducing the prostate volume	**Efficacy:** positive histological findings, PSA failure, PSA nadir, disease-free survival, prostate cancer-related death, death from other causes **Functional outcomes:** ED, difficult voiding, urgency, incontinence **Adverse events:** urethral stricture, rectourethral fistula, urinary infection, acute epididymitis, prostatic urethral stone, vesical stone **Procedural outcomes:** operation time, anaesthesia used, hospital stay

Patient characteristics	HIFU
Number of patients enrolled	137
Low risk, *n* (%)	29 (21)
Intermediate risk, *n* (%)	68 (50)
High risk, *n* (%)	40 (29)
Age (years)	
Median (range)	70 (50–82)
PSA level (ng/ml)	
Median (range)	7.2 (2.8–100)
< 10, *n* (%)	90 (66)
10–19, *n* (%)	40 (29)
≥ 20, *n* (%)	7 (5)
Clinical stage, *n* (%)	
T1b	8 (6)
T1c	58 (42)
T2a	52 (38)
T2b	14 (10)
T2c	5 (4)
Biopsy Gleason score, *n* (%)	
≤ 6	41 (30)
7	64 (47)
≥ 8	32 (23)
Prostate size (ml)	
Median (range)	20 (8–52)

Staging method: DRE, CT, MRI, bone scintigram

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Kibel 2012[144,165] **Language:** English **Publication type:** full-text paper **Number of study centres:** 2 **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** 1995–2005 **Study design:** NRCS **Prospective/retrospective data collection:** prospective database **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** median 67 (IQR 43–96) months **Source of funding:** supported by Robert Wood Johnson Foundation, Astellas-American Urology Association Foundation, Maltz Family Foundation and St. Louis Men's Group Against Cancer **Systematic reviewer:** SJ	**Inclusion criteria:** consecutive people with clinically localised prostate cancer were treated at Barnes-Jewish Hospital and Cleveland Clinic **Exclusion criteria:** N/R	**BT:** delivered using intraoperative treatment planning with ultrasound guidance Dose: median 144 cGy (Cleveland Clinic) and 14500 cGy (Barnes-Jewish Hospital) **RP:** performed with the retropubic or laparoscopic approach **EBRT:** at Barnes-Jewish Hospital, EBRT consisted of 3D-CRT from 1995 to 1999 and IMRT from 1999 to 2005. At Cleveland Clinic, it consisted of four-field conventional EBRT in 1995 only, 3D-CRT from 1995 to 1997 and IMRT in all patients since 1998 Dose: median EBRT doses at Barnes-Jewish Hospital and Cleveland Clinic were 7400 cGy (IQR 7070–7544 cGy) and 7800 cGy (IQR 7400–8000 cGy) respectively	**Efficacy:** prostate cancer-specific mortality, overall deaths from prostate cancer, overall survival **QoL:** N/R

Patient characteristics	BT	EBRT	RP
Number of patients enrolled			
Total	1680	2264	6485
Cleveland Clinic	1330	1638	2843
Barnes-Jewish Hospital	350	626	3642
Age (years)			
Cleveland Clinic, median (range)	68 (62–72)	69 (63–73)	60 (56–95)
Barnes-Jewish Hospital, median (range)	69 (63–73)	70 (65–75)	61 (55–66)
PSA level (ng/ml)			
Cleveland Clinic, median (range)	6.1 (4.8–8.0)	8.9 (6.0–15.9)	5.9 (4.6–8.2)
Barnes-Jewish Hospital, median (range)	5.2 (3.8–6.8)	6.8 (4.7–10.7)	5.4 (4.1–7.8)
Clinical stage, *n* (%)			
T1ab			
Total	7 (0.4)	32 (1.4)	55 (0.8)
Cleveland Clinic	7 (0.5)	25 (2)	15 (0.5)
Barnes-Jewish Hospital	0 (0)	7 (1)	40 (1)
T1c			
Total	1301 (77)	1279 (57)	4995 (77)
Cleveland Clinic	1036 (83)	883 (54)	2074 (73)
Barnes-Jewish Hospital	265 (76)	396 (62)	2921 (80)

Study details	Participant characteristics				Intervention characteristics	Outcomes
	Patient characteristics	**BT**	**EBRT**	**RP**		
	T2a					
	Total	277 (16)	463 (21)	918 (14)		
	Cleveland Clinic	211 (16)	351 (22)	554 (20)		
	Barnes-Jewish Hospital	66 (19)	112 (19)	364 (10)		
	T2b					
	Total	26 (2)	212 (9)	374 (6)		
	Cleveland Clinic	9 (1)	158 (10)	124 (4)		
	Barnes-Jewish Hospital	17 (5)	54 (9)	250 (7)		
	T2c					
	Total	9 (0.5)	112 (5)	97 (2)		
	Cleveland Clinic	7 (0.5)	92 (6)	48 (2)		
	Barnes-Jewish Hospital	2 (1)	20 (3)	49 (1)		
	T3					
	Total	0 (0)	166 (7)	46 (0.7)		
	Cleveland Clinic	0 (0)	129 (8)	28 (1)		
	Barnes-Jewish Hospital	0 (0)	37 (6)	18 (0.5)		
	Missing	60 (4.5)	0 (0)	0 (0)		
	Cleveland Clinic	60 (4.5)	0 (0)	0 (0)		
	Barnes-Jewish Hospital	0 (0)	0 (0)	0 (0)		

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics				Intervention characteristics	Outcomes
	Patient characteristics	BT	EBRT	RP		
	Biopsy Gleason score, *n* (%)[a]					
	2–6					
	Total	1393 (82.9)	1179 (52)	4754 (73.3)		
	Cleveland Clinic	1080 (81)	789 (47)	1980 (70)		
	Barnes-Jewish Hospital	313 (89)	390 (61)	2774 (76)		
	7					
	Total	283 (16.8)	778 (34.4)	1455 (22.4)		
	Cleveland Clinic	247 (18)	606 (37)	745 (26)		
	Barnes-Jewish Hospital	36 (10)	172 (29)	710 (20)		
	8–10					
	Total	14 (0.8)	307 (13.6)	276 (4.3)		
	Cleveland Clinic	13 (1)	243 (16)	118 (4)		
	Barnes-Jewish Hospital	1 (1)	64 (10)	158 (4)		
	Comorbidity: Charlson comorbidity index, *n* (%)[b]					
	None					
	Total	972 (57.8)	1304 (57.6)	4464 (68.8)		
	Cleveland Clinic	809 (61)	1084 (66)	2307 (81)		
	Barnes-Jewish Hospital	163 (47)	220 (35)	2157 (59)		

Study details	Participant characteristics				Intervention characteristics	Outcomes
	Patient characteristics	**BT**	**EBRT**	**RP**		
	Mild					
	Total	445 (26.5)	594 (26.2)	1590 (24.5)		
	Cleveland Clinic	322 (24)	317 (19)	377 (13)		
	Barnes-Jewish Hospital	123 (35)	277 (44)	1213 (33)		
	Moderate					
	Total	235 (14)	348 (15.4)	387 (6)		
	Cleveland Clinic	179 (14)	241 (12)	150 (5)		
	Barnes-Jewish Hospital	56 (16)	107 (17)	237 (7)		
	Severe					
	Total	28 (1.7)	61 (2.7)	44 (0.7)		
	Cleveland Clinic	20 (1)	39 (3)	9 (0.3)		
	Barnes-Jewish Hospital	8 (2)	22 (3)	35 (1)		
	a Ten additional patients were reported in the BT group. b Forty-three additional patients were reported in the EBRT group.					
	Staging method: N/R					

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Burdick 2009[112] (secondary to Kibel 2012[144,165])	**Inclusion criteria:** consecutive patients with biopsy GS7 prostate cancer with both primary and secondary grade included in prospectively maintained database. (Biopsy protocol used in the institution was 10–12 cores, laterally directed biopsy)	**BT:** BT patients were prescribed 144 Gy with I-125 using ultrasound guidance, according to American Brachytherapy Society guidelines	**Efficacy:** biochemical relapse-free survival
Language: English	**Exclusion criteria:** cases of biopsy GS7 prostate cancer without mention of primary and secondary grade were excluded from this study. Also excluded patients who underwent surgery treated with adjuvant radiotherapy or adjuvant hormonal therapy	**RP:** laparoscopic (*n*/*N*): 41/705 (13%); laparotomy (*n*/*N*): 269/705 (87%)	**QoL:** N/R
Publication type: full-text paper		**EBRT:** all EBRT patients received a minimal dose of 70 Gy at 2 Gy/fraction. Lymph nodes were not included when contouring the clinical target volume for EBRT	
Number of study centres: single		**3D-CRT:** $n = 53$ (20%)	
Setting: hospital		**IMRT:** $n = 215$ (80%)	
Country: USA			
Recruitment/treatment dates: September 1996–March 2005			
Study design: NRCS			
Prospective/retrospective data collection: prospective			
Patients recruited consecutively (Y/N): yes			
Length of follow-up: median 54 (range 24–123) months			
Source of funding: N/R			
Systematic reviewer: SJ			

Patient characteristics	BT	EBRT	RP
Number of patients enrolled	127	268	310
Age (years)			
Median (range)	70 (51–80)	69.5 (46–85)	62 (42–76)
PSA level (ng/ml)			
Median (range)	6.2 (1.5–33.9)	8.7 (2.2–250)	6.3 (0.6–55.0)
Clinical stage, *n* (%)			
T1–T2a	125 (98)	202 (75)	267 (86)
T2b–T2c	2 (2)	43 (16)	40 (13)
T3	0 (0)	23 (9)	3 (1)
Biopsy Gleason score, *n* (%)			
≤ 6	Gleason score of 7 for all patients		
7			
8–10			

Staging method: N/R

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Ciezki 2004[118] (secondary to Kibel 2012[144,165]) **Language:** English **Publication type:** full-text paper **Number of study centres:** N/R **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** 1996–2001 **Study design:** NRCS **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** median 48 (range 24–94) months	**Inclusion criteria:** patients with low- and intermediate-risk prostate cancer were treated definitively with BT, EBRT and RP **Exclusion criteria:** N/R	**BT:** radiation dose 144 Gy **RP:** type of prostatectomy: RRP **EBRT:** median radiation dose 78 Gy	**Efficacy:** biochemical relapse-free survival **QoL:** N/R

Patient characteristics	BT	EBRT	RP	Total
Number of patients enrolled	386	519	763	1668
Low-risk patients (*n*)	295	282	497	1074
Intermediate-risk patients (*n*)	91	237	266	594
Age (years)				
Low-risk patients, median (range)				65 (40–87)
Intermediate-risk patients, median (range)				66 (42–84)
PSA level (ng/ml)				
Low-risk patients, median (range)				6.0 (0.1–10)
Intermediate-risk patients, median (range)				8.6 (0.6–20.0)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics					Intervention characteristics	Outcomes
Source of funding: N/R	**Patient characteristics**	**BT**	**EBRT**	**RP**	**Total**		
Systematic reviewer: SJ	Clinical stage, *n* (%)						
	T1 (low-/intermediate-risk patients)				762 (70.9)/361 (60.8)		
	T2a (low-/intermediate-risk patients)				258 (24.0)/160 (26.9)		
	T2b (low-/intermediate-risk patients)				38 (3.5)/53 (8.9)		
	T2c (low-/intermediate-risk patients)				16 (1.5)/20 (3.4)		
	Biopsy Gleason score, *n* (%)						
	Low-risk patients						
	< 6				146 (13.6)		
	6				928 (86.4)		
	Intermediate-risk patients						
	< 7				243 (40.9)		
	7				351 (59.1)		
	Staging method: N/R						

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Vassil 2010[200] (secondary to Kibel 2012[144,165])	**Inclusion criteria:** patients who were identified as recurrence risk groups were included, with clinical stage of T2b or T2c, biopsy Gleason score of 7 or a pretreatment PSA between 10 and 20 ng/ml (intermediate-risk prostate cancer). Eligible participants recruited between 1996 and 2005, with a minimum of 2 years of follow-up after treatment and at least four PSA tests, were included	**BT:** all BT patients were treated with I-125 transperineal implants prescribed to a dose of 144 Gy. The implants were done under real-time ultrasound guidance with a peripheral seed-loading pattern and followed ABS guidelines	**Efficacy:** biochemical recurrence-free survival
Language: English	**Exclusion criteria:** patients with more than one risk factor (clinical stage of T2b or T2c, biopsy Gleason score of 7 or a pretreatment PSA between 10 and 20 ng/ml) were classified as high risk and were excluded from this analysis. RP patients who received adjuvant radiation therapy were excluded from this study	**EBRT:** median total dose was 80 Gy (range 70–80 Gy), estimated using an α/β of 1.5 at 2 Gy per fraction. 72% of the EBRT patients were treated with an IMRT technique, 27% were treated with a conformal radiotherapy technique and 1% were treated with a four-field box technique. All EBRT patients were treated with prostate only with or without seminal vesicle treatment. No patients were treated with a radiation field that included the pelvic lymph nodes	
Publication type: full-text paper		**RP:** two methods were used: RRP and LRP	
Number of study centres: N/R (used National Cancer Network database)			
Setting: hospital			
Country: USA			
Recruitment/treatment dates: 1996–2005			
Study design: NRCS			
Prospective/retrospective data collection: prospective			
Patients recruited consecutively (Y/N): N/R			
Length of follow-up: 5 years			

Patient characteristics	BT	EBRT	RRP/LRP, RP
Number of patients enrolled	256	305	354/64, 418
Age (years)			
Median (range)	69 (49–81)	68 (44–87)	62 (42–75)/ 63 (42–75)
Median BMI (range)	28.4 (20.2–45.0)	27.9 (17.9–48.3)	27.4 (16.4–45.6)/ 27.5 (19.3–43.2)
PSA level (ng/ml)			
Median (range)	7.3 (1.5–19.8)	8.6 (2.0–19.6)	6.7 (0.6–20)/ 6.3 (2.2–20)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics				Intervention characteristics	Outcomes
PSA follow-up, median 61 (range 24–135) months **Source of funding:** N/R **Systematic reviewer:** SJ	**Patient characteristics**	**BT**	**EBRT**	**RRP/LRP, RP**	**RRP/LRP groups:** 75%/61% had a pelvic lymph node dissection, of which 2%/0% were found to be positive. The positive margin rate was 29%/44%, 39%/47% had extracapsular extension and 10%/9% had seminal vesicle involvement. Surgeons had less experience conducting LRP than RRP. The median number of cases was 126 (range 3–465) for the LRP surgeons and 246 (range 1–1550) for the RRP surgeons	
	Clinical stage, *n* (%)					
	T1, T2a	250 (97.7)	290 (95.1)	323 (91.2)/64 (100), 387 (93)		
	T2b, T2c	6 (2.3)	15 (4.9)	31 (8.8)/0, 31 (7)		
	Biopsy Gleason score, *n* (%)					
	≤ 6	102 (39.8)	135 (44.3)	125 (35.3)/13 (20.3), 138 (33)		
	7	154 (60.2)	170 (55.7)	229 (64.7)/51 (79.7), 280 (67)		
	Comorbidity, *n* (%)					
	Mean Charlson comorbidity index score (range)	0.6 (0–4)	0.4 (0–6)	0.3 (0–6)/0.4 (0–3)		
	Staging method: N/R					

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Kirschner-Hermanns 2008[145] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** Germany **Recruitment/treatment dates:** January 1999–December 2002 **Study design:** NRCS **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** 1 year **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** low-dose BT: T1–T2a N0 M0 category, PSA ≤ 10 ng/ml, Gleason score of 2–6 and a prostate volume of < 60 ml and no significant residual urine; RP: N/R **Exclusion criteria:** residual urine > 50 ml, maximum uroflow < 15 ml/s and prostate volume > 50 ml were excluded from BT	**BT:** I-125 at a prescription dose of 145 Gy covered the prostate with a margin of 3–5 mm, with the exception of the posterior border. The urethral dose was limited to 250 Gy, 30% of the urethra to 220 Gy and 10% of the anterior rectal wall was limited to 145 Gy **RP:** RPP was done using the extrasphincteric Young approach and extrafascial extended type according to Weldon *et al.*[293] Minor modifications including partial transection of the dorsal vein complex, early and extrafascial mobilisation of the seminal vesicle and wide excision of neurovascular bundles and bladder neck were made. No patient had adjuvant hormone therapy before surgery	**Functional outcomes:** incontinence, bothersome incontinence, stress incontinence, bothersome stress incontinence, having to wear pads, LUTS, bothersome LUTS, urgency, bothersome urgency **QoL:** emotional functioning EORTC, global HRQoL EORTC **Procedural:** nature of anaesthetic

Patient characteristics	BT	RP
Number of patients enrolled	33	61
Age (years)		
Median (range)	67 (57–75)	64 (54–75)
PSA level (ng/ml)		
Median (range)	7.7 (3.2–17.0)	9.2 (1.6–55.6)
Clinical stage, *n* (%)		
T1	12 (36)	21 (34)
T2	21 (64)	37 (61)
T3	N/A	3 (5)
Biopsy Gleason score		
Median (range)	5.0 (2–7)	5.0 (3–8)
Prostate size (ml)		
Median (range)	Not documented	56 (35–125)
Comorbidity, *n* (%)		
OCO > 1	8 (24)	20 (32)
Instabilities	16 (49)	27 (44)
Maximum flow < 10 ml/s	7 (21)	18 (30)
Residual volume > 50 ml	4 (12)	21 (34)
Maximum bladder capacity < 200 ml	2 (6)	9 (15)
Median OCO (range)	0.74 (0.34–1.70)	0.78 (0.08–2.67)

Staging method: N/R

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Klotz 2010[146–148,157] **Language:** English **Publication type:** full-text paper **Number of study centres:** single **Setting:** hospital **Country:** Canada **Recruitment/treatment dates:** November 1995 **Study design:** case series **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** median 6.8 (range 1–13) years **Source of funding:** N/R **Systematic reviewer:** SJ	**Inclusion criteria:** this study was offered to all favourable-risk patients (i.e. Gleason 6 or less, PSA 10 ng/ml or less) and to patients older than age 70 years with PSA up to 15 ng/ml or Gleason up to 3 + 4 From January 2000, the study was restricted to favourable-risk patients only (i.e. Gleason 6 or less, PSA 10 ng/ml or less) **Exclusion criteria:** N/R **Staging method:** N/R	**AS:** PSA was performed every 3 months for 2 years and then every 6 months in stable patients. A confirmatory biopsy was performed 6–12 months after the initial biopsy and then every 3–4 years until the patient reached 80 years old **Definition of failure:** clinical progression was defined as development of an unequivocal palpable nodule during surveillance. Histology of the nodule was evaluated by directed biopsies. If the nodule was confirmed as evidence of cancer progression, patients were offered definitive therapy PSA failure was defined as PSA > 0.2 ng/ml for patients who underwent surgery and PSA nadir + 2 ng/ml for patients who underwent radiation	**Efficacy:** overall survival, case-specific survival

Patient characteristics	AS
Number of patients enrolled	450
Median age (years)	70.3
PSA level, *n* (%)	
0–2.5 ng/ml	54 (12)
> 2.5–5 ng/ml	112 (25)
> 5–10 ng/ml	216 (48)
> 10–15 ng/ml	56 (12)
> 15 ng/ml	10 (2)
Unknown	2 (0.4)
Clinical stage, *n* (%)	
T1a	1 (0.2)
T1b	26 (5.8)
T1c	302 (67)
T2	3 (0.7)
T2a	80 (18)
T2b	22 (5)
T2c	12 (3)
T3	4 (0.9)
Biopsy Gleason score, *n* (%)	
≤ 6	374 (83)
7	76 (17)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Kobuke 2009[149] **Language:** English **Publication type:** full-text paper **Number of study centres:** 2 **Setting:** hospital **Country:** Japan **Recruitment/treatment dates:** January 2004–March 2005 **Study design:** NRCS **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** 12 months **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** RP: age up to 75 years, T1–T2, any Gleason score, any PSA level; BT: T1c–T2, Gleason score of 6 or 7 (primary grade 3), PSA < 10 ng/ml **Exclusion criteria:** N/R **Staging method:** N/R	**BT:** I-125 seeds at a dose of 145 Gy were implanted 13/36 (36%) patients received neoadjuvant hormonal therapy **RP:** nerve sparing was performed in 13/37 (35%) patients and 3/37 (8%) received neoadjuvant hormonal therapy	**Efficacy:** biochemical recurrence, clinical recurrence, PSA level **Functional outcomes:** urinary function, urinary bother, bowel function, bowel bother, sexual function, sexual bother, I-PSS score **QoL:** physical functioning, role physical functioning, body pain, general health, vitality, social functioning, mental health

Patient characteristics	BT	RP
Number of patients enrolled	36	37
Age (years)		
Median (range)	67 (53–76)	67 (54–75)
PSA level (ng/ml)		
Median (range)	7.73 (1.13–74)	8.31 (1.796–27.44)
Clinical stage, *n* (%)		
T1	17 (47)	19 (51)
T2	19 (53)	18 (49)
Biopsy Gleason score, *n* (%)		
≤ 6	21 (58)	14 (38)
7	7 (19)	18 (49)
8–10	8 (22)	5 (14)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Koch 2007[150] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** November 2000–August 2004 **Study design:** case series **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** 180 days **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** pathologically confirmed prostate cancer, Gleason score of 7 or less, pretreatment PSA 10 ng/ml or less and stage T1–T2 disease **Exclusion criteria:** N/R **Staging method:** bone scan	**HIFU:** treatment of the entire prostate using Sonablate® 500, no hormone therapy for at least 3 months prior to therapy	**Efficacy:** death from unrelated causes, PSA level, prostate biopsy **Functional outcomes:** urinary dysfunction, UI, transient urinary retention, ED **Adverse events:** anal discomfort, bladder stone, bladder spasm, dysuria, epididymitis, gross haematuria, perineal discomfort, urinary tract infection, bladder neck contracture, urethral stricture, rectourethral fistula

Patient characteristics	HIFU
Number of patients enrolled	20
Mean PSA level (ng/ml)	4.9

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Kupelian 2004[151] **Language:** English **Publication type:** full-text paper **Number of study centres:** 2 **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** 1990–8 **Study design:** NRCS **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** yes **Length of follow-up, median (range):** overall, 56 (12–145) months; RP, 66 (12–145) months; EBRT < 72 Gy, 75 (13–140) months; EBRT ≥ 72 Gy, 49 (12–125) months; BT, 47 (12–111) months	**Inclusion criteria:** cT1 and cT2 patients with available pretreatment PSA levels and biopsy Gleason scores, no adjuvant androgen deprivation after local therapy or radiotherapy in the postoperative setting or neoadjuvant androgen deprivation for > 6 months, minimal follow-up of 12 months **Exclusion criteria:** N/R	**Permanent seed implantation (BT):** I-125 prescribed to 144 Gy (Task Group 43) and Pd-103 prescribed to 136 Gy (National Institute of Standards and Technology 1999 guidelines); 24% (225/950) had neoadjuvant hormones ≤ 6 months **EBRT:** delivered using megavoltage X-rays 5 days weekly at a median total dose of 68.4 Gy (range 63.0–83.0 Gy) EBRT < 72 Gy: median dose of 68.4 Gy (range 63.0–70.4 Gy) and 5% (25/484) had neoadjuvant hormones ≤ 6 months EBRT ≥ 72 Gy received a median dose of 78 Gy (range 72.0–83.0 Gy) and 39% (118/301) had neoadjuvant hormones ≤ 6 months **RP:** RRP 97%; perineal prostatectomy 3%	**Efficacy:** biochemical relapse-free survival

Patient characteristics	BT	EBRT < 72 Gy	EBRT ≥ 72 Gy	RP
Number of patients enrolled	950	484	301	1034
Age, *n* (%)				
< 65 years	204 (21)	133 (27)	93 (31)	689 (67)
≥ 65 years	746 (79)	351 (73)	208 (69)	345 (33)
Mean age (years)	63	70	68	63
PSA level, *n* (%)				
≤ 4 ng/ml	60 (6)	44 (9)	11 (4)	121 (12)
> 4–10 ng/ml	629 (55)	210 (43)	172 (57)	622 (60)
> 10–20 ng/ml	205 (22)	142 (29)	79 (26)	215 (21)
> 20 ng/ml	56 (6)	88 (18)	39 (13)	76 (7)
Mean PSA level (range), ng/ml	9.56 (0.4–112)	15.29 (0.4–276)	11.22 (1–56.5)	9.56 (0.2–210)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics					Intervention characteristics	Outcomes
Source of funding: N/R **Systematic reviewer:** TEA	**Patient characteristics**	**BT**	**EBRT < 72 Gy**	**EBRT ≥ 72 Gy**	**RP**	Bilateral or unilateral nerve-sparing procedure: 55%; neoadjuvant hormones: 17% (175/1034)	
	Clinical stage, *n* (%)						
	T1a	0 (0)	1 (< 1)	0 (0)	4 (< 1)		
	T1b	5 (1)	16 (3)	4 (1)	7 (1)		
	T1c	507 (53)	164 (34)	140 (47)	489 (47)		
	T2a	385 (41)	236 (49)	137 (46)	482 (47)		
	T2b	53 (6)	67 (14)	20 (7)	52 (5)		
	Biopsy Gleason score, *n* (%)						
	≤ 6	723 (76)	321 (66)	173 (57)	765 (74)		
	7	199 (21)	114 (24)	99 (33)	211 (20)		
	≥ 8	28 (3)	49 (10)	29 (10)	58 (6)		
	Staging method: transrectal ultrasonography, bone scan, chest X-rays, CT of the abdomen and pelvis (at the discretion of the physician)						

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Lian 2011[154] **Language:** English **Publication type:** full-text paper **Number of study centres:** N/R **Setting:** hospital **Country:** China **Recruitment/treatment dates:** January 2006–December 2009 **Study design:** case series **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** median 30 (range 9–56) months **Source of funding:** N/R **Systematic reviewer:** SJ	**Inclusion criteria:** patients diagnosed with clinically localised prostate cancer (T1c–T2c) **Exclusion criteria:** N/R **Staging method:** ultrasound-guided transperineal prostatic biopsy, CT or MRI and whole-body bone scan	**CRYO:** third-generation cryotechnology was used. These patients underwent a dual freeze–thaw cycle using ultrathin 17-gauge cryoneedles Cryoablation procedures were performed using Cryo-Hit system (Galil Medical Ltd, Yokneam, Israel) by a single urologist. Patients were placed in a modified lithotomy position after induction with general anaesthesia	**Efficacy:** overall survival, biochemical disease-free status, positive biopsy on follow up, reintervention rates **Functional outcomes:** impotent after therapy, UI **Adverse events:** rectourethral fistula formation, urethral sloughing, urethral stricture formation, acute urinary retention, pelvic pain

Patient characteristics	CRYO
Number of patients enrolled	102
Age (years)	
Median (range)	69 (50–83)
PSA level (ng/ml)	
Median (range)	10.8 (3.6–19.2)
Clinical stage, *n* (%)	
T1c	49 (48)
T2a	35 (34)
T2b	13 (12)
T2c	5 (5)
Biopsy Gleason score, *n* (%)	
5–6	55 (54)
7	47 (46)
Pre-existing erectile dysfunction, *n* (%)	63 (62)
Pre-existing urinary incontinence, *n* (%)	1 (1)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Lee 2001[153] **Language:** English **Publication type:** full-text paper **Number of study centres:** single **Setting:** Comprehensive Cancer Center of Wake Forest University School of Medicine **Country:** USA **Recruitment/treatment dates:** May 1998–June 1999 **Study design:** NRCS **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Randomisation method:** non-RCT **Length of follow-up:** 12 months **Source of funding:** N/R **Systematic reviewer:** SJ	**Inclusion criteria:** people with T1–T2 localised prostate cancer received treatment with BT, EBRT and RP at Wake Forest University School of Medicine **Exclusion criteria:** N/R **Staging method:** N/R	**BT:** radiation source I-125; dose 144 Gy according to the TG-T43 All 44 people treated with BT alone. Eleven people received ADT to reduce size of prostate gland All patients were treated by the same two physicians **RP:** all people underwent RP. A nerve-sparing technique was performed at the discretion of the operating surgeon. Pelvic lymph node dissection was routinely performed. Two different urologists contributed patients to this study **EBRT:** all people were treated with10-MV photons **Dose:** median dose 70.2 Gy (range 70.2–72 Gy) Prescribed to the 95% volume Patients treated with EBRT alone. CT was performed on all patients to assist in the treatment planning process. The four-field technique (AP: PA: right: left) and Cerrobend blocking were routinely used	**Efficacy:** N/R **QoL:** FACT-G, consisting of five subscales (physical well-being, functional well-being, emotional well-being, social/family well-being and doctor/patient relationship) FACT-P I-PSS

Patient characteristics	BT	EBRT	RP
Number of patients enrolled	44	23	23
Age (years)			
Median (range)	67.1 (49–79)	68.8 (51–79)	61 (42–68)
PSA level (ng/ml)			
Median (range)	6.5 (1.3–13.5)	8.1 (2.9–19.6)	6.2 (1.3–12)
Clinical stage, *n*/*N* (%)			
T1	26/44 (59)	12/23 (52)	19/23 (83)
T2	18/44 (41)	11/23 (48)	4/23 (17)
Biopsy Gleason score, *n*/*N* (%)			
≤ 6	38/44 (86)	11/23 (48)	16/23 (70)
7	6/44 (14)	10/23 (43)	5/23 (22)
8–10	0	2/23 (9)	2/23 (13)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Lindner 2009[155] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** Canada **Recruitment/treatment dates:** N/R **Study design:** case series **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** 6 months **Source of funding:** Muzzo Fund of the Princess Margaret Hospital Foundation **Systematic reviewer:** TEA	**Inclusion criteria:** people with low-risk prostate cancer (T1c, T2a, PSA < 10 ng/ml, Gleason sum ≤ 6, < 30% of the cores taken were positive for cancer and < 50% of one core was taken up by cancer), no prior prostate cancer treatment **Exclusion criteria:** N/R **Staging method:** N/R	**Laser:** image-guided targeted focal therapy delivered by Indigo® OPTIMA laser and monitored with CEUS using Definity® microbubbles (Lantheus Medical Imaging, Inc., North Billerica, MA)	**Efficacy:** negative biopsy rate, reintervention rate **Adverse events:** perioperative complications, mild haematuria, haematospermia **QoL:** sexual function, urinary symptoms

Patient characteristics	Laser
Number of patients enrolled	12
Age (years)	
Median (range)	56.5 (51–62)
PSA level (ng/ml)	
Mean (SD)	5.7 (1.1)
Clinical stage, *n* (%)	
T1c	12 (100)
Biopsy Gleason score	3 + 3
Prostate size (ml)	
Median (range)	37 (16–85)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Litwin 2004[156] **Language:** English **Publication type:** full-text paper **Number of study centres:** multicentre ($n = 31$) **Setting:** hospital (usual practices) **Country:** USA **Recruitment/treatment dates:** unclear **Study design:** NRCS (observational cohort) **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** 2 years Mean duration of follow-up was 13.4–14.3 months **Source of funding:** N/R **Systematic reviewer:** SJ	**Inclusion criteria:** patients who had undergone RP, EBRT or BT alone for clinically localised prostate cancer within 6 months of diagnosis and had submitted at least two HRQoL surveys during the 2 years **Exclusion criteria:** N/R	**BT:** N/R **RP:** N/R **EBRT:** N/R	**Efficacy:** N/R **QoL:** bowel function and bother were measured with the UCLA Prostate Cancer Index

Patient characteristics	BT	EBRT	RP
Number of patients enrolled	209	99	1276
Age (years)			
Mean (SD)	68.6 (7.4)	70.9 (6.1)	61.2 (6.8)
Clinical stage, *n*/*N* (%)			
T1	81/190 (43)	44/99 (44)	470/1114 (42)
T2	109/190 (57)	52/99 (53)	616/1114 (55)
T3	0/190 (0)	3/99 (3)	28/1114 (2)
Biopsy Gleason score, *n*/*N* (%)			
≤ 6	181/203 (89)	64/96 (67)	935/1158 (78)
7	19/203 (9)	24/96 (25)	223/1158 (19)
8–10	3/203 (1)	8/96 (8)	43/1158 (4)
Number of comorbidities, *n*/*N* (%)			
0	27/191 (14)	21/95 (22)	355/1178 (30)
1	60/191 (31)	18/95 (19)	390/1178 (33)
2	47/191 (25)	27/95 (28)	265/1178 (22)
3	35/191 (18)	18/95 (19)	109/1178 (9)
4 or more	22/191 (12)	11/95 (12)	59/1178 (5)

Staging method: N/R

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Mack 1997[158] **Language:** English **Publication type:** full-text paper **Number of study centres:** N/R **Setting:** N/R **Country:** Austria **Recruitment/treatment dates:** 1976–89 **Study design:** case series **Prospective/retrospective data collection:** N/R **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** mean follow-up period of survivors (38 patients) was 8.5 years **Source of funding:** N/R **Systematic reviewer:** SJ	**Inclusion criteria:** unclear. 66 patients agreed to perineal cryotherapy on following stages: T1c, T2a, T2b, T2c, T3a, T3b and T3c (all patients had biopsy-proven adenocarcinoma of the prostate) **Exclusion criteria:** N/R **Staging method:** cystoscopy and rectal palpation. Additional examination like X-ray, bone scan, sonography and lymphangiography (until 1979). After 1979 CT scan of the abdomen and pelvis was performed instead of lymphangiography	**CRYO:** open perineal cryosurgery was performed In brief: the prostate was exposed in extreme dorsosacral (lithotomy) position by the classical perineal belt incision. A curved retractor was placed in the bladder. The rectum as well as Denonvillier's fascia was dissected from the posterior surface of the prostate. By blunt dissection, the seminal vesicles were exposed. A Ch-18 cryoprobe was insert into the prostate at several locations. For the freezing procedure, liquid nitrogen was used (–170 °C) and cryotherapy equipment from the Frigitronics® brand (Coopersurgical, Trumbull, CT). Monitoring of the freezing process was by eye and/or palpating finger. The probe was easily removed by heating the tip. Finally, a drainage tube was inserted into the wound, the centrum tendineum reconstructed and the wound closed layers. The retractor was replaced by silastic catheter ch-16, which was kept in place for 10 days. The wound drain was removed after 8–10 days. Antibiotics were given for 14 days	**Efficacy:** disease-free survival, overall survival, biochemical disease-free status, positive biopsy on follow-up, reintervention rates **Functional outcomes:** impotent after therapy, stress incontinence **Adverse events:** rectourethral fistula formation

Patient characteristics	CRYO
Number of patients enrolled	66
Age (years)	
Median (range)	68.2 (49–78)
Clinical stage, *n* (%)	
T1c	3 (4.5)
T2a	32 (48.5)
T2b	9 (13.6)
T2c	11 (16.7)
T3a	4 (6.1)
T3b	5 (7.6)
T3c	2 (3)
Biopsy Gleason score, *n* (%)	
≤ 6	41 (62)
7	13 (20)
8–10	4 (6)
Missing	8 (12)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Maestroni 2008[159] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** Italy **Recruitment/treatment dates:** May 2006–November 2007 **Study design:** case series **Prospective/retrospective data collection:** N/R **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** 12 months **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** primary treatment of localised prostate cancer, local relapse after radiotherapy, age > 70 years **Exclusion criteria:** anal stenosis, previous rectal surgery, prostatic anteroposterior diameter > 25 mm, coxofemoral anchilosis **Staging method:** N/R	**HIFU:** performed using Ablatherm® with spinal block and midazolam (Ipnovel®, Roche). Seven patients had TURP in the same session as HIFU, 11 had this 2 months before and seven underwent TURP or transvesical adenomectomy more than 2 months before HIFU. The focus was not to preserve the neurovascular bundle	**Efficacy:** treatment failure, positive biopsy, PSA level **Functional outcomes:** urinary urge, incontinence, stress incontinence, sexual potency **Adverse events:** urinary tract infections, transient dysuria, transient perineal pain, acute urinary retention cause by clot urgency, haemorrhoidal crisis, referred painful tenesmus and diarrhoea caused by a pseudoactinic rectosigmoiditis, transient haematuria, rectovesical fistula, urethral stenosis **QoL:** quality of life index

Patient characteristics	HIFU
Number of patients enrolled	25
Low risk, *n* (%)	17 (68)
Intermediate risk, *n* (%)	6 (24)
High risk, *n* (%)	2 (4)
Age (years)	
Mean (range)	71.6 (56–78)
PSA level (ng/ml)	
Mean (range)	9.7 (0.78–54.9)
Clinical stage, *n* (%)	
T1	19 (76)
T2	5 (16)
T3	2 (8)
Prostate weight (g)	
Mean (range)	25.2 (5.0–38.4)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Malcolm 2010[160] **Language:** English **Publication type:** full-text paper **Number of study centres:** N/R **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** February 2000–December 2008 **Study design:** NRCS **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** mean 23.8 (median 30, range 3–36) months Mean follow-up for each treatment type was 31.5 months for ORP, 20.0 for RAP, 30.0 for BT and 23.8 for CRYO **Source of funding:** N/R **Systematic reviewer:** SJ	**Inclusion criteria:** patients undergoing operative treatment of localised prostate cancer at Virginia Prostate Center at Eastern Virginia Medical School were asked to participate **Exclusion criteria:** patients were excluded from the analysis if multimodal treatment was administered	**BT:** a modified peripheral loading low dose-rate technique was used with permanent palladium seeds delivering an average dose of 125 Gy. BT was performed by a single radiation oncologist in conjunction with one of three urologists **CRYO:** all patients were treated using third-generation technology (Endocare, Inc., Irvine, CA). All cryotherapy was performed by a fellowship-trained urologist **RP:** ORP and RAP nerve-sparing techniques were used where clinically appropriate as determined by the surgeon. ORP was performed by one of four fellowship-trained urological oncologists via the retropubic ($n = 132$) or perineal ($n = 3$) route. RAP was performed by one of three fellowship-trained (endourology or oncology) surgeons	**Efficacy:** N/R **Functional outcomes:** sexual, urinary and bowel function

Patient characteristics	RP	BT	CRYO
Number of patients enrolled	582	122	81
ORP (*n*)	135		
RAP (*n*)	447		
Age (years)			
Mean (SD)		66 (7)	71 (7)
ORP	59 (7)		
RAP	59 (6)		
PSA level (ng/ml)			
Median (range)		6.0 (4.5–8.2)	6.2 (5.0–8.6)
ORP	5.7 (4.7–7.3)		
RAP	5.2 (3.9–6.8)		
Clinical stage, *n* (%)			
T1c or less			
Total	452 (78)	98 (80)	57 (70)
ORP	112 (83)		
RAP	340 (76)		
T2a			
Total	85 (15)	16 (13)	10 (12)
ORP	17 (13)		
RAP	68 (15)		

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics				Intervention characteristics	Outcomes
	Patient characteristics	**RP**	**BT**	**CRYO**		
	T2b					
	Total	38 (6)	3 (2)	13 (16)		
	ORP	6 (4)				
	RAP	32 (7)				
	Unknown					
	Total	7 (1)	5 (4)	1 (1)		
	ORP	0 (0)				
	RAP	7 (2)				
	Biopsy Gleason score, *n* (%)					
	≤ 6					
	Total	362 (62)	88 (72)	40 (50)		
	ORP	93 (69)				
	RAP	269 (60)				
	7					
	Total	188 (32)	28 (23)	34 (41)		
	ORP	34 (25)				
	RAP	154 (34)				
	8–10					
	Total	32 (6)	6 (5)	7 (9)		
	ORP	8 (6)				
	RAP	24 (5)				
	Staging method: N/R					

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Mearini 2009[161] **Language:** English **Publication type:** full-text paper **Number of study centres:** 2 **Setting:** hospital **Country:** Italy **Recruitment/treatment dates:** 2004–7 **Study design:** case series **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** median 23.8 (range 11.8–40.8) months for 98.2% of the cohort **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** T1c–T2 and limited cT3a N0 M0 disease **Exclusion criteria:** prostate volume > 50 ml (two treatments scheduled), intraprostatic calcification > 1 cm and concomitant anal stricture **Staging method:** N/R	**HIFU:** performed using Sonablate® 500. No patient underwent TURP or received neoadjuvant hormonal therapy. Twenty-eight patients received ADT	**Efficacy:** biochemical failure, local failure (positive biopsy), median PSA nadir, biochemical disease-free survival **Functional outcomes:** urinary function, sexual function, UI, urinary obstruction **Adverse events:** rectourethral fistula, urinary infection, urethral stricture, intraoperative or perioperative complications

Patient characteristics	HIFU
Number of patients enrolled	163
Low risk, *n* (%)	80 (49.1)
Intermediate risk, *n* (%)	47 (28.8)
High risk, *n* (%)	14 (8.6)
Very high risk, *n* (%)	22 (13.5)
Age (years)	
Median (IQR)	72 (68–75)
PSA level (ng/ml)	
Median (IQR)	7.3 (5.2–10.0)
Clinical stage, *n* (%)	
T1	72 (44.2)
T2	69 (42.3)
T3	22 (13.4)
Biopsy Gleason score, *n* (%)	
2–4	23 (14.1)
5–7	125 (76.7)
8–10	15 (9.2)
Prostate size (ml)	
Median (IQR)	32.4 (24.7–40.0)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Misrai 2008[162] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** Hospital **Country:** France **Recruitment/treatment dates:** January 2001–November 2006 **Study design:** case series **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** mean 3.9 (range 1.0–6.8) years **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** clinical stage T1/T2, normal bone scintigraphy, normal abdominal CT and refusal of other treatment options **Exclusion criteria:** any previous treatment for prostate cancer, lymph node invasion	**HIFU:** performed using Ablatherm® device under general anaesthesia, TURP when prostate volume was > 50 ml or for lower urinary tract voiding symptoms	**Efficacy:** biochemical recurrence, positive biopsy, biochemical-free survival rate, death from prostate cancer, death from unrelated causes **Procedural outcomes:** type of anaesthetic

Patient characteristics	HIFU
Number of patients enrolled	119
Low risk, *n* (%)	65 (55)
Intermediate risk, *n* (%)	50 (42)
High risk, *n* (%)	4 (3)
Age (years)	
Mean (SD, range)	68 (7.8, 46–83)
PSA level (ng/ml)	
Mean (range)	8.2 (1.95–25.0)
Clinical stage, *n* (%)	
T1a	3 (3)
T1b	2 (2)
T1c	98 (82)
T2a	16 (13)
Biopsy Gleason score, *n* (%)	
4–6	81 (68)
7–8	38 (32)
Prostate volume (ml)	
Mean (SD)	32 (8)

Staging method: N/R

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Mohamed 2012[163] **Language:** English **Publication type:** full-text paper **Number of study centres:** multicentre **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** 1998–December 2003 **Study design:** NRCS **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** 6 months **Source of funding:** this work was supported by grant CA6136–04 and grant PADOH ME-98155 from the Commonwealth of Pennsylvania, grant DAMD 17–1–1–006 from the Department of Defense, and CA129094–01 **Systematic reviewer:** SJ	**Inclusion criteria:** diagnosis of localised prostate cancer (T1–2N0M0) during the past 4–6 weeks and fluency in English **Exclusion criteria:** lack of serious co-existent diseases that would limit patients' treatment options, as prostatectomy is not recommended for people with health complications such as diabetes and cardiovascular diseases **Staging method:** N/R	**BT:** N/R **EBRT:** N/R **RP:** N/R	**Functional outcomes:** sexual dysfunction, sexual bother, urinary dysfunction, urinary bother, urinary limitation

Patient characteristics	Total
Number of patients enrolled	869
BT, *n* (%)	240 (27.6)
EBRT, *n* (%)	483 (55.6)
RP, *n* (%)	146 (16.8)
Age (years)	
Mean (SD)	65.45 (7.57)
PSA level (ng/ml)	
Mean (SD)	7.60 (7.08)
Mean biopsy Gleason score (SD)	6.3 (0.8)
SAQ, mean (SD)	
Sexual dysfunction	2.40 (0.92)
Sexual bother	2.25 (1.24)
AUA symptom index, mean (SD)	
Urinary dysfunction	1.78 (0.81)
Urinary bother	1.67 (0.90)
Urinary limitation	1.19 (0.55)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Onik 2008[166] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** June 1995–2002 **Study design:** case series **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** mean 50 (range 24–105) months **Source of funding:** N/R **Systematic reviewer:** SJ	**Inclusion criteria:** patients were considered for cancer-targeted cryoablation if cancer was confined to one prostate lobe. The second criterion was patients who were potent, based on their history **Exclusion criteria:** patients with combined hormonal therapy after cryoablation were excluded **Staging method:** N/R	**CRYO:** for cryotherapy, focal cryoablation was performed using biplane TRUS if the tumour was confined to only one prostate lobe (lumpectomy-type procedure). There were changes made to the procedure to accommodate the concept of tumour targeting and to increase the safety and efficacy of the procedure: • The cryoprobes were 3.4-mm blunt-tipped probes placed using a Seldinger technique • Freezing temperatures of −35 °C were used. Freezing was carried out using copper/constantan thermocouples placed by ultrasound guidance. A continuous reading of the thermocouple temperature was provided by the cryosurgical equipment (Endocare, Irvine, CA, USA) **Extent of ablation:** focal	**Efficacy:** PSA stable or not, positive biopsy on follow-up **Functional outcomes:** potency, incontinence **Adverse events:** fistula

Patient characteristics	CRYO
Number of patients enrolled	21
Age (years)	
Median (range)	64 (51–75)
PSA level (ng/ml)	
Mean (SD)	7.64 (4.03)
Median	6.0
Clinical stage, *n* (%)	
T1c	12 (57)
T2a	7 (33)
T2b	2 (10)
Biopsy Gleason score, *n* (%)	
≤ 6	13 (62)
7	5 (24)
8–10	2 (9)
Unknown	1 (5)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Paulson, 1982a[168] and 1982b[169] **Language:** English, German (Paulson 1982b) **Publication type:** full-text paper **Number of study centres:** multiple **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** N/R **Study design:** RCT **Prospective/retrospective data collection:** prospective **Randomisation method:** N/R **Length of follow-up:** 5 years **Source of funding:** National Cancer Institute Grant and Medical Research Services, Veterans Administration Hospital, North Carolina **Systematic reviewer:** TEA	**Inclusion criteria:** newly diagnosed, previously untreated, biopsy-confirmed prostate adenocarcinoma, stage A2 or B (T1–2N0M0) **Exclusion criteria:** patients with occult focal carcinoma and stage C disease **Staging method:** rectal examination, serum prostatic acid phosphatase, radioisotopic bone scanning, staging lymphadenectomy	**EBRT:** 4500–5000 rad in approximately 40 days via the pelvic field and an additional minimum of 2000 rad in approximately 14 days using a reduced field (boost fields) using a cobalt linear accelerator of betatron X-ray beam **RP:** retropubic or perineal approach	**Efficacy:** treatment failure

Patient characteristics	EBRT	RP
Number of patients randomised	59	47

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Pe 2009[170] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** 1993–2006 **Study design:** NRCS **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** BT, median 37 (range 1–114) months; 3D-CRT, median 51 (range 1–148) months **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** low-risk prostate cancer (PSA ≤ 10 ng/ml, Gleason score of ≤ 6 and clinical stage T1c or T2a) **Exclusion criteria:** patients undergoing androgen suppression therapy **Staging method:** DRE, staging bone scans and CT scans	**BT:** I-125 seeds were implanted to give a minimal dose of 145 Gy with a margin of 3–5 mm **3D-CRT:** doses were prescribed to the 95% isodose line, with a median dose of 73.8 Gy. IMRT was the preferred modality in 2003	**Efficacy:** biochemical failure-free survival, PSA nadir

Patient characteristics	BT	EBRT
Number of patients enrolled	171	189
Number of patients analysed	193	197
Age (years)		
Median (range)	65 (42–78)	70 (49–83)
PSA level (ng/ml)		
Median (range)	5.7 (0.8–9.8)	6.5 (0.6–9.9)
Clinical stage, *n*/*N* (%)		
T1a	0/193 (0)	1/197 (1)
T1b	2/193 (1)	1/197 (1)
T1c	154/193 (80)	151/197 (77)
T2a	37/193 (19)	44/197 (22)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Pickles 2010[171] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** institution **Country:** Canada **Recruitment/treatment dates:** BT database, July 1998–January 2001; Prostate Cohort Outcomes Initiative database, 1998–January 2001 **Study design:** NRCS **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** BT, median 68 months; EBRT, median 67 months **Source of funding:** Abbott Labs Ltd and the Canadian Association of Radiation Oncology **Systematic reviewer:** TEA	**Inclusion criteria:** T1/T2, Gleason score of ≤ 6 or 7 **Exclusion criteria:** N/R **Staging method:** N/R	**BT:** low dose rate I-125 at a minimum peripheral dose of 144 Gy **EBRT:** dose 52.5–72 Gy	**Efficacy:** bNED **Adverse events:** acute and late gastrointestinal and genitourinary toxicities

Patient characteristics	BT	EBRT
Number of patients enrolled	394	1369
Number matched and analysed	139	139
Age (years) ($n = 139$)		
Median (range)	64 (48–79)	71 (54–84)
Median PSA level (ng/ml) ($n = 139$)	5.6	6.4
Clinical stage, *n/N* (%)		
T1a–c	54/139 (38.8)	58/139 (41.7)
T2a	75/139 (54.0)	70/139 (50.4)
T2b	10/139 (7.2)	11/139 (7.9)
Biopsy Gleason score, *n/N* (%)		
6	122/139 (87.8)	122/139 (87.8)
7	17/139 (12.2)	17/139 (12.2)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Pinkawa 2009[172] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** Germany **Recruitment/treatment dates:** 2003–6 **Study design:** NRCS **Prospective/retrospective data collection:** prospective Patients recruited consecutively (Y/N): N/R **Length of follow-up:** 3D-CRT, median 16 (range 12–21) months; BT, median 16 (range 12–24) months	**Inclusion criteria:** T1–2N0M0 **Matching criteria:** age ± 5 years, prostate volume ± 10 cc, use of antiandrogens, and erectile function (no ability to have an erection; at least a poor ability to have an erection; erection sufficient for sexual intercourse); 52 patients in the EBRT group could not be matched **Exclusion criteria:** N/R	**BT:** iodine (permanent seeds) at 145 Gy; 14 (27%) had neoadjuvant hormonal therapy **3D-CRT (EBRT):** 1.8–2.0-Gy fractions up to a total dose of 70.2–72.0 Gy; 14 (27%) had neoadjuvant hormonal therapy	**Functional outcomes:** sexual function, sexual bother, erectile ability, erections sufficient for sexual intercourse, urinary function, UI, urinary bother, UI bother, urinary obstructive/irritative bother, pain on urination, bowel function, bowel bother, bloody stools, painful bowel movements, increased frequency of bowel movements, hormonal function, hormonal bother **Procedural outcomes:** type of anaesthetic

Patient characteristics	BT	EBRT
Number of patients enrolled	62	224
	61 returned baseline questionnaire	146 returned baseline questionnaire
	52 were matched	52 were matched
Age (years) ($n = 52$)		
Median (range)	68 (51–77)	68 (48–77)
PSA level (ng/ml) ($n = 52$)		
Median (range)	7 (1.5–14)	8 (2.5–24)
Clinical stage, *n*/*N* (%)		
≤ T2a	51/52 (98)	43/52 (83)

Study details	Participant characteristics			Intervention characteristics	Outcomes
Source of funding: N/R **Systematic reviewer:** TEA	**Patient characteristics**	**BT**	**EBRT**		
	Biopsy Gleason score, *n/N* (%)				
	< 7	50/52 (96)	39/52 (75)		
	Prostate size (ml) ($n = 52$)				
	Median (range)	37 (18–60)	35 (22–68)		
	Comorbidity, *n/N* (%)				
	Hypertension	11/52 (21)	11/52 (21)		
	Coronary heart disease	6/52 (12)	13/52 (25)		
	Diabetes	6/52 (12)	7/52 (14)		
	COPD	4/52 (8)	6/52 (12)		
	Staging method: N/R				

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Pinthus 2012[173] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** Canada **Recruitment/treatment dates:** May 2005–December 2010 **Study design:** NRCS **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** median 24 (IQR 15–36, range 6–48) months **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** clinical stage T1 and T2, Gleason score of ≤ 7, serum PSA < 20 ng/ml **Exclusion criteria:** previous radiation therapy, androgen deprivation or HIFU, less than two consecutive PSA measurements, pretreatment prostate volume > 40 ml **Staging method:** N/R	**HIFU:** single session of HIFU using Ablatherm®, average power ranging 41–48 W, no peri-HIFU TURP	**Efficacy:** biochemical failure, biochemical failure-free survival, prostate cancer-related death, death from unrelated causes, PSA nadir, positive biopsy

Patient characteristics	HIFU
Number of patients enrolled	402
Low risk, *n* (%)	183 (46)
Intermediate risk, *n* (%)	219 (54)
Age (years)	
Mean (SD)	62.7 (7.5)
PSA level (ng/ml)	
Mean (SD)	6.6 (3.1)
Clinical stage, *n* (%)	
T1b	2 (1)
T1c	307 (76)
T2a	74 (18)
T2b	19 (5)
Biopsy Gleason score, *n* (%)	
5	4 (1)
6	205 (51)
3 + 4	130 (32)
4 + 3	63 (16)
Prostate size (ml)	
Mean (SD)	36.7 (7.6)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Poissonnier 2007[174] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** France **Recruitment/treatment dates:** April 1994–July 2003 **Study design:** case series **Prospective/retrospective data collection:** N/R **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** mean 27.5 (SD 20, range 12–107) months **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** localised prostate cancer, clinical stage T1–T2, PSA ≤ 15 ng/ml, prostate volume < 40 cc, no previous radical treatment for prostate cancer, at least 1 year of follow-up **Exclusion criteria:** N/R **Staging method:** N/R	**HIFU:** fifty-one (22%) patients were treated with the prototypes (1995–9) whereas 176 (78%) were treated with the commercially available device (2000–3); the latter group also had the HIFU session combined with TURP. Seventy-six (33%) patients had neoadjuvant hormonal deprivation because the prostate volume was > 40 ml. Twenty-six of 67 patients who were potent at baseline had a nerve-sparing procedure	**Efficacy:** treatment failure, disease-free rate, reintervention rate, death from other causes **Functional outcomes:** stress incontinence, potency **Adverse events:** bladder neck or urethral stricture

Patient characteristics	HIFU
Number of patients enrolled	227
Age (years)	
Mean (SD)	68.8 (5.82)
PSA level (ng/ml)	
Mean (SD)	6.99 (3.48)
Clinical stage, *n* (%)	
T1a	6 (3)
T1b	17 (7)
T1c	99 (44)
T2	105 (46)
Biopsy Gleason score, *n* (%)	
2–6	152 (67)
7	75 (33)
Prostate size (ml)	
Mean (SD)	23.9 (10.26)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Reeve 2012[176] **Language:** English **Publication type:** full-text paper **Number of study centres:** multicentre **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** 1998–2003 **Study design:** NRCS **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** no **Length of follow-up:** mean 11.5 (SD 7.1) months **Source of funding:** Dr Reeve's work was supported under a National Cancer Institute contract to the University of North Carolina at Chapel Hill **Systematic reviewer:** SJ	**Inclusion criteria:** patients with prostate cancer whose first SEER-confirmed diagnosis occurred after their baseline MHOS and before the follow-up MHOS **Exclusion criteria:** patients diagnosed with regional or metastatic prostate cancer	**BT:** N/R **EBRT:** N/R **RP:** N/R	**Functional outcomes:** UI **QoL:** physical component, role physical, general health, vitality, social functioning, mental health (SF-36)

Patient characteristics	BT	EBRT	RP
Number of patients enrolled	41	169	72
Age (years)			
Mean (SD)	71.51 (4.31)	71.69 (3.82)	69.54 (3.30)
Clinical stage, *n* (%)			
T1	15 (36.6)	69 (40.8)	29 (40.3)
T2	9 (22)	50 (29.6)	21 (29.2)
T1 or T2	5 (12.2)	11 (6.5)	12 (16.7)
T2 prostatic apex	6 (14.6)	30 (17.8)	7 (9.7)
Unstaged	6 (14.6)	9 (5.3)	3 (4.2)
Urinary incontinence at baseline, *n* (%)	6 (14.63)	34 (20.12)	10 (13.89)

Staging method: N/R

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Selvadurai 2013[181,196] **Language:** English **Publication type:** full-text paper **Number of study centres:** single **Setting:** hospital **Country:** UK **Recruitment/treatment dates:** March 2002–May 2011 **Study design:** case series **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** median 5.7 years **Source of funding:** none **Systematic reviewer:** SJ	**Inclusion criteria:** eligibility criteria included histologically proven prostate adenocarcinoma, age 50–80 years, stage T1/T2, PSA level < 15 ng/ml, Gleason score of ≤ 3 + 3 (≤ 3 + 4 if aged > 65 years) and percentage-positive biopsy cores ≤ 50% (extent of single-cores involvement was not an eligibility criterion). Patients were required to be fit for radical treatment based on clinical judgement **Exclusion criteria:** those who were not were followed on a watch-and-wait policy and are excluded in this report **Staging method:** DRE	**AS:** the AS protocol consisted of clinical assessment with DRE and serum PSA levels taken at 3-month intervals in the first year, 4-month intervals in the second year and 6-month intervals thereafter. The Abbott Architect assay (Abbott Laboratories, Abbott Park, IL, USA) was used. TRUS-guided prostate biopsy was performed after 18–24 months on surveillance, and every 2 years thereafter. Radical treatment was recommended in the event of either a PSA velocity > 1 ng/ml per year or adverse histology on repeat biopsy, defined as primary Gleason score of ≥ 4 + 3 or the presence of cancer in > 50% of the total number of cores. Treatment modality (ADT with radical EBRT, RP or BT) was selected according to local protocol, clinician judgement and patient preference	**Efficacy:** prostate cancer deaths, overall survival, deferred treatment

Patient characteristics	AS
Number of patients enrolled	471
Age (years)	
Median (range)	66 (51–79)
PSA level (ng/ml)	
Median (range)	6.4 (0.2–14.5)
Clinical stage, *n* (%)	
T1	417 (88.5)
T2a	49 (11.7)
T2b	5 (1)
Biopsy Gleason score, *n* (%)	
≤ 6	438 (93)
7	33 (7)
Prostate size (ml)	
Median (range)	45 (10–159)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Shah 2012[182,201] **Language:** English **Publication type:** full-text paper **Number of study centres:** single **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** 1984–2009 **Study design:** NRCS **Prospective/retrospective data collection:** prospective (retrospectively analysed) **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** mean 7, median 6.6 (range 0.6–22.43) years **Source of funding:** none **Systematic reviewer:** SJ	**Inclusion criteria:** all patients were treated with definitive radiation therapy using modalities, which included traditional EBRT ($n = 1154$), dose escalation with an ART ($n = 1036$), BT alone ($n = 540$) **Exclusion criteria:** all cases without race information, with follow-up < 6 months and 0–1 post-treatment PSA levels were excluded from the analysis. Patients with recurrent cancer or treated following prostatectomy were also excluded from the analysis	**BT:** BT alone (HDR or LDR; $n = 540$). The mean dose received for BT was 34.4 Gy **EBRT:** all patients were treated with definitive radiation therapy using modalities, which included traditional EBRT ($n = 1154$) and dose escalation with an ART ($n = 1036$). Mean dose was 67.4 Gy (EBRT) and 75.4 Gy (ART)	**Efficacy:** overall survival, disease-specific survival, local recurrence **Functional outcomes:** UI **Adverse events:** urethral stricture, acute urinary retention, dysuria, diarrhoea, rectal pain, rectal bleeding

Patient characteristics	Total
Number of patients enrolled	3180[a]
EBRT, *n*	1154
ART, *n*	1036
BT, *n*	540
Age (years)	
Mean/median (range)	70/71 (40–92)
PSA level, *n* (%)	
< 4.0 ng/ml	447 (14)
4.0–9.9 ng/ml	1789 (56)
10–20 ng/ml	543 (17)
≥ 20 ng/ml	400 (13)

Study details	Participant characteristics		Intervention characteristics	Outcomes
	Patient characteristics	**Total**		
	Mean PSA level (ng/ml)	11.6		
	Clinical stage, *n* (%)			
	T1a–c	1461 (46)		
	T2a–c	1568 (50)		
	T3a–c	141 (4)		
	Biopsy Gleason score, *n* (%)			
	≤ 7	1898 (60)		
	≥ 7	1266 (40)		
	a Including patients with EBRT + BT (total participant characteristics include patients with BT and EBRT combined).			
	Staging method: N/R			

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Mohammed 2012[164] (secondary to Shah 2012[182,201]) **Language:** English **Publication type:** full-text paper **Number of study centres:** single **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** 1992–2006 **Study design:** NRCS **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** median 4.8 years **Source of funding:** N/R **Systematic reviewer:** SJ	**Inclusion criteria:** a total of 1903 consecutive patients with clinical stage II to III (T1–T3, N0, M0) adenocarcinoma of the prostate were treated at William Beaumont Hospital with any of three modern high-dose RT techniques. Treatment modality was selected based on a combination of disease characteristics, patient symptomatology, comorbidities, technical qualification and patient/physician preference. Inclusion criteria for each treatment modality are reported in intervention characteristics section **Exclusion criteria:** N/R	**BT:** BT as monotherapy was delivered with either HDR (Ir-192) or LDR (Pd-103). Patients receiving BT alone had clinical stage II (T1c–T2b) disease, Gleason score of ≤ 7, pretreatment PSA ≤ 10 ng/ml and gland size ≤ 70 cc For both HDR and LDR, a perineal template was affixed to a 7.5-MHz biplanar ultrasound probe. For HDR treatment, optimal needle positions were generated intraoperatively using an online, interactive, in-house software program. A total dose of 38 Gy was delivered in four fractions of 9.5 Gy each with an interfraction time of at least 6 hours For LDR implants, the needles were placed in preplanned positions on the reference image. The final plan was evaluated by CT 2 weeks after the procedure. A total dose of 120 Gy was prescribed to the PTV in LDR	**Adverse events:** acute genitourinary, late genitourinary, acute gastrointestinal, late gastrointestinal

Patient characteristics	BT	EBRT
Number of patients enrolled	417	1039
Age (years)		
Mean/median (range)	64.9/65 (40–83)	70.8/72 (45–88)
PSA level, *n* (%)		
≤ 4.0 ng/ml	98 (24)	155 (15)
4.1–10.0 ng/ml	301 (72)	661 (64)
> 10 ng/ml	18 (4)	218 (21)
Missing	0	5
Clinical stage, *n* (%)		
T1a–c	273 (65)	689 (67)
T2a–c	144 (35)	321 (31)
T3–T4	0 (0)	16 (2)
Unknown		13 (1)

Study details	Participant characteristics		Intervention characteristics	Outcomes
	Patient characteristics	**BT** / **EBRT**	**EB-IGRT:** patients receiving EB-IGRT were treated from 1997 to 2006. Patients treated after 1999 were enrolled in image-guided phase II dose escalation study using CT-based offline IGRT. In brief, a virtual CT simulation in the supine position with urethral contrast was performed. The bladder, prostate and seminal vesicles were contoured. The rectum was defined from the base of the sacroiliac joint or the rectosigmoid junction to the ischial tuberosity For low-risk patients (Gleason score of ≤ 6, PSA < 10 ng/ml and clinical stage $\leq$ T2a), the CTV included the prostate only (group 1). If any intermediate-/high-risk factors were present, the CTV included the prostate and the proximal seminal vesicles (group 2). For the initial treatment week, PTV included the CTV + 1-cm margin to a total dose of 900 cGy. For each of the first four fractions, daily electronic portal images were taken and CT scans were acquired immediately before or after treatment	
	Biopsy Gleason score, *n* (%)			
	4–6	371 (89) / 544 (53)		
	7	42 (10) / 377 (36)		
	8–10	3 (1) / 110 (11)		
	Missing	1 / 8		
	Prostate size (ml)			
	Mean/median	35/36.6 / 44/50.6		
	Staging method: N/R			

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Smith 2009[184] **Language:** English **Publication type:** full-text paper **Number of study centres:** N/A **Setting:** population-based **Country:** Australia **Recruitment/treatment dates:** October 2000–October 2002 **Study design:** NRCS **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** 3 years **Source of funding:** Australian Commonwealth Department of Veterans Affairs and National Health and Medical Research Council of Australia **Systematic reviewer:** TEA	**Inclusion criteria:** all people aged < 70 years, resident in New South Wales, diagnosed with histopathologically confirmed prostate cancer (cT1a N0M0 to cT2c N0M0) between October 2000 and October 2002, and notified to the population-based New South Wales central cancer registry by May 2003 or no more than 12 months after their diagnosis **Exclusion criteria:** N/R	**BT:** LDR BT **EBRT:** N/R **RP:** 494/981 had RPs with nerve-sparing intent	**Efficacy:** disease recurrence or spread **Functional outcomes:** impotence, UI, bowel problems **QoL:** UCLA-PCI physical component, mental component, urinary function, urinary bother, bowel function, bowel bother, sexual function, sexual bother

Patient characteristics	BT	EBRT	RP
Number of patients enrolled	58	123	981
Age (years)			
Mean (95% CI)	60.0 (58.6 to 61.4)	63.9 (63 to 64.7)	60.2 (59.9 to 60.6)
PSA level, *n* (%)			
< 4 ng/ml	2 (3)	8 (7)	77 (8)
4–9.9 ng/ml	46 (79)	67 (55)	643 (67)
10–19.9 ng/ml	8 (14)	38 (31)	195 (20)
20+ ng/ml	2 (3)	10 (8)	48 (5)
Median PSA level (range) (ng/ml)	7.2 (2.1–23.3)	8.2 (0.2–45)	7.2 (0.3–602)
Clinical stage, *n* (%)			
T1a	0 (0)	1 (1)	4 (< 1)
T1b	0 (0)	4 (3)	15 (2)
T1c	43 (74)	56 (46)	516 (53)
T2a	12 (21)	31 (25)	239 (24)
T2b	2 (3)	19 (15)	120 (12)
T2c	1 (2)	12 (10)	87 (9)

Study details	Participant characteristics				Intervention characteristics	Outcomes
	Patient characteristics	**BT**	**EBRT**	**RP**		
	Biopsy Gleason score, *n* (%)					
	≤ 6	53 (91)	57 (47)	539 (55)		
	7	5 (9)	55 (46)	356 (36)		
	8–10	0 (0)	9 (7)	83 (9)		
	Mean biopsy Gleason score (95% CI)	6.0 (5.9 to 6.1)	6.5 (6.4 to 6.7)	6.5 (6.4 to 6.5)		
	Comorbidity score, *n* (%)					
	0	24 (41)	33 (27)	427 (44)		
	1	20 (35)	39 (32)	311 (32)		
	2+	14 (24)	51 (42)	243 (25)		
	Staging method: N/R					

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Sumitomo 2010[185] **Language:** English **Publication type:** full-text paper **Number of study centres:** 2 **Setting:** hospital **Country:** Japan **Recruitment/treatment dates:** April 2002–March 2010 **Study design:** case series **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** HIFU, mean 45.7 (SD 24.4)/range 12–93 months; HIFU + TURP, mean 38.6 (SD 15.3)/ range 12–72 months **Source of funding:** N/R **Systematic reviewer:** SJ	**Inclusion criteria:** the inclusion criteria for HIFU were biopsy-proven prostate cancer with no previous prostate cancer treatment other than NADT for 12 months or less **Exclusion criteria:** patients who had received NADT for > 12 months or whose PSA levels at diagnosis were > 50 ng/ml	**HIFU:** this study evaluated the records of 129 patients whose HIFU treatments had been carried out by the same surgeon and in accordance with the standard HIFU procedure guideline defined at the HIFU User Meeting in Japan. The TURP procedure – mainly resecting the lateral parts of the prostate and, if necessary, incising the bladder neck – was carried out immediately after the HIFU treatment, and the resected volume was based on a channelling of the prostate. Patients were classified into two groups: those who had received HIFU alone (HIFU-only group; $n = 65$) and those whose initial HIFU treatment had been combined with TURP (HIFU + TURP group; $n = 64$)	**Efficacy:** disease-free survival **Functional outcomes:** urinary function **Adverse effects:** rectourethral fistula formation, urethral stricture formation, acute urinary retention, bladder neck contracture, epididymitis

Patient characteristics	HIFU	TURP + HIFU	Total
Number of patients enrolled	65	64	129
Age (years)			
Mean (SD)	68.5 (6.2)	69.0 (6.9)	
Range	57–80	44–82	
PSA level (ng/ml)			
Mean (SD)	12.1 (8.3)	11.9 (7.2)	
Range	3.9–44.3	4.3–47.0	
n (%)			
0–10	32 (49)	32 (50)	64 (50)
10–20	25 (39)	27 (42)	52 (40)
20–50	8 (12)	5 (8)	13 (10)
Clinical stage, *n* (%)			
T1	28 (43)	41 (64)	69 (53)
T2a	8 (12)	5 (8)	13 (10)
T2b	11 (17)	4 (6)	15 (12)
T2c	2 (3)	6 (9)	8 (6)
T3	16 (25)	8 (12)	24 (19)

Study details	Participant characteristics				Intervention characteristics	Outcomes
	Patient characteristics	**HIFU**	**TURP + HIFU**	**Total**		
	Biopsy Gleason score, *n* (%)					
	≤ 6	32 (49)	30 (47)	62 (48)		
	7	14 (22)	24 (37)	38 (29)		
	8–10	19 (29)	10 (16)	29 (23)		
	Prostate size (ml)					
	Mean (SD)	21.8 (7.8)	19.9 (7.5)			
	Range	9.0–40.2	5.6–37.5			
	Staging method: DRE, needle biopsy and TRUS findings by using the 2002 American Joint Committee on Cancer staging guidelines					

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Talcott 2003[186] **Language:** English **Publication type:** full-text paper **Number of study centres:** multicentre **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** 1 June 1994–31 August 2000 **Study design:** NRCS **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** no **Length of follow-up:** 3, 12, 24 and 36 months **Source of funding:** Healthcare Research and Quality grant **Systematic reviewer:** SJ	**Inclusion criteria:** patients treated with primary therapy (pathologically confirmed), untreated early (non-metastatic) prostate cancer at recruitment sites **Exclusion criteria:** unclear	**BT:** N/R **RP:** two types of RP were used [non-nerve sparing, nerve sparing (unilateral and bilateral)] Nerve-sparing statues were unknown in some patients **EBRT:** N/R	**Efficacy:** N/R **QoL:** functional outcomes (four symptom indexes and four parallel symptom distress scales)

Patient characteristics	BT	EBRT	RP
Number of patients enrolled	80	182	129
Age (years)			
Median/mean (range)	64/63 (47–76)	69/69 (51–82)	60/60 (46–74)
PSA level (ng/ml)			
Median/mean (range)	5.8/6.3 (1.3–18.3)	7.8/11.2 (0.9–77.4)	6.3/8.3 (0.8–70.3)
≤ 10 ng/dl, *n* (%)	74 (93)	123 (68)	104 (81)
10–20 ng/dl, *n* (%)	6 (7)	42 (23)	18 (14)
> 20 ng/dl, *n* (%)	0	16 (9)[a]	7 (5)
Unknown (*n*)		1	
Clinical stage, *n* (%)			
T1	62 (78)	136 (75)	97 (75)
T2	18 (22)	45 (25)	32 (25)

Study details	Participant characteristics				Intervention characteristics	Outcomes
	Patient characteristics	**BT**	**EBRT**	**RP**		
	Biopsy Gleason score, *n* (%)					
	≤ 6	61 (76)	87 (48)	65 (50)		
	7	18 (23)	62 (34)	50 (39)		
	8–10	1 (1)	33 (18)	14 (11)		
	Comorbidity: index of co-existent disease, *n* (%)					
	0	28 (35)	42 (23)	49 (38)		
	1	51 (64)	129 (71)	80 (62)		
	2 or 3	1 (1)	11 (6)	0 (0)		
	a Study authors presented as 19%.					
	Staging method: N/R					

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Tosoian 2011[187] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** January 1995–March 2010 **Study design:** case series **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** median 2.7 (range 0.01–15.0) years **Source of funding:** H Ballentine Carter **Systematic reviewer:** TEA	**Inclusion criteria:** very low-risk cancer including T1c disease, PSA density < 0.15 ng/ml, Gleason score of ≤ 6, two or fewer biopsy cores with cancer, a maximum of 50% involvement of any core with cancer **Exclusion criteria:** N/R **Staging method:** N/R	**AS:** semi-annual PSA measurements and DRE, and annual 12- to 14-core surveillance biopsy. Curative therapy was offered when biopsy enrolment criteria were no longer met	**Efficacy:** death from prostate cancer, death from other causes, number treated

Patient characteristics	AS
Number of patients enrolled	769
Age (years)	
Median (range)	66 (45–92)
Clinical stage, *n* (%)	
≤ T1c	763 (99)
> T1c	6 (1)
Biopsy Gleason score, *n* (%)	
≤ 6	769 (100)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Truesdale 2010[188] **Language:** English **Publication type:** full-text paper **Number of study centres:** single **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** 2002–9 **Study design:** case series **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** median 24 (range 0–87) months Follow-up at 1, 24, 36, 48, 60 and 72 months **Source of funding:** no founding received for this study **Systematic reviewer:** SJ	**Inclusion criteria:** patients with confirmed unilateral prostate cancer. Patients were stratified using task force selection criteria **Exclusion criteria:** included any prior treatment for prostate cancer, including history of radiation or hormone therapy	**CRYO:** patients were treated with primary focal cryosurgery, defined as hemiablation confined to a single lobe of the prostate. Unilateral nerve-sparing cryoablation was performed as an outpatient procedure in the operating room In brief, the prostate was analysed to determine the optimal configuration for placement of either 17-gauge cryoneedles or 2.4-mm cryoprobes. Under TRUS guide lines, cryoprobes/cryoneedles were placed approximately 1 cm apart and within 5 mm of the capsule on the side of the tumour. Two freeze–thaw cycles were performed. Temperatures were monitored with thermal multisensorial couples to ensure complete ablation of targeted tissue. Cryoablation was limited to the side of the gland with histologically proven adenocarcinoma. The neurovascular bundle was destroyed on the ipsilateral side with cancer, and contralateral side was spared **Extent of ablation:** focal	**Efficacy:** biochemical disease-free survival (progression-free survival), pathological survival rate **Functional outcomes:** ED/impotence (International Index of Erectile Dysfunction), urinary continence, AUA Symptom Index score

Patient characteristics	CRYO
Number of patients enrolled	77
Age (years)	
Mean (SD)	69.5 (6.7)
PSA level (ng/ml)	
Mean (SD)	6.54 (4.87)
Clinical stage, *n* (%)	
pT1c	67 (87)
pT2a	10 (13)
Biopsy Gleason score, *n* (%)	
5–6	50 (65)
7	25 (32)
8	2 (3)
Prostate size (ml)	
Mean (SD)	44.8 (20.7)
Pretreatment AUA symptom index, mean (SD)	9 (5.8)
IIEF, mean (SD)	42.5 (24.2)

Staging method: prostate cancer confirmed by TRUS biopsy

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Lambert 2007[152] (secondary to Truesdale 2010[188]) **Language:** English **Publication type:** full-text paper **Number of study centres:** single **Setting:** N/R **Country:** USA **Recruitment/treatment dates:** June 2002–December 2005 **Study design:** case series **Prospective/retrospective data collection:** unclear (retrospectively reviewed) **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** median 28 (range 9–72) months **Source of funding:** N/R **Systematic reviewer:** SJ	**Inclusion criteria:** patients who identified as having undergone focal cryosurgery, with freezing confined to a single lobe of the prostate, patients with Gleason score of 6 or 7 (3 + 4) in one lobe in one or two contiguous biopsy cores and a tumour volume of < 10% in a 12-core biopsy **Exclusion criteria:** patients who had not undergone hormonal therapy or radiotherapy **Staging method:** N/R	**CRYO:** the ultrasound-guided percutaneous cryosurgery procedure was used In brief, prostate was analysed to determine the optimal geometry for placement of either 17-gauge cryoneedles or 2.4-mm cryoprobes and thermal couples. Under TRUS guidance, cryoneedles/cryoprobes were placed approximately 1 cm apart and within 5 mm of the capsule on the side of the tumour. The extent of freezing was limited to the side of the gland with histologically proven adenocarcinoma of the prostate. The NVB was destroyed on the ipsilateral side with cancer and the contralateral NVB was spared	**Efficacy:** biochemical disease-free survival **Functional outcomes:** ED, UI **Adverse events:** urinary retention, rectal pain, perineal discomfort, fistula formation

Patient characteristics	CRYO
Number of patients enrolled	25
Age (years)	
Median (range)	69 (48–78)
PSA level (ng/ml)	
Median (range)	6.00 (1.0–13.10)
Clinical stage, *n* (%)	
T1c	25 (100)
Biopsy Gleason score, *n* (%)	
6	13 (52)
7	12 (48)
Erectile dysfunction, *n*/*N* (%), potent	24/25 (96)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Tsui 2005[189] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** Canada **Recruitment/treatment dates:** 1998–2000 **Study design:** NRCS **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** BT, median 45 (range 18–63) months; 3D-CRT, median 62 (range 18–79) months **Source of funding:** none **Systematic reviewer:** TEA	**Inclusion criteria:** T1c–T2b, no evidence of nodal metastases, pretreatment PSA ≤ 20.0 ng/ml and Gleason ≤ 8, treated with 3D-CRT or BT between 1998 and 2000, minimum of 12 months follow-up **Exclusion criteria:** N/R	**BT:** I-125 at 145 Gy (TG43), tamsulosin (Flomax®, IMPAX Laboratories, Inc.) to manage urinary symptoms for a minimum of 3 months after treatment, 28/85 had prior hormonal therapy, 3/85 had α-blockers, 3/86 had TURP **3D-CRT:** 75.6 Gy in 180-cGy daily fractions over a period of 8.5 weeks using a six-field coplanar technique. 10/76 had prior hormonal therapy, 5/76 had α-blockers, 7/76 had TURP	**Efficacy:** recurrence (biochemical failure and positive biopsy) **Functional outcomes:** I-PSS score, urinary frequency, urgency, weak stream, nocturia, potency **Procedural outcomes:** nature of anaesthetic

Patient characteristics	BT	3D-CRT
Number of patients enrolled	86	76
Age (years)		
Mean (SD)	64.8 (6.5)	66.3 (5.1)
PSA level (ng/ml)		
Mean (SD)	6.2 (2.3)	9.1 (3.7)
Clinical stage, *n/N* (%)		
T1c	50/79 (63)	35/73 (48)
T2a	28/79 (35)	21/73 (29)
T2b	1/79 (1)	16/73 (22)
T2c	0/79 (0)	1/73 (1)
Biopsy Gleason score, *n/N* (%)		
≤ 6	83/85 (98)	30/74 (41)
7	2/85 (2)	41/74 (55)
8–10	0/85 (0)	3/74 (4)

Staging method: N/R

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Uchida 2005[191] **Language:** English **Publication type:** full-text paper **Number of study centres:** multicentre **Setting:** hospital **Country:** Japan **Recruitment/treatment dates:** N/R **Study design:** case series **Prospective/retrospective data collection:** N/R **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** median 14 (range 2–24) months **Source of funding:** N/R **Systematic reviewer:** SJ	**Inclusion criteria:** patients with biopsy-proven and untreated stage T1c–2N0M0 localised prostate cancer. Age < 80 years, serum PSA level 20 ng/ml, treatable with a 4.0 focal length probe which means a prostatic volume < 50 ml and WHO performance status 0–1 **Exclusion criteria:** patients with urethral stricture, anal stricture, bleeding tendency, renal dysfunction with serum Cr > 2.0 mg/dl, hydronephrosis, larger than 5 mm calcifications in the prostate, uncontrolled diabetes mellitus, hypertension, angina, history of cardiac infarction or other malignant disease were excluded from the study None of the patients receiving neoadjuvant hormonal and/or chemotherapy before HIFU **Patient characteristics** / **HIFU** Number of patients enrolled: 72 Age (years) Median (range): 72 (45–79) PSA level (ng/ml) Median (range): 8.10 (2.10–19.80) Clinical stage, *n* (%) T1c: 40 (56) T2a: 18 (25) T2b: 14 (19)	**HIFU:** this study used Sonablate® 500. In this treatment, module includes the ultrapower generator, transrectal probe positioning system and a continuous cooling system. The transrectal HIFU probes use proprietary transducer technology with low-energy ultrasound (4 MHz) for imaging of the prostate and for the delivery of high-energy ablative pulses (site intensity 1300–2200 W/cm^2) All patients were anaesthetised by general, epidural, spinal or intravenous anaesthesia, and were placed in a supine and open-leg position	**Efficacy:** biochemical disease-free survivals **Functional outcomes:** ED, UI, stooly incontinence, retrograde ejaculation **Adverse events:** urethral stricture, epididymitis, prostatitis, nephrotic syndrome, balanoposthitis

Study details	Participant characteristics		Intervention characteristics	Outcomes
	Patient characteristics	**HIFU**		
	Biopsy Gleason score, *n* (%)			
	2–4	9 (13)		
	5–7	55 (76)		
	8–10	6 (8)		
	Unknown	2 (3)		
	Prostate size (ml)			
	Median (range)	22.1 (8.5–52.8)		
	Staging method: N/R			

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Uchida 2009[190,192–195] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** Japan **Recruitment/treatment dates:** January 1999–December 2007 **Study design:** case series **Prospective/retrospective data collection:** N/R **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** median 24 (range 2–88) months **Source of funding:** N/R **Systematic reviewer:** SJ	**Inclusion criteria:** patients with biopsy-proven and stage T1c–3N0M0 localised prostate cancer **Exclusion criteria:** none of the patients received adjuvant therapy during follow-up **Staging method:** N/R	**HIFU:** this study used three generations of HIFU devices: the Sonablate® 200 [SB200 – 31 patients (6%)] from January 1999 to February 2000, the Sonablate® 500 [SB500 – 385 patients (74%)] from March 2000 to October 2006 and the Sonablate® 500 version 4 [SB500 V4 – 101 patients (20%)] from October 2006 onwards (all devices Focus Surgery, Indianapolis, IN). This treatment module includes the ultrasound power generator, transrectal probes, the probe positioning system and a continuous cooling system. The transrectal HIFU probes use proprietary transducer technology with low-energy ultrasound (4 MHz) for imaging of the prostate and for the delivery of high-energy ablative pulses (site intensity 1300–2200 W/cm^2). All patients were anaesthetised by general, epidural or spinal anaesthesia, and were placed in a supine and open-leg position The prostate was treated in one ($n = 415$), two ($n = 86$), three ($n = 14$) or four ($n = 2$) sessions. In total, 637 HIFU procedures were performed (average 1.2 sessions/patient)	**Efficacy:** biochemical disease-free status **Functional outcomes:** ED, UI (grade 1) **Adverse events:** rectourethral fistula, urethral stricture, prolonged urinary retention, epididymitis, bladder neck contracture, hematospermia, perineal oedema, retrograde ejaculation

Patient characteristics	HIFU
Number of patients enrolled	517
Age (years)	
Median (range)	68 (45–88)
PSA level (ng/ml)	
Median (range)	9.2 (2.8–49.6)
Clinical stage, *n* (%)	
T1c	294 (57)
T2a	22 (4)
T2b	82 (16)
T2c	87 (17)
T3	32 (6)
Biopsy Gleason score, *n* (%)	
2–4	37 (7)
5–7	413 (80)
8–10	67 (13)
Prostate size (ml)	
Median (range)	21.9 (4.6–68.8)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Shoji 2010[183] (secondary to Uchida 2009[190,192–195]) **Language:** English **Publication type:** full-text paper **Number of study centres:** N/R **Setting:** hospital **Country:** Japan **Recruitment/treatment dates:** January 1999–April 2007 **Study design:** case series **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** 24 months **Source of funding:** N/R **Systematic reviewer:** SJ	**Inclusion criteria:** patients with newly diagnosed localised prostate cancer treated with single HIFU therapy. [When the prostate volumes of patients were > 40 ml ($n = 18$), TURP was carried out 1 month before HIFU therapy to reduce prostate volume] **Exclusion criteria:** patients who received NADT for evaluating erectile function because the terms of NADT were intermingled	**HIFU:** patients received a single HIFU therapy with Sonablate® systems. During HIFU therapy, the total prostate was abated while avoiding the NVBs using a colour Doppler system to maintain potency	**QoL:** I-PSS, QoL index, maximum flow rate (ml/s), residual urine (ml), FACT-G and domains, FACT-P, IIEF-5 (non-neoadjuvant therapy)

Patient characteristics	HIFU
Number of patients enrolled	326
Age (years)	
Mean (SD)	68 (6.8)
Range	45–88
PSA level (ng/ml)	
Mean (SD)	12.7 (9.4)
Range	3.39–69.4
Clinical stage, *n* (%)	
T1c	173 (53)
T2a	106 (33)
T2b	47 (14)
Biopsy Gleason score, *n* (%)	
2–4	29 (9)
5–7	259 (79)
8–10	38 (12)
Prostate size (ml)	
Mean (SD)	21.7 (13)
Range	7.1–45.8

Staging method: N/R

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: van den Bergh 2012[198] **Language:** English **Publication type:** full-text paper **Number of study centres:** multiple **Setting:** hospital **Country:** the Netherlands **Recruitment/treatment dates:** PRIAS study participants: December 2006 and July 2008; ERSPC study participants: up to December 2006 **Study design:** NRCS **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** 12 months (AS), 18 months (RP and EBRT) **Source of funding:** Prostate Cancer Research Foundation (SWOP), Rotterdam **Systematic reviewer:** TEA	**Inclusion criteria:** AS: Gleason score of 6, PSA ≤ 10 ng/ml, PSA density < 0.2 ng/ml, clinical stage ≤ T2 and less than 3 positive biopsies; active treatment: Gleason score of > 6 **Exclusion criteria:** AS: N/R; active treatment: clinical stage ≥ T3 **Staging method:** N/R	**AS:** participants were followed according to a strict protocol and were advised to switch to radical treatment in case of risk reclassification during follow-up **EBRT:** radiation therapy (details were not reported) without neoadjuvant hormonal therapy **RP:** RP (details were not reported) without neoadjuvant hormonal therapy	**Functional outcomes:** sexual function **QoL:** physical function, mental function, depression, general anxiety

Patient characteristics	AS	EBRT	RP
Number of patients enrolled	129	70	67
Mean age (years)	64.9	68.1	62.1
Mean PSA level (ng/ml)	5.7	7.4	5.5
Clinical stage, *n* (%)			
T1	92 (71)	14 (20)	15 (22)
T2	37 (29)	56 (80)	52 (78)
Biopsy Gleason score, *n* (%)			
6	129 (100)	47 (67)	56 (84)
7	0 (0)	20 (29)	10 (15)
8	0 (0)	3 (4)	1 (1)
Comorbidities, *n* (%)			
None	43 (33)	26 (37)	40 (60)
≥ 1	86 (67)	44 (63)	27 (40)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Vasarainen 2012[199] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** Finland **Recruitment/treatment dates:** from December 2006 **Study design:** case series **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** 1 year **Source of funding:** Finnish Cancer Society and Ida Montini Foundation **Systematic reviewer:** TEA	**Inclusion criteria:** prostate adenocarcinoma, PSA ≤ 10 ng/ml, clinical stage ≤ T2, PSA density < 0.2 ng/ml, a maximum of two positive biopsies, Gleason score of ≤ 6, no contraindications to RP or radiation therapy **Exclusion criteria:** N/R **Staging method:** N/R	**AS:** PSA and DRE 3- and 6-monthly respectively for the first 2 years, after which they were done every 6 months and annually respectively. Biopsies were done 1, 4 and 7 years after diagnosis and annually if the PSA doubling time was 3–10 years. Deferred active treatment was offered when clinical stage was > 2, PSA doubling time < 3 years, cancer in more than two rebiopsies or Gleason score of > 6	**Functional outcomes:** erectile function, urinary function **QoL:** physical functioning, physical role, emotional role, vitality, mental health, social functioning, body pain, general health

Patient characteristics	AS
Number of patients enrolled	124
Number who returned baseline questionnaire	105
Age (years) (*n* = 75)	
Median (IQR)	64 (60–69)
PSA level (ng/ml) (*n* = 75)	
Median (range)	5.1 (2.0–10.0)
Clinical stage, *n*/*N* (%)	
T1	75/75 (100)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Ward 2012[202] **Language:** English **Publication type:** full-text paper **Number of study centres:** multicentre **Setting:** N/R **Country:** USA **Recruitment/treatment dates:** 1999–2007 **Study design:** case series **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** mean 21.1 (SD 19.7) months Follow-up 6, 12, 24 and 36 months **Source of funding:** the M.D. Anderson Cancer Center is supported by a Core grant. The COLD Registry is supported by an unrestricted educational grant from Healthtronics, Austin, TX **Systematic reviewer:** SJ	**Inclusion criteria:** people with localised prostate cancer (cT1–T2) receiving primary CRYO that was categorised as partial-gland ablation by the surgeon **Exclusion criteria:** patients who had received preoperative hormone therapy or TURP were excluded from analysis **Staging method:** N/R	**CRYO:** focal cryoablation (partial-gland ablation) technique used **Extent of ablation:** focal	**Efficacy:** biochemical disease-free status, positive biopsy on follow-up **Functional outcomes:** ED, urinary continence **Adverse events:** rectourethral fistula formation, acute urinary retention > 30 days

Patient characteristics	CRYO
Number of patients enrolled	1160
Age (years)	
Mean (SD)	67.8 (7.8)
PSA level, *n/N* (%)	
< 4 ng/ml	211/1149 (18)
4 < 10 ng/ml	782/1149 (68)
10 < 20 ng/ml	126/1149 (11)
20+ ng/ml	30/1149 (3)
Clinical stage, *n* (%)	
< T2b	1013 (87)
≥ T2c	147 (13)
Biopsy Gleason score, *n/N* (%)	
≤ 6	844/1148 (74)
7	240/1148 (21)
≥ 8	64/1148 (6)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Williams 2012[203] **Language:** English **Publication type:** full-text paper **Number of study centres:** multicentre (16) **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** 1 January 2001–31 December 2005 **Study design:** NRCS **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** no **Length of follow-up:** 2 years **Source of funding:** this work was supported by a Department of Defense Prostate Cancer Physician Training Award. This study used the linked SEER-Medicare database **Systematic reviewer:** SJ	**Inclusion criteria:** the study investigators identified 143,613 people aged ≥ 65 years who were diagnosed with prostate cancer. They restricted their analyses to people diagnosed with prostate cancer as their only cancer. Included patients were primary CRYO and primary BT from Medicare inpatient, outpatient and carrier component files **Exclusion criteria:** people undergoing combined therapies, e.g. BT with external beam radiation boost, were excluded. Furthermore, patients who underwent salvage CRYO were excluded. Additionally, people with clinical stage T4 disease, distant metastasis or insufficient 2-year follow-up, and people treated > 9 months after diagnosis, were excluded	**CRYO:** N/R **BT:** N/R	**Functional outcomes:** UI, ED **Complications:** cystitis, retention, urethral stricture, urethral fistula, proctitis/haemorrhage, rectal injury/ulcer

Patient characteristics	CRYO	BT
Number of patients enrolled	943	9985
Age, *n* (%)		
65–69 years	218 (23.1)	3233 (32.4)
70–74 years	336 (35.6)	3643 (36.5)
≥ 75 years	389 (41.3)	3109 (31.1)
PSA level, *n* (%)		
Elevated	641 (68)	7051 (70.6)
Normal	65 (6.9)	817 (8.2)
Unknown	237 (25.1)	2117 (21.2)
Clinical stage, *n* (%)		
T1	369 (39.1)	4956 (49.6)
T2	530 (56.2)	4811 (48.2)
T3/unknown	44 (4.7)	218 (2.2)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics			Intervention characteristics	Outcomes
	Patient characteristics	**CRYO**	**BT**		
	Comorbidity (Charlson score), *n* (%)				
	0	666 (70.6)	7534 (75.5)		
	1	201 (21.3)	1732 (17.4)		
	≥ 2	65 (6.9)	563 (5.6)		
	Unknown	11 (1.2)	156 (1.6)		
	Erectile dysfunction, *n* (%)				
	No	840 (89.1)	9018 (90.3)		
	Yes	103 (10.9)	967 (9.7)		
	Incontinence diagnosis				
	No	909 (96.4)	9772 (97.9)		
	Yes	34 (3.6)	213 (2.1)		
	Staging method: N/R				

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Wong 1997[204] **Language:** English **Publication type:** full-text paper **Number of study centres:** N/R **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** April 1993–September 1995 **Study design:** case series **Prospective/retrospective data collection:** N/R **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** 30 months (3, 6, 12, 24 and 30 months) **Source of funding:** N/R	**Inclusion criteria:** unclear **Exclusion criteria:** unclear 7/83 (8%) salvage patients were included in the baseline characteristics	**CRYO:** all procedures were performed with the AccuProbe System (Cryomedical Sciences, Inc., Rockville, MD). The Aloka 650 ultrasound scanner (Aloka, Walling Ford, CT), with a biplane probe (transaxial sector 5 MHz and linear 7.5 MHz), was used to guide the cryogenic probe placement and to monitor the freezing process for all patients. All procedures were performed by a two-physician team composed of a urologist and a radiologist experienced in ultrasound From April to May 1993, first 12 patients underwent prostate cryosurgery and interventional radiology and transurethral ultrasound guidance alone were used to monitor the freezing process	**Efficacy:** PSA, positive biopsy rate **Adverse events:** urethral sloughing, bladder neck contracture, incontinence

Patient characteristics	CRYO
Number of patients enrolled	83
Age (years)	
Mean (range)	69 (53–84)
PSA level (ng/ml)	
Mean/median (range)	
At diagnosis	11.2/7.5 (0.6–83.6)
At cryosurgery	6.9/4.5 (0.2–83.6)
Clinical stage, *n* (%)	
T2a	16 (19.4)
T2c	54 (65)
T3	13 (15.6)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics		Intervention characteristics	Outcomes
Systematic reviewer: SJ	**Patient characteristics**	**CRYO**	From June 1993 to September 1993, modified the original technique of Onik *et al.* by using thermocouples as part of the procedure on 29 patients. Initially, a thermocouple was placed in Denonvilliers' fascia as an extra safety device to prevent freezing the rectal wall, which would result in urethrorectal fistula. Later, started placing thermocouples in the region of the NVB Since October 1993, consistently placed five thermocouples in the following areas: (1) anterior portion at mid-gland, (2) apex, (3) Denonvilliers' fascia, (4) right NVB and (5) left NVB	
	Biopsy Gleason score, *n* (%)			
	2–4	21 (25.3)		
	5–7	55 (66.3)		
	8–10	7 (8.4)		
	Staging method: staged by TRUS-guided biopsies in which the sextant approach was used/DRE and bone scan			

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Wong 2009[205] **Language:** English **Publication type:** full-text paper **Number of study centres:** single **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** May 1993–July 2004 **Study design:** NRCS **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** median follow-up of 58 months **Source of funding:** N/R	**Inclusion criteria:** this study included 853 consecutive patients who were treated with radiotherapy for localised prostate cancer (T1c–T3N0M0 disease) between May 1993 and July 2004 at Mayo Clinic, Arizona **Exclusion criteria:** N/R	**BT:** transperineal BT was performed in 225 patients using I-125 or Pd-103 seeds. The prescribed minimal peripheral dose was 144 Gy for I-125 and 120 Gy for Pd-103 respectively. Short-term ADT (2–14 months) was used in 72 patients to downsize the prostate gland if the prostate gland size was significantly enlarged, or if there was significant pubic arch interference noted on pelvic CT scans **EBRT:** between 1993 and 2000, 270 patients were treated with EBRT using 3D-CRT. The techniques generally included a four-field box technique, delivering 45 Gy to the prostate and seminal vesicles, while the prostate was boosted to a median dose of 68.4 Gy (range 66–71 Gy). Treatment was administered in daily fractions of 1.8–2 Gy. Pelvic lymph nodes were not treated	**Efficacy:** bNED, overall survival, local control of disease, distant control of disease **Adverse events:** genitourinary, gastrointestinal

Patient characteristics	BT	EBRT
Number of patients enrolled	225	584
PSA level, *n* (%)		
≤ 10 ng/ml	193 (86)	430 (74)
10.1–20 ng/ml	28 (12)	106 (18)
≥ 20 ng/ml	4 (2)	48 (8)
Clinical stage, *n* (%)		
T1c	114 (51)	151 (26)
T2a	83 (37)	200 (34)
T2b	24 (11)	95 (16)
T2c	4 (2)	97 (17)
T3	0	41 (7)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics			Intervention characteristics	Outcomes
Systematic reviewer: SJ	**Patient characteristics**	**BT**	**EBRT**	From November of 2000, high-dose IMRT was used for the delivery of EBRT. Three hundred and fourteen patients were treated with IMRT and were included in this analysis. The treatment volume included the prostate and seminal vesicles, with a 6–10-mm margin. The median dose to the prostate gland was 75.6 Gy (range 75.6–77.4 Gy), whereas the seminal vesicles received 50.4 Gy. Daily transabdominal ultrasonography was performed to localise the prostate gland at the time of treatment Adjuvant ADT was administered to 161 patients (28%) who received 3D-CRT or IMRT	
	Biopsy Gleason score, *n* (%)				
	≤ 6	173 (77)	313 (54)		
	≥ 7	52 (23)	271 (46)		
	Staging method: DRE				

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Zelefsky 1999[206] **Language:** English **Publication type:** full-text paper **Number of study centres:** single **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** 1988–1995 **Study design:** NRCS **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** BT: median 24 (range 6–103) months [17 patients (12%) followed for ≥ 5 years]; EBRT: median 36 (range 12–109) months [25 patients (15%) followed for ≥ 5 years] **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** BT: PSA ≤ 10 ng/ml, Gleason score of < 7, clinical stage ≤ T2b; EBRT: ≤ stage T2b disease, pretreatment PSA ≤ 10.0 ng/ml, Gleason score of ≤ 6 **Exclusion criteria:** N/R **Staging method:** N/R	**Transperineal permanent implantation (BT):** I-125 at a prescribed minimum radiation dose of 140–160 Gy. Nine and 16 patients had prior TURP and NAAD respectively for a median duration of 2 months before transperineal implantation **3D-CRT (EBRT):** 64.8 Gy escalated to 70.2 Gy, 75.6 Gy and 81.0 Gy. Twenty-three and 21 patients had NAAD and prior TURP respectively. NAAD was used concurrently to reduce the volume of rectum or bladder exposed to the high doses of therapy and terminated when radiation was completed	**Efficacy:** PSA relapse, PSA relapse-free survival rates, median time to biochemical failure **Adverse events:** median time for development of impotence after treatment, 2-year likelihood of post-treatment ED, 5-year likelihood of post-treatment ED, acute genitourinary toxicity, late urinary symptoms, urethral stricture, late urinary toxicity, acute rectal toxicity, late rectal toxicity, rectal bleeding, late gastrointestinal toxicity

Patient characteristics	BT	EBRT
Number of patients enrolled	145	137
Median age (years)	64	68
Median PSA level (ng/ml)	6.1	6.6
Clinical stage, *n* (%)		
T1c	98 (68)	58 (42)
T2a	29 (20)	32 (23)
T2b	18 (12)	47 (34)

continued

TABLE 73 Characteristics of the included studies (primary review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Zelefsky 2010[207] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** 1993–2003 **Study design:** NRCS **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** yes **Length of follow-up:** median 77 months (range 1–11 years) overall; BT, 77 months; EBRT, 76 months **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** stage T1–2a, Gleason score of ≤ 6 and pretreatment serum PSA < 10 ng/ml **Exclusion criteria:** N/R **Staging method:** N/R	**BT:** I-125 to a prescribed dose of 144 Gy. 310/448 (69%) had short-course ADT to reduce prostate size **EBRT:** 1.8 Gy daily to a prescription dose of 81 Gy using IMRT. 192/281 (68%) had short-course ADT to reduce prostate size	**Efficacy:** PSA relapse-free survival **Functional outcomes:** sexual function **Adverse events:** rectal bleeding, urinary toxicity

Patient characteristics	BT	EBRT
Number of patients enrolled	448	281
Age, *n* (%)		
< 65 years	188 (42)	86 (31)
≥ 65 years	260 (58)	195 (69)
PSA level, *n* (%)		
< 4 ng/ml	93 (21)	43 (15)
≥ 4 ng/ml	355 (79)	238 (85)
Clinical stage, *n* (%)		
T1c	365 (82)	197 (70)
T2a	83 (19)	84 (30)

ABS, American Brachytherapy Society; ADT, androgen deprivation therapy; AP, anteroposterior; ART, adaptive radiotherapy; AST, androgen suppression therapy; AUA, American Urological Association; BMI, body mass index; bNED, biochemical no evidence of disease; BPH, benign prostatic hyperplasia; BT, brachytherapy; CaPSURE, Cancer of the Prostate Strategic Urologic Research Endeavor; COLD, Cryo On-Line Database; COPD, chronic obstructive pulmonary disease; CRYO, cryotherapy; CT, computerised tomography; CTV, clinical target volume; EB-IGRT, External Beam Image-Guided Radiation Therapy; EPIC, Expanded Prostate Cancer Index Composite; FACT-G, Functional Assessment of Cancer Therapy – General; FACT-P, Functional Assessment of Cancer Therapy – Prostate; HDR, high dose rate; HT, hormonal therapy; IQR, interquartile range; LDR, low dose rate; LRP, laparoscopic radical prostatectomy; LUTS, lower urinary tract symptoms; MHOS, Medicare Health Outcomes Survey; mp-MRI, multiparametric magnetic resonance imaging; N/A, not applicable; NAAD, neoadjuvant androgen deprivation; NADT, neoadjuvant androgen deprivation therapy; NCRI, National Cancer Research Institute; NIH, National Institutes of Health; N/R, not reported; NVB, neurovascular bundle; OCO, obstruction coefficient; ORP, open radical prostatectomy; PA, posteroanterior; PDE5-I, phosphodiesterase-5 inhibitor; PTV, planning target volume; QoL, quality of life; PRIAS, Prostate Cancer Research International Active Surveillance; RAP, robotic assistant laparoscopic; RPP, radical perineal prostatectomy; RRP, radical retropubic prostatectomy; RT, radiotherapy; SAQ, sexual adjustment questionnaire; SD, standard deviation; SEER, Surveillance, Epidemiology and End Results; SHIM, Sexual Health Inventory for Men; TG-143, American Association of Physicists in Medicine Task Group 43; TPM, template-guided prostate mapping; TURP, transurethral resection of the prostate; TVS, transperineal volume-adjusted saturation; uroflow-Qmax, maximum urinary flow rate; UTI, urinary tract infection; WW, watchful waiting; Y/N, yes/no.

TABLE 74 Characteristics of the included studies (salvage review)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Chin 2001[208] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** Canada **Recruitment/treatment dates:** December 1994–September 1999 **Study design:** case series **Prospective/retrospective data collection:** N/R **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** median 18.6 (range 3–54) months **Source of funding:** authors have financial interest and/or other relationship with AstraZeneca and EndoCare, Inc. **Systematic reviewer:** TEA	**Inclusion criteria:** patients with three consecutive rising PSA levels at least 2 years after radiotherapy, acceptable anaesthetic risks, negative CT and radionuclide bone scans **Exclusion criteria:** N/R	**Salvage CRYO:** all patients – except the first 11, who were treated with a Candela system (Candela, Inc., Boston, MA) – were treated with the Cryocare® system. A urethral warming device was used in all. Seventy-one (60%) patients had endocrine therapy which was immediately discontinued postoperatively	**Efficacy:** biochemical failure, PSA nadir, positive biopsy, reintervention rate **Functional outcomes:** incontinence **Adverse events:** bladder neck contracture, debris sloughing, outlet obstruction, rectourethral fistula, vesicourethral fistula beyond external sphincter

Patient characteristics	Salvage CRYO	
Number of patients enrolled	118	
Median age (years)	68	
	Before radiation	**Before cryoablation**
PSA level, *n* (%)		
< 5 ng/ml	0 (0)	60 (51)
5–10 ng/ml	55 (47)	40 (34)
> 10 ng/ml	63 (53)	18 (15)
Clinical stage, *n* (%)		
T1	13 (11)	0 (0)
T2	95 (81)	48 (41)
T3	10 (8)	66 (56)
T4	0 (0)	4 (3)
Biopsy Gleason score, *n*/*N* (%)		
2–4	13/118 (11)	2/115[a] (2)
5–7	88/118 (75)	65/115 (57)
8–10	17/118 (14)	48/115 (42)

a 115 patients had postradiation Gleason scores because three had negative postradiation biopsy.

Staging method: N/R

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Colombel 2006[120] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** France **Recruitment/treatment dates:** N/R **Study design:** case series **Prospective/retrospective data collection:** N/R **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** mean 15 months **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** low- or intermediate-risk prostate cancer at the time of diagnosis, local recurrence at biopsy, no distant metastasis **Exclusion criteria:** N/R **Staging method:** N/R	**Salvage HIFU:** performed using the Ablatherm® device with no nerve-sparing intent	**Efficacy:** negative biopsy rate, success rate **Functional outcomes:** incontinence **Adverse events:** rectourethral fistula, bladder neck stenosis

Patient characteristics	Salvage HIFU
Number of patients enrolled	71
Mean PSA level at recurrence (ng/ml)	7.73
Biopsy Gleason score at recurrence, *n* (%)	
< 8	37 (52)
Prostate size at recurrence (ml)	21

continued

TABLE 74 Characteristics of the included studies (salvage review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Darras 2006[209] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** Belgium **Recruitment/treatment dates:** 1989–2004 **Study design:** case series **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** mean 83 months; median 63 (range 27–151) months **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** evidence of recurrent prostate cancer demonstrated on biopsy and by increasing PSA levels, no evidence of systemic dissemination, life expectancy > 10 years **Exclusion criteria:** N/R	**Salvage RP:** standard retropubic procedure and a classical limited obturator fossa dissection	**Efficacy:** biochemical failure, biochemical disease-free survival, cancer-specific death, cancer-specific survival, overall survival **Functional outcomes:** continence, impotence **Adverse events:** anastomotic stricture, bladder neck contracture, intraoperative complications **Procedural outcomes:** procedure time

Patient characteristics	Salvage RP
Number of patients enrolled	11
Age (years)	
Mean (range)	60.5 (55–66)
PSA (ng/ml)	
Initial, mean (range)	8.3 (3.8–17.0)
Pre-salvage (at biochemical recurrence), mean (range)	5.2 (2.5–10.5)
Initial clinical stage, *n* (%)	
T1b	1 (9)
T1c	4 (36)
T2a	4 (36)
T3a	2 (18)
Initial biopsy Gleason score, *n* (%)	
≤ 6	6 (55)
7	5 (45)

Staging method: N/R

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Gheiler 1998[210] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** March 1992–February 1997 **Study design:** case series **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** all patients, mean 36.1 (range 2–65) months; RP, mean 36.29 (range 6–61) months; cystoprostatectomy, mean 34.51 (range 13–60) months **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** biopsy-proven recurrence of prostate adenocarcinoma > 12 months after radiotherapy associated with rising serum PSA level, no evidence of metastases at time of salvage surgery and a life expectancy of > 10 years **Exclusion criteria:** N/R	**Salvage RP:** thirty patients (75%) had salvage RRP and 10 (25%) had radical cystoprostatectomy. Four patients had androgenic therapy for < 3 months	**Efficacy:** disease-free survival, biochemical evidence of progression, death **Functional outcomes**: incontinence **Adverse events:** deep-vein thrombosis, vesicorectal fistula, ureteral fistula, epididymitis, prolonged postoperative ileus, intraoperative ureteral transection, prolonged urinary extravasation, bladder neck contracture, incisional hernia

Patient characteristics	Salvage RP	
Number of patients enrolled	40	
Age (years)		
Mean (range)	64.2 (45–76)	
	Pre-radiation	**Pre-operative**
Clinical stage, *n* (%)[a]		
T1b	5 (12.5)	0 (0)
T1c	2 (5)	5 (12.5)
T2a	6 (15)	7 (17.5)
T2b	8 (20)	13 (32.5)
T2c	8 (20)	8 (20)
T3a	5 (12.5)	3 (7.5)
T3b	2 (5)	2 (5)
T3c	4 (10)	2 (5)
Mean biopsy Gleason score (range)	7 (6–9)	7.5 (6–9)

a The proportion who were cT1/T2 was < 80%, but their outcome results were reported separately.

Staging method: physical examination, CT scan of the abdomen and pelvis, bone scan, pre-operative cystoscopy

continued

TABLE 74 Characteristics of the included studies (salvage review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Neerhut 1988[211] **Language:** English **Publication type:** full-text paper **Number of study centres:** 2 **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** 1984–7 **Study design:** case series **Prospective/retrospective data collection:** N/R **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** median 20 (range 3–39) months **Source of funding:** Ralph A Johnston Laboratory Fund and National Institutes of Health **Systematic reviewer:** TEA	**Inclusion criteria:** patients with biopsy-proved, clinically confined prostate tumour at least 12 months after definitive irradiation therapy, stage A2, B or small C at time of initial therapy, good overall health, life expectancy of 10 years or more and no recent or long-term hormonal therapy **Exclusion criteria:** presence of lymph node metastasis, radiation cystitis making patients unsuitable for RP **Staging method:** N/R	**Salvage RP:** non-nerve-sparing standard RP	**Adverse events:** rectal injury, rectovesical fistula, prolonged leakage of urine from the anastomosis, anastomotic stricture, uretero–vesical junction stricture, incontinence, anastomotic stone, ureteral transection, mild acute tubular necrosis, death **Procedural outcomes:** operating time, postoperative hospital stay

Patient characteristics	Salvage RP
Number of patients enrolled	16
Age (years)	
Mean (range)	66.6 (55–72)
Clinical stage, *n* (%)	
A2 (T1b)	3 (19)
B1 (T2a)	5 (31)
B2 (T2b)	7 (44)
C (T3a)	1 (6)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Robinson 2006[212] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** Canada **Recruitment/treatment dates:** November 1997–March 2002 **Study design:** case series **Prospective/retrospective data collection:** prospective	**Inclusion criteria:** histologically confirmed recurrence of prostate or seminal vesicle carcinoma, PSA ≤ 20 ng/ml, no evidence of metastases **Exclusion criteria:** N/R	**Salvage CRYO:** the cryosurgical technique of Onik *et al.*[216] was used. Twelve patients were placed on ADT including 10 on flutamide before surgery	**Efficacy:** PSA level, prostate cancer death, death from other causes, reintervention **QoL:** EORTC-QLQ-C30 physical function, role function, emotional function, cognitive function, social function, health function, fatigue, pain, nausea and vomiting, UCLA-PCI bowel function, sexual function, urinary function

Patient characteristics	Salvage CRYO	
Number of patients enrolled	46	
Age (years)		
Mean (range)	70 (57–79)	
	Pre-radiation	**Pre-cryosurgery**
PSA level, *n*/*N* (%)		
0–10 ng/ml	10/45 (22)	40/46 (87)
11–20 ng/ml	20/45 (44)	6/46 (13)
≥ 21 ng/ml	15/45 (33)	N/A

continued

TABLE 74 Characteristics of the included studies (salvage review) (*continued*)

Study details	Participant characteristics			Intervention characteristics	Outcomes
Patients recruited consecutively (Y/N): N/R **Length of follow-up:** 24 months **Source of funding:** the Alberta Cancer Board **Systematic reviewer:** TEA		Pre-radiation	Pre-cryosurgery		
	Pre-radiation clinical stage, *n*/*N* (%)				
	T1b	2/46 (4)			
	T1c	1/46 (2)			
	T2	4/46 (9)			
	T2a	12/46 (26)			
	T2b	11/46 (24)			
	T2c	12/46 (26)			
	T3a	3/46 (7)			
	T3b	1/46 (2)			
		Pre-radiation	Pre-cryosurgery		
	Biopsy Gleason score, *n*/*N* (%)				
	< 5	10/42 (24)	N/A		
	5–7	25/42 (60)	26/45 (58)		
	8–10	7/42 (17)	19/45 (42)		
	Staging method: N/R				

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Seabra 2009[213] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** Brazil **Recruitment/treatment dates:** January 2005–June 2007 **Study design:** case series **Prospective/retrospective data collection:** prospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** median 18 (range 1–36) months **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** proven recurrent, localised prostate cancer, no limits placed on PSA value **Exclusion criteria:** negative rebiopsy, locally advanced disease, metastatic disease	**Salvage RP:** N/R	**Efficacy:** PSA level **Functional outcomes:** incontinence, ED **Adverse events:** urinary flow, obstruction, rectovesical fistula **Procedural outcomes:** operating time

Patient characteristics	Salvage RP	
Number of patients enrolled	42	
Age (years)		
Mean (range)	61 (59–69)	
	Pre-radiation	**Pre-salvage RP**
PSA level (ng/ml)		
Mean (range)	9.2 (4.5–39.0)	5.7 (2.9–18.0)
Pre-radiation clinical stage, *n* (%)		
T1c	11 (27)	
T2a	11 (27)	
T2b	16 (37)	
T2c	4 (9)	
Pre-radiation biopsy Gleason score, *n* (%)		
5 (3 + 2)	17 (40)	
6 (3 + 3)	14 (33)	
7 (4 + 3)	8 (20)	
8 (4 + 4)	3 (7)	

Staging method: N/R

continued

TABLE 74 Characteristics of the included studies (salvage review) (*continued*)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: Tefilli 1998[214] **Language:** English **Publication type:** full-text paper **Number of study centres:** 2 **Setting:** hospital **Country:** USA **Recruitment/treatment dates:** December 1989–December 1995 **Study design:** case series **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** mean 37 months, median 36.1 months **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** histologically proven prostate cancer, isolated biochemical recurrence, no clinical evidence of metastases, patients were alive at time of study **Exclusion criteria:** N/R **Staging method:** N/R	**Salvage RP:** twenty-one (87.5%) and three (12.5%) patients had RP and radical cystoprostatectomy with urinary diversion respectively	**Efficacy:** biochemical disease recurrence **Functional outcomes:** urinary continence, sexual potency **QoL:** TOI-P, TOI-U

Patient characteristics	Salvage RP
Number of patients enrolled	24
Age (years)	66.2
Pre-salvage PSA level (ng/ml)	
Mean (range)	8.9 (1.2–18.41)
Pre-radiation clinical stage, *n* (%)	
T1c	5 (21)
T2a	4 (17)
T2b	6 (25)
T2c	9 (38)
Pre-salvage biopsy Gleason score	
Mean (range)	7.1 (5–8)

Study details	Participant characteristics	Intervention characteristics	Outcomes
Author, year: van der Poel 2008[215] **Language:** English **Publication type:** full-text paper **Number of study centres:** 1 **Setting:** hospital **Country:** the Netherlands **Recruitment/treatment dates:** N/R **Study design:** case series **Prospective/retrospective data collection:** retrospective **Patients recruited consecutively (Y/N):** N/R **Length of follow-up:** 10 years **Source of funding:** N/R **Systematic reviewer:** TEA	**Inclusion criteria:** primary clinically organ-confined disease (< cT3), biopsy-confirmed recurrence, life expectancy of 10 years or more **Exclusion criteria:** N/R	**Salvage RP:** non-nerve-sparing prostatectomy combined with node dissection when the risk of node metastases, estimated by Palin tables, was > 5%	**Efficacy:** PSA recurrence after salvage treatment, disease-specific survival, death from other causes **Functional outcomes:** ED, urinary continence **Adverse events:** urethral and bladder neck strictures, grade 3 and 4 rectal complaints

Patient characteristics	Salvage RP
Number of patients enrolled	32
Mean age at radiotherapy (years)	61.9
Mean age at salvage RP (years)	66.5
Mean PSA level (ng/ml)	
Before radiotherapy	9.8
Before salvage RP	4.9
Pre-radiation clinical stage, *n* (%)	
T1b	2 (6)
T1c	7 (22)
T2a	15 (47)
T2b	7 (22)
T2c	1 (3)
Pre-radiation biopsy Gleason score, *n* (%)	
4	3 (9)
5	6 (19)
6	7 (22)
7	10 (31)
8	6 (19)

Staging method: DRE and TRUS

ADT, androgen deprivation therapy; CRYO, cryotherapy; CT, computerised tomography; N/A, not applicable; N/R, not reported; RRP, radical retropubic prostatectomy; TOI-P, trial outcome index using prostate cancer subscale; TOI-U, trial outcome index using incontinence–urinary subscale; Y/N, yes/no.

Appendix 9 Detailed risk-of-bias and quality assessment

TABLE 75 Risk-of-bias assessment: RCTs and non-randomised comparative studies (primary review)

			Confounding					Blinding				
Study ID	Sequence generation	Allocation concealment	Efficacy	Erectile function	Urinary function	Bowel function	QoL	Efficacy	Erectile function	Urinary function	Bowel function	QoL
[a]Crook 2011[121]	?	?							?	?		?
[a]Donnelly 2010[125]	?	?						✓				
[a]Giberti 2009[49]	✓	?						✓	✓	✓	✓	✓
[a]Paulson 1982a[168]	?	?						✓				
Alemozaffar 2011[100]	✗	✗		✗					✗			
Arvold 2011[101]	✗	✗	✗					✓				
Barret 2013[103]	✗	✗	✓	?	✗			✓	?	?		
Beyer 2000[105]	✗	✗	✗					✓				
Boettcher 2012[108]	✗	✗			✗		?			✗		?
Borchers 2004[109]	✗	✗	✓	✓	✓	✓	✓	✓	✗	✗	✗	✗
Bradley 2004[110]	✗	✗		✗	✗	✗	✗		✗	✗	✗	✗
Buron 2007[113]	✗	✗		✗	✗	✗			✗	✗	✗	
Chen 2009[117]	✗	✗		✗	✗	✗			✗	✗	✗	
Coen 2012[119]	✗	✗	✓					✓				
Crook 2011[121]	✗	✗		✗	✓		✓		✗	✗		✗
D'Amico 1998[36]	✗	✗	✗					✓				
D'Amico 2003[123]	✗	✗	✗					✓				
Eade 2008[126]	✗	✗	✗	✗	✗	✗		✓	✓	✓	?	
Elliott 2007[128]	✗	✗										
Ferrer 2008[130]	✗	✗	?	✓	✓	✓	✗		✗	✗	✗	✗
Frank 2007[131]	✗	✗	?	?	?	?	?		✗	✗	✗	✗
Goldner 2012a[135]	✗	✗	✓					✓				
Goldner 2012b[136]	✗	✗	✗					✓				
Kibel 2012[144]	✗	✗	✓					✓				
Kirschner-Hermans 2008[145]	✗	✗			✗		✓			✗		✗
Kobuke 2009[149]	✗	✗	✗	✗	✓	✗	✓	✓	✗	✗	✗	✗
Kupelian 2004[151]	✗	✗	✗					✓				
Lee 2001[153]	✗	✗			✓		✓			✗		✗
Litwin 2004[156]	✗	✗				✓	?				✗	
Malcolm 2010[160]	✗	✗		✗	✗	✗	✗		✗	✗	✗	✗
Mohamed 2012[163]	✗	✗		✗	✗				✗	✗		
Pe 2009[170]	✗	✗	✗					✓				
Pickles 2010[171]	✗	✗	✗					✓				
Pinkawa 2009[172]	✗	✗		✓	✓	✗	✓		✗	✗	✗	✗
Reeve 2012[176]	✗	✗			✓		?			✗		✗

Incomplete outcome data					Free of selective reporting					
Efficacy	Erectile function	Urinary function	Bowel function	QoL	Efficacy	Erectile function	Urinary function	Bowel function	QoL	Other bias
	✗	✗		✗		✗	✗		✗	✗
✓					✓					?
?	?	?	?	?	?	?	?	?	?	?
✗					?					✗
	✓					?				?
?					?					?
?	?	?			✗	✗	✗			✗
✗					✗					?
		✓		✓			✗		✗	?
✓	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗
	✓	✓	✓	✓		?	?	?	?	?
	?	?	?			?	?	?		?
	✓	✓	✓			?	?	?		?
✓					✓					?
	?	?		?		?	?		?	✗
✓					?					?
✗					?					?
✓	✓	✓	✓		?	?	?	?		?
										✓
	✓	✓	✓	✓		✓	✓	✓	✓	?
	✓	✓	✓	✓		✗	✗	✗	✗	?
?					?					?
?					?					?
✓					✓					✗
		?		✗			?		?	?
?	?	?	?	?	?	?	?	?	?	✗
?					?					✗
		✓		✓			✓		✓	?
			✗					✗		✓
	✗	✗	✗	✗		✓	✓	✓	✓	✓
	✓	✓				✓	✓			✗
?					?					?
✓					?					?
	✗	✗	✗	✗		?	?	?	?	?
		✗		✗			✓	✓	✗	?

continued

TABLE 75 Risk-of-bias assessment: RCTs and non-randomised comparative studies (primary review) (*continued*)

			Confounding					Blinding				
Study ID	Sequence generation	Allocation concealment	Efficacy	Erectile function	Urinary function	Bowel function	QoL	Efficacy	Erectile function	Urinary function	Bowel function	QoL
Shah 2012[182]	✗	✗	?		?	?		✓		?	?	
Smith 2009[184]	✗	✗	✓	✓	✓	✓	✓	✓	✗	✗	✗	✗
Talcott 2003[186]	✗	✗		✓	✓	✓			✗	✗	✗	
Tsui 2005[189]	✗	✗	✗	✓	✗	✓		✓	✗	✗	✗	
van den Bergh 2012[198]	✗	✗		✗			✗		✗			
Williams 2012[203]	✗	✗		✓	✓	?			?	?	?	
Wong 2009[205]	✗	✗	✓					✓				
Zelefsky 1999[206]	✗	✗	✓	✗	✓	✓		✓	✗	✓	✓	
Zelefsky 2011[207]	✗	✗	✗	✗				✓	✗			

QoL, quality of life.
a Randomised controlled studies.

Incomplete outcome data					Free of selective reporting					
Efficacy	Erectile function	Urinary function	Bowel function	QoL	Efficacy	Erectile function	Urinary function	Bowel function	QoL	Other bias
✓		✓	✓		✓		✓			?
✓	✓	✓	✓	✓	?	?	?	?	?	?
	✓	✓	✓			✓	✓	✓		✗
?	?	?	?		?	?	?	?		?
	✗					?				?
	✓	✓	?			✓	✓	?		✓
?					✓					?
?	?	?	?		?	?	?	?		?
?	?				?	?				?

TABLE 76 Quality assessment: case series (primary review)

Study ID	Spectrum representative	Description of eligibility criteria	Similarity in disease severity	Consecutive patient selection	Prospective data collection	Clear definition of intervention
Ahmed 2011[98]	✓	✓	✓	?	✓	✓
Ahmed 2012[99]	✓	✓	✓	?	✓	✓
Bahn 2002[102]	✓	✓	✓	✓	✗	✓
Bellardita 2013[104]	✓	✓	✓	?	?	✓
Blana 2009[106]	✓	✓	✓	✓	✗	✗
Blana 2012[107]	✓	✓	✓	✓	✗	✗
Bul 2013[111]	✓	✓	✓	?	✓	✓
Caso 2012[114]	✓	?	✓	✓	✓	✓
Chaussy 2003[116]	✓	✓	✓	?	?	✓
Colombel 2006[120]	✓	✗	?	?	?	✗
Cytron 2003[122]	✓	?	✓	✓	?	✓
Donnelly 2002[124]	✓	✓	✗	✓	✓	✓
El Fegoun 2011[127]	✓	✓	✓	?	✗	✓
Ellis 2007[129]	✓	✓	✓	✓	?	✓
Ganzer 2008[132]	✓	✓	✓	?	?	✓
Ganzer 2011[133]	✓	✓	✓	✓	✗	✓
Godtman 2013[134]	✓	?	?	?	✓	?
Hale 2013[138]	✓	✓	✓	?	?	✓
Han 2003[139]	✓	?	✓	?	✓	✓
Hardie 2005[140]	✓	✓	✓	?	✓	✓
Hilton 2012[141]	✓	✓	✓	?	✓	✓
Hubosky 2007[52]	✓	✓	✓	✓	✓	✓
Illing 2006[142]	✓	✓	✓	?	?	✓
Inoue 2011[143]	✓	✓	✓	✓	✓	✓
Klotz 2010[146]	✓	✓	✓	?	✓	✓
Koch 2007[150]	✓	✓	?	?	✓	✓
Lian 2011[154]	✓	✓	✓	✓	✗	✓
Lidner 2009[155]	✓	✓	✓	?	✓	✓
Mack 1997[158]	✓	✗	✓	?	?	✓
Maestroni 2008[159]	✓	✗	✗	?	?	✓
Mearini 2009[161]	✓	✓	✗	✓	✓	✓
Misrai 2008[162]	✓	✓	✗	?	✗	✓
Onik 2008[166]	✓	?	✓	?	?	✓

Procedure carried out by experienced doctor	Adequate and appropriate facilities	Important outcomes considered	Objective (valid and reliable) outcome measures	Adequate follow-up period	Information on dropouts	Dropouts similar to completers	Pre-operative identification of prognostic factors
?	?	✓	✓	✓	✓	✓	✓
?	?	✓	✓	✓	✓	?	✓
?	?	✓	✓	✓	✗	✗	✓
?	?	✓	✓	✗	✓	?	✓
?	?	✓	✓	✓	✗	✗	✓
?	?	✓	✓	✓	✗	✗	✓
?	?	✓	✓	✓	✓	?	✓
?	?	✓	✓	✓	?	?	✓
?	?	✓	✓	✓	✗	?	?
?	?	✓	✓	✓	✗	✗	?
?	?	✓	✓	✓	?	✗	✓
?	?	✓	✓	✓	✓	✓	✓
?	?	✓	✓	✓	✗	✗	✓
?	?	✓	✓	✓	✗	✓	✓
?	?	✓	✓	✓	✓	?	✓
?	?	✓	✓	✓	✗	✗	✓
?	?	✓	✓	✓	✓	?	✓
?	?	✓	✓	✓	✓	?	✓
?	?	✓	?	✓	?	?	✓
?	?	✓	✓	✓	✓	✓	✓
?	?	✓	✓	✓	✓	✓	✓
?	?	✓	✓	✓	✓	✓	✓
?	?	✓	✓	✗	✓	✓	✓
?	?	✓	✓	✓	✗	✗	✓
?	?	✓	✓	✓	?	?	✓
?	?	✓	✓	✗	✓	✓	?
?	?	✓	✓	✗	✗	?	✓
?	?	✓	✓	✗	✓	✓	✓
?	?	✓	✓	✓	✓	?	✓
?	?	✓	✓	✓	✗	✗	✓
?	?	✓	✓	✓	✗	✗	✓
?	?	✓	✓	✓	✗	✗	✓
?	?	✓	✓	✓	✗	?	✓

continued

TABLE 76 Quality assessment: case series (primary review) (*continued*)

Study ID	Spectrum representative	Description of eligibility criteria	Similarity in disease severity	Consecutive patient selection	Prospective data collection	Clear definition of intervention
Pinthus 2012[173]	✓	✓	✗	✓	✗	✓
Poissonnier 2007[174]	✓	✓	✓	✓	✓	✓
Selvadurai 2013[181]	✓	✓	✓	?	✓	✓
Sumitomo 2010[185]	✓	✓	✓	?	✗	✓
Tosoian 2011[187]	✓	✓	✓	?	✓	✓
Truesdale 2010[188]	✓	✓	✓	✗	✗	✓
Uchida 2005[191]	✓	✓	?	✓	✓	✓
Uchida 2009[195]	✓	✓	✓	✓	?	✓
Vasarainen 2012[199]	✓	✓	✓	?	✓	✓
Ward 2012[202]	✓	✓	✓	✗	✓	?
Wong 1997[204]	✓	?	✓	?	?	✓

TABLE 77 Quality assessment: case series (salvage review)

Study ID	Spectrum representative	Description of eligibility criteria	Similarity in disease severity	Consecutive patient selection	Prospective data collection	Clear definition of intervention
Chin 2001[208]	✓	✓	?	?	?	✓
Colombel 2006[120]	✓	✓	?	?	?	✓
Darras 2006[209]	✓	✓	?	?	?	✓
Gheiler 1998[210]	✓	✓	?	?	✗	✓
Neerhut 1988[211]	✓	✓	?	?	?	✓
Robinson 2006[212]	?	✓	?	?	✓	✓
Seabra 2009[213]	✓	✓	?	?	✓	✗
Tefilli 1998[214]	✓	✓	✗	?	✗	✗
van der Poel 2008[215]	?	✓	?	?	?	✓

Procedure carried out by experienced doctor	Adequate and appropriate facilities	Important outcomes considered	Objective (valid and reliable) outcome measures	Adequate follow-up period	Information on dropouts	Dropouts similar to completers	Pre-operative identification of prognostic factors
?	?	✓	✓	✓	✓	?	✓
?	?	✓	✓	✓	✗	✗	✓
?	?	✓	✓	✓	✓	✓	✓
?	?	✓	✓	✓	✓	?	✓
?	?	✓	✓	✓	✓	✗	✓
?	?	✓	✓	✓	✗	✗	✓
?	?	✓	✓	✓	✓	✓	✓
?	?	✓	✓	✓	?	?	✓
?	?	✓	✓	✓	✓	✗	✓
?	?	✓	✓	✓	✗	✗	✓
?	?	✓	?	✓	?	?	✓

Procedure carried out by experienced doctor	Adequate and appropriate facilities	Important outcomes considered	Objective (valid and reliable) outcome measures	Adequate follow-up period	Information on dropouts	Dropouts similar to completers	Pre-operative identification of prognostic factors
?	?	✓	✓	✓	✗	?	✓
?	?	✓	✓	✓	✗	?	✓
?	?	✓	?	✓	✗	?	✓
?	?	✓	?	✓	✓	✗	✓
?	?	✓	?	✓	✗	?	✓
?	?	✓	✓	✓	✓	?	✓
?	?	✓	?	✓	✗	?	✓
?	?	✓	?	✓	✓	✓	✓
?	?	✓	?	✓	✗	?	✓

Appendix 10 Data tables of the primary review

TABLE 78 Cancer-related efficacy outcomes

			BT			CRYO		
Study ID	Timeline	Outcome	*N*	*n*	%	*N*	*n*	%
Prostate cancer specific mortality (PCSM)								
Klotz 2010[146] (Klotz 2005,[148] Klotz 2012,[147] Loblaw 2010[157])	2 years	PCSM						
Bul 2013,[111] van den Bergh 2010[197]	2.8 years	PCSM						
Tosoian 2011[187]	Median 2.7 years	PCSM						
Hardie 2005[140]	Median 3.5 years (42 months)	PCSM						
D'Amico 2003[123]	Median 3.9 years (BT) and 4.2 years (RP)	PCSM	196	0	0			
Misrai 2008[162]	Mean 3.9 (range 1–6.8) years	PCSM						
Arvold 2011[101]	Median 3.6 (range 1.8–5.9) years	PCSM	5902	29	0.57			
Klotz 2010[146] (Klotz 2005,[148] Klotz 2012,[147] Loblaw 2010[157])	4 years	PCSM						
Pinthus 2012[173]	4 years	PCSM						
Selvadurai 2013[181]	4 years	PCSM						
Donnelly 2010,[125] Robinson 2009[179]	5 years	PCSM				117	5	4.3
Pickles 2010[171]	67–68 months	PCSM	139	1	0.72			
Kibel 2012[144]	Median 5.6 years (IQR 43–96 months)	PCSM	1680	12	0.7			
Klotz 2010[146] (Klotz 2005,[148] Klotz 2012,[147] Loblaw 2010[157])	6 years	PCSM						
Inoue 2011[143]	7 years	PCSM						
Selvadurai 2013[181]	8 years	PCSM						
Uchida 2009[195]	Median 8 years	PCSM						
Kibel 2012[144]	10 years	PCSM (unadjusted)	1680		2.4 (95% CI 0.6 to 4.2)			
Kibel 2012[144]	10 years	PCSM (adjusted)	1680		2.3 (95% CI 2 to 2.6)			

HIFU			AS			EBRT			RP		
N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
			450	0	0						
			2494	0	0						
			769	0	0						
			80	0	0						
									322	0	0
119	0	0									
									2937	15	0.51
			450	1	0.22						
402	0	0									
			471	1	0.21						
						114	5	4.4			
						139	1	0.72			
						2264	94	4.2	6485	76	1.2
			450	3	0.67						
137	0	0									
			471	2	0.42						
517	0	0									
						2264		6.1 (95% CI 4.7 to 7.5)	6485		2.2 (95% CI 1.6 to 2.8)
						2264		2.9 (95% CI 2.6 to 3.3)	6485		1.8 (95% CI 1.6 to 2.1)

continued

TABLE 78 Cancer-related efficacy outcomes (*continued*)

Study ID	Timeline	Outcome	BT			CRYO		
			N	*n*	%	*N*	*n*	%
Klotz 2010[146] (Klotz 2005,[148] Klotz 2012,[147] Loblaw 2010[157])	10 years	PCSM						
Godtman 2013[134]	12.7 years	PCSM						
Mack 1997[158]	3–16 years	PCSM				66	18	27
Overall survival (OS)								
Lian 2011[154]	Postoperative	OS				102	102	100
Barret 2013[103]	Median 9 (IQR 6–15) months	OS	12	12	100	50	50	100
Bul 2013,[111] van den Bergh 2010[197]	Median 1.2 (IQR 1.0–1.6) years	OS						
Bul 2013,[111] van den Bergh 2010[197]	2 years	OS[a]						
Klotz 2010[146] (Klotz 2005,[148] Klotz 2012,[147] Loblaw 2010[157])	2 years	OS[a]						
Selvadurai 2013[181]	2 years	OS[a]						
Tosoian 2011[187]	2.7 years	OS						
Hardie 2005[140]	3.5 years	OS						
Misrai 2008[162]	Mean 3.9 (range 1–6.8) years	OS						
Bul 2013,[111] van den Bergh 2010[197]	4 years	OS[a]						
Klotz 2010[146] (Klotz 2005,[148] Klotz 2012,[147] Loblaw 2010[157])	4 years	OS[a]						
Pinthus 2012[173]	4 years	OS						
Donnelly 2002[124]	5 years	OS				73	68	93.2
Donnelly 2010,[125] Robinson 2009[179]	5 years	OS				117	108	92.3
Selvadurai 2013[181]	5 years	OS[a]						
Shah 2012,[182] Vicini 2011[201]	5 years	OS:[a] African American	36		97			
Shah 2012,[182] Vicini 2011[201]	5 years	OS:[a] white	504		92.8			

HIFU			AS			EBRT			RP		
N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
			450	5	1.1						
			439	1	0.2						
21	21	100									
			2494	2476	99.3						
			2494		97.1						
			450		86.4						
			471		99 (95% CI 98 to 100)						
			769	755	98.2						
			80	75	94						
119	118	99.1									
			2494		86.5						
			450		92.7						
402	401	99.7									
						114	103	90.4			
			471		96 (95% CI 95 to 98)						
						12		86.3			
						469		83.3			

continued

TABLE 78 Cancer-related efficacy outcomes (*continued*)

Study ID	Timeline	Outcome	BT			CRYO		
			N	*n*	%	*N*	*n*	%
Klotz 2010[146] (Klotz 2005,[148] Klotz 2012,[147] Loblaw 2010[157])	6 years	OS[a]						
Selvadurai 2013[181]	6 years	OS						
Inoue 2011[143]	7 years	OS						
Coen 2012[119]	8 years	OS	141		96			
Klotz 2010[146] (Klotz 2005,[148] Klotz 2012,[147] Loblaw 2010[157])	8 years	OS[a]						
Godtman 2013[134]	10 years	OS[a]						
Kibel 2012[144]	10 years	OS[a] (unadjusted)	1680		59.8 (95% CI 52.2 to 66.5)			
Kibel 2012[144]	10 years	OS[a] (adjusted)	1680		81.7 (95% CI 78.7 to 84.4)			
Kibel 2012[144]	10 years	OS	1680	1481	88.1			
Klotz 2010[146] (Klotz 2005,[148] Klotz 2012,[147] Loblaw 2010[157])	10 years	OS[a]						
El Fegoun 2011[127]	Median 10.6 (range 7.5–11.1) years	OS						
Klotz 2010[146] (Klotz 2005,[148] Klotz 2012,[147] Loblaw 2010[157])	12 years	OS[a]						
Mack 1997[158]	3–16 years	OS				66	38	57.6
Biochemical failure/recurrence or clinical failure								
Lian 2011[154]	3 months	Biochemical failure (PSA $\geq$ 0.5 ng/ml)				102	8	7.8
Coen 2012[119]	1 year	Biochemical failure[a] (Phoenix definition)	141		0.7			
Donnelly 2010,[125] Robinson 2009[179]	1 year	Cumulative incidence of failure[a] (updated Trifecta definition with biochemical failure defined as PSA nadir + 2 ng/ml)				117		3.4

HIFU			AS			EBRT			RP		
N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
			450		84.3						
			471	444	94.3						
137	132	96.4									
						141		93			
			450		77.2						
			439		81.1						
						2264		63.2 (95% CI 60 to 66.1)	6485		87 (95% CI 85.5 to 88.3)
						2264		82.6 (95% CI 79.8 to 85)	6485		88.9 (95% CI 87.5 to 90.1)
						2264	1674	73.9	6485	6018	92.8
			450		68 (95% CI 62 to 74)						
12	10	83									
			450		55.8						
						141		1.4			
						114		1.7			

continued

TABLE 78 Cancer-related efficacy outcomes (*continued*)

			BT			CRYO		
Study ID	Timeline	Outcome	*N*	*n*	%	*N*	*n*	%
Donnelly 2010,[125] Robinson 2009[179]	1 year	Cumulative incidence of failure[a] (original Trifecta definition with failure defined as radiological evidence of disease or biochemical failure 2 PSA rises and final PSA value > 1 ng/ml or initiation of secondary treatment)				117		7
Kobuke 2009[149]	1 year	Biochemical recurrence (PSA > 0.2 ng/ml)	36	0	0			
Maestroni 2008[159]	1 year	Treatment failure (ASTRO criterion: PSA rise in 3 consecutive samples)						
Pinthus 2012[173]	1 year	Biochemical failure (Stuttgart definition: nadir + 1.2 ng/ml 'at call')						
Pinthus 2012[173]	1 year	Biochemical failure (Horwitz definition: 2 consecutive increases of at least 0.5 ng/ml, backdated)						
Polascik 2007,[175] Caso 2012,[114] Caso 2012[115]	Median 1.5 years (range 3 months–3.5 years)	PSA failure (PSA ≥ 0.5 ng/ml)				50	5	10
Coen 2012[119]	2 years	Biochemical failure[a] (Phoenix definition)	141		2.04			
Donnelly 2010,[125] Robinson 2009[179]	2 years	Cumulative incidence of failure[a] (updated Trifecta definition with failure defined as biochemical failure: PSA nadir + 2 ng/ml)				117		12.1
Donnelly 2010,[125] Robinson 2009[179]	2 years	Cumulative incidence of failure[a] (original Trifecta definition with failure defined as radiological evidence of disease or biochemical failure 2 PSA rises and final PSA value > 1 ng/ml or initiation of secondary treatment)				117		18.8

HIFU			AS			EBRT			RP		
N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
						114		1			
									37	3	8.1
25	4	16									
402	33	8.2									
402	89	22.1									
						141		2.2			
						114		8.9			
						114		12.5			

continued

TABLE 78 Cancer-related efficacy outcomes (*continued*)

			BT			CRYO		
Study ID	Timeline	Outcome	*N*	*n*	%	*N*	*n*	%
Pinthus 2012[173]	2 years	Biochemical failure (Stuttgart definition: nadir + 1.2 ng/ml 'at call')						
Pinthus 2012[173]	2 years	Biochemical failure (Horwitz definition: 2 consecutive increases of at least 0.5 ng/ml, backdated)						
Truesdale 2010,[188] Lambert 2007[152]	Median 2 (range 0–7.25) years	Biochemical failure (Phoenix criterion: PSA nadir + 2 ng/ml)				77	21	27.3
Zelefsky 1999[206]	Median 1.7 years (BT) and 2.1 years (EBRT)	PSA relapse (3 successive PSA elevations from the post-treatment nadir)	145	12	8			
Hale 2013[138]	2.5 years	Biochemical failure (PSA nadir + 0.5 ng/ml)				26	3	12
Coen 2012[119]	3 years	Biochemical failure[a] (Phoenix definition)	141		2.1			
Donnelly 2010,[125] Robinson 2009[179]	3 years	Cumulative incidence of failure[a] (Trifecta with biochemical failure defined as PSA nadir + 2 ng/ml)				117		17.1
Donnelly 2010,[125] Robinson 2009[179]	3 years	Cumulative incidence of failure[a] [Trifecta with failure defined as radiological evidence of disease or biochemical failure and final PSA values (2 PSA rises and final PSA value > 1 ng/ml), or initiation of secondary treatment]				117		23.9
Smith 2009[184]	3 years	Disease recurrence or spread	58	0	0			
Misrai 2008[162]	Mean 3.9 (range 1–6.8) years	Biochemical recurrence (ASTRO definition: nadir + 2 ng/ml)						
Pinthus 2012[173]	4 years	Biochemical failure (Stuttgart definition: nadir + 1.2 ng/ml 'at call')						
Pinthus 2012[173]	4 years	Biochemical failure (Horwitz definition: 2 consecutive increases of at least 0.5 ng/ml, backdated)						

HIFU			AS			EBRT			RP		
N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
402	67	16.7									
402	99	24.6									
						137	11	8			
						141		2.8			
						114		13.2			
						114		23.7			
						123	2	2	981	64	7
119	53	44.5									
402	81	20.1									
402	99	24.6									

continued

TABLE 78 Cancer-related efficacy outcomes (*continued*)

Study ID	Timeline	Outcome	BT			CRYO		
			N	*n*	%	*N*	*n*	%
Blana 2009[106]	Median 4.7 years	Clinical failure (positive prostate biopsy, initiation of secondary prostate cancer therapy, radiographic evidence of prostate cancer metastases or prostate cancer-related death)						
Burdick 2009,[112] Ciezki 2004,[118] Vassil 2010,[200] Kibel 2012,[144] Nepple 2013[165]	Median 4.5 (range 2–10.25) years	Biochemical failure (RP: PSA > 0.3 ng/ml on one reading; BT and EBRT: PSA level > 2 ng/ml)	127	14	11			
Coen 2012[119]	5 years	Biochemical failure[a] (Phoenix definition)	141		6.4			
Donnelly 2010,[125] Robinson 2009[179]	5 years	Cumulative incidence of failure[a] (Trifecta with biochemical failure defined as PSA nadir + 2 ng/ml)				117		23.9
Giberti 2009[49]	5 years	Biochemical failure (RP: 2 consecutive PSA increases ≥ 0.2 ng/ml; BT: PSA nadir + ≥ 2 ng/ml, independent of the serum concentration of nadir)	85	7	8.3			
Goldner 2012a[135]	5 years	Biochemical evidence of disease rate (Phoenix definition: absolute nadir + 2 ng/ml rise or in case of the start of hormonal therapy, owing to rising PSA): low risk	667	30	4			
Paulson 1982[168]	5 years	Treatment failure (positive acid phosphatase elevation)						
Inoue 2011[143]	7 years	PSA failure (Phoenix criterion, PSA nadir + > 2 ng/ml)						
El Fegoun 2011[127]	Median 10.6 (range 7.5–11.1) years	Treatment failure (positive biopsy irrespective of side and/or need for salvage therapy for a positive biopsy or when PSA increased above pretreatment levels)						

HIFU			AS			EBRT			RP		
N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
285	71	25									
						268	50	19	310	98	32
						141		5.7			
						114		23.7			
									89	8	9
						252	31	12.3			
						41	3	7.3	56	2	3.6
137	11	8									
12	5	41.7									

continued

TABLE 78 Cancer-related efficacy outcomes (*continued*)

Study ID	Timeline	Outcome	BT			CRYO		
			N	*n*	%	*N*	*n*	%
Biochemical disease-free survival								
Eade 2008[126]	6 months	Freedom from biochemical failure[a] (failure defined as PSA nadir + 2 ng/ml)	158		100			
Giberti 2009[49]	6 months	Biochemical disease-free survival rate[a]	100		99.5			
Saliken 1999,[180] Donnelly 2002,[124] Robinson 1999,[177] Robinson 2002[178]	6 months	PSA control (undetectable PSA < 0.3 ng/ml)				71	53	75
Ward 2012[202]	6 months	Biochemical disease-free survival[a] (ASTRO definition)				1160		84.2
Cytron 2003[122]	9 months	PSA nadir ≤ 0.5 ng/ml				22	16	72.7
Cytron 2003[122]	9 months	PSA nadir ≤ 1 ng/ml				22	17	77.3
Mearini 2009[161]	10 months	Biochemical disease-free survival[a] (Phoenix criterion: post-treatment PSA nadir + 2 ng/ml)						
Wong 2009[205]	10 months	Biochemical no evidence of disease[a] (PSA < 2 ng/ml above the nadir with no backdating): IMRT	225		100			
Blana 2012[107]	1 year	Biochemical disease-free survival rate[a] (Phoenix definition)						
Cytron 2003[122]	1 year	PSA nadir ≤ 0.5 ng/ml				14	9	64.3
D'Amico 2003[123]	1 year	PSA failure-free survival[a] (BT: 3 consecutive increments; RP: > 0.2 ng/ml post operation)	196		100			
Eade 2008[126]	1 year	Freedom from biochemical failure[a] (failure defined as PSA nadir + 2 ng/ml)	158		100			
Ellis 2007[129]	Median 12 (range 3–36) months	Biochemical disease-free survival[a] (ASTRO criteria)				51	41	80.4
Ganzer 2011[133]	1 year	Biochemical disease-free survival[a] (Phoenix definition)						
Giberti 2009[49]	1 year	Biochemical disease-free survival rate[a]	100		95.9			

HIFU			AS			EBRT			RP		
N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
						216		100			
									100		100
160		84.4									
						314		98.5			
356		97.4									
									322		97.1
						216		100			
804		96.5									
									100		98.2

continued

TABLE 78 Cancer-related efficacy outcomes (*continued*)

			BT			CRYO		
Study ID	Timeline	Outcome	*N*	*n*	%	*N*	*n*	%
Goldner 2012a[135]	1 year	Actuarial biochemical no evidence of disease rate[a] (Phoenix definition: absolute nadir + 2 ng/ml rise or in case of the start of hormonal therapy, due to rising PSA): EBRT 70 Gy, low risk	667		98.9			
Goldner 2012a[135]	1 year	Actuarial biochemical no evidence of disease rate[a] (Phoenix definition: absolute nadir + 2 ng/ml rise or in case of the start of hormonal therapy, due to rising PSA): EBRT 74 Gy, low risk						
Goldner 2012b[136]	1 year	Actuarial biochemical no evidence of disease rate[a] (Phoenix definition: absolute nadir + 2 ng/ml rise or in case of the start of hormonal therapy, due to rising PSA): intermediate risk	601		98.1			
Han 2003[139]	1 year	PSA control (PSA < 0.4 ng/ml)				89	66	74
Hubosky 2007[52]	1 year	Cumulative biochemical disease-free survival[a] (ASTRO definition)				81		94
Kupelian 2004[151]	1 year	Biochemical relapse-free survival[a] [ASTRO definition: 3 consecutive rising PSA levels after a nadir (EBRT, BT); 2 consecutive detectable PSA levels (> 0.2 ng/ml) (RP)]: EBRT < 72 Gy	950		99			
Pe 2009[170]	1 year	Biochemical failure-free rate[a] (PSA failure defined by Phoenix criterion: PSA nadir + ≥ 2 ng/ml)	171		100			
Pickles 2010[171]	1 year	Biochemical non-evidence of disease[a]	139		100			
Saliken 1999,[180] Donnelly 2002[124]	1 year	PSA control (undetectable PSA < 0.3 ng/ml)				64	43	67

HIFU			AS			EBRT			RP		
N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
						82		100			
						170		99.4			
						289		97.5			
						484		94	1034		92
						189		100			
						139		98.5			

continued

TABLE 78 Cancer-related efficacy outcomes (*continued*)

Study ID	Timeline	Outcome	BT			CRYO		
			N	*n*	%	*N*	*n*	%
Sumitomo 2010[185]	1 year	Disease-free survival rate[a] (Phoenix definition: PSA nadir + 2 ng/ml)						
Sumitomo 2010[185]	1 year	Disease-free survival rate[a] (Phoenix definition: PSA nadir + 2 ng/ml) HIFU + TURP						
Uchida 2005[191]	1 year	Biochemical disease-free survival[a] (ASTRO criterion)						
Vassil 2010,[200] Burdick 2009,[112] Ciezki 2004,[118] Kibel 2012,[144] Nepple 2013[165]	1 year	Biochemical recurrence-free survival[a] [failure defined as nadir + 2 ng/ml (BT and RT); PSA ≥ 0.4 ng/ml (RP)]: Laparoscopic RP	256		100			
Vassil 2010,[200] Burdick 2009,[112] Ciezki 2004,[118] Kibel 2012,[144] Nepple 2013[165]	1 year	Biochemical recurrence-free survival[a] [failure defined as nadir + 2 ng/ml (BT and RT); PSA ≥ 0.4 ng/ml (RP)]: Retropubic RP						
Ward 2012[202]	1 year	Biochemical disease-free survival[a] (ASTRO definition)				1160		80.7
Zelefsky 1999[206]	1 year	Actuarial PSA relapse-free survival[a]	145		96.2			
Mearini 2009[161]	1.25 years	Biochemical disease-free survival[a] (Phoenix criterion: post-treatment PSA nadir + 2 ng/ml)						
Saliken 1999,[180] Donnelly 2002[124]	1.5 years	PSA control (undetectable PSA < 0.3 ng/ml)				43	40	93
Giberti 2009[49]	2 years	Biochemical disease-free survival rate[a]	100		95			
Uchida 2005[191]	2 years	Biochemical disease-free survival[a] (ASTRO definition)						
Borchers 2004[109]	2.3 years	PSA relapse-free survival (patients with a decrease in serum PSA level < 0.1 ng/ml)	52	44	85			

HIFU			AS			EBRT			RP		
N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
65		87.7									
64		93.8									
60		78									
						305		100	64		92.8
									354		94
						137		99.6			
160		79.9									
									100		93.6
60		76									
									42	40	96

continued

TABLE 78 Cancer-related efficacy outcomes (*continued*)

			BT			CRYO		
Study ID	Timeline	Outcome	*N*	*n*	%	*N*	*n*	%
Mearini 2009[161]	2.5 years	Biochemical disease-free survival[a] (Phoenix definition: post-treatment PSA nadir + 2 ng/ml)						
Blana 2012[107]	3 years	Biochemical disease-free survival rate[a] (Phoenix definition)						
D'Amico 2003[123]	3 years	PSA failure-free survival[a] [BT: ASTRO criterion (3 consecutive PSA increments) RP: > 0.2 ng/ml post operation was considered as detectable]	196		100			
Eade 2008[126]	3 years	Freedom from biochemical failure[a] (failure defined as PSA nadir + 2 ng/ml)	158		99.5			
Ganzer 2011[133]	3 years	Biochemical disease-free survival[a] (Phoenix definition)						
Giberti 2009[49]	3 years	Biochemical disease-free survival rate[a]	100		93.6			
Goldner 2012a[135]	3 years	Actuarial biochemical no evidence of disease rate[a] (Phoenix definition: absolute nadir + 2 ng/ml rise or in case of the start of hormonal therapy, due to rising PSA): EBRT 70 Gy, low risk	667		96.3			
Goldner 2012a[135]	3 years	Actuarial biochemical no evidence of disease rate[a] (Phoenix definition: absolute nadir + 2 ng/ml rise or in case of the start of hormonal therapy, due to rising PSA): EBRT 74 Gy, low risk						
Goldner 2012b[136]	3 years	Actuarial biochemical no evidence of disease rate[a] (Phoenix definition: absolute nadir + 2 ng/ml rise or in case of the start of hormonal therapy, due to rising PSA): intermediate risk	601		85.9			

HIFU			AS			EBRT			RP		
N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
160		71.9									
356		91.7									
									322		94.3
						216		99.5			
804		87									
									100		92.7
						82		94.7			
						170		95.9			
						289		90			

continued

TABLE 78 Cancer-related efficacy outcomes (*continued*)

			BT			CRYO		
Study ID	Timeline	Outcome	*N*	*n*	%	*N*	*n*	%
Kupelian 2004[151]	3 years	Biochemical relapse-free survival[a] [ASTRO definition: 3 consecutive rising PSA levels after a nadir (EBRT, BT); 2 consecutive detectable PSA levels (> 0.2 ng/ml) (RP)]< 72 Gy	950		92			
Pe 2009[170]	3 years	Biochemical failure-free rate[a] (PSA failure defined by Phoenix criterion: PSA nadir + ≥ 2 ng/ml)	171		96.1			
Pickles 2010[171]	3 years	Biochemical non-evidence of disease[a]	139		97			
Sumitomo 2010[185]	3 years	Disease-free survival rate[a] (Phoenix definition: PSA nadir + 2 ng/ml)						
Sumitomo 2010[185]	3 years	Disease-free survival rate[a] (Phoenix definition: PSA nadir + 2 ng/ml): HIFU + TURP						
Vassil 2010,[200] Burdick 2009,[112] Ciezki 2004,[118] Kibel 2012,[144] Nepple 2013[165]	3 years	Biochemical recurrence-free survival[a] [failure defined as nadir + 2 ng/ml (BT and RT); PSA ≥ 0.4 ng/ml (RP)]: laparoscopic RP	256		91.4			
Vassil 2010,[200] Burdick 2009,[112] Ciezki 2004,[118] Kibel 2012,[144] Nepple 2013[165]	3 years	Biochemical recurrence-free survival[a] [failure defined as nadir + 2 ng/ml (BT and RT); PSA ≥ 0.4 ng/ml (RP)]: retropubic RP						
Ward 2012[202]	3 years	Biochemical disease-free survival[a] (ASTRO definition)				1160		75.7
Zelefsky 1999[206]	3 years	Actuarial PSA relapse-free survival[a]	145		86.4			
Ganzer 2008[132]	3.3 years	Disease-free survival rates[a] (disease-free status defined as PSA nadir ≤ 0.2 ng/ml)						

HIFU			AS			EBRT			RP		
N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
						484		62	1034		85
						189		98.5			
						139		94			
65		70.6									
64		83.7									
						305		94.3	64		63.1
									354		84.4
						137		90.5			
66		95									

continued

TABLE 78 Cancer-related efficacy outcomes (*continued*)

			BT			CRYO		
Study ID	Timeline	Outcome	*N*	*n*	%	*N*	*n*	%
Mearini 2009[161]	3.3 years	Biochemical disease-free survival[a] (Phoenix definition of failure: post-treatment PSA nadir + 2 ng/ml)						
Wong 2009[205]	3.3 years	Biochemical no evidence of disease[a] (ASTRO – Phoenix definition: PSA nadir + < 2 ng/ml with no backdating): IMRT	225		94.1			
Eade 2008[126]	3.5 years	Freedom from biochemical failure[a] (failure defined as PSA nadir + 2 ng/ml)	158		20.9			
Onik 2008[166]	Median 4 (range 2–8.75) years	PSA stability rate (ASTRO definition)				21	20	95
Pe 2009[170]	4 years	Biochemical failure-free rate[a] (Phoenix definition: nadir + ≥ 2 ng/ml)[a]	171		96.1			
Pickles 2010[171]	4 years	Biochemical non-evidence of disease[a]	139		96.5			
Pinthus 2012[173]	4 years	Biochemical failure-free rate[a] (Stuttgart definition: nadir + 1.2 ng/ml 'at call')						
Beyer 2000[105]	5 years	Failure-free survival[a] (failure defined as rising PSA at the time of analysis)	695		71			
Blana 2012[107]	5 years	Biochemical disease-free survival rate[a] (Phoenix definition)						
D'Amico 2003[123]	5 years	PSA failure-free survival[a] [BT: ASTRO criterion (3 consecutive increments) RP: > 0.2 ng/ml post operation was considered as detectable]	196		97.8			
Ganzer 2008[132]	5 years	Disease-free survival rates[a] (disease-free status defined as PSA nadir ≤ 0.2 ng/ml)						

HIFU			AS			EBRT			RP		
N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
160		71.9									
						314		93.1			
						216		20.8			
						189		97			
						139		88.1			
402		68									
						1527		69			
356		84.7									
									322		92.3
66		94.9									

continued

TABLE 78 Cancer-related efficacy outcomes (*continued*)

			BT			CRYO		
Study ID	Timeline	Outcome	*N*	*n*	%	*N*	*n*	%
Ganzer 2011[133]	5 years	Biochemical disease-free survival[a] (Phoenix definition)						
Giberti 2009[49]	5 years	Biochemical disease-free survival rate[a]	100		91.4			
Goldner 2012a[135]	5 years	Actuarial biochemical no evidence of disease rate[a] (Phoenix definition: absolute nadir + 2 ng/ml rise or in case of the start of hormonal therapy, due to rising PSA): EBRT 70 Gy, low risk	667		93			
Goldner 2012a[135]	5 years	Actuarial biochemical no evidence of disease rate[a] (Phoenix definition: absolute nadir + 2 ng/ml rise or in case of the start of hormonal therapy, due to rising PSA): EBRT 74 Gy, low risk						
Goldner 2012b[136]	5 years	Actuarial biochemical no evidence of disease rate[a] (Phoenix definition: absolute nadir + 2 ng/ml rise or in case of the start of hormonal therapy, due to rising PSA): intermediate risk	601		78			
Kupelian 2004[151]	5 years	Biochemical relapse-free survival[a] [ASTRO definition: 3 consecutive rising PSA levels after a nadir (EBRT, BT); 2 consecutive detectable PSA levels (> 0.2 ng/ml) (RP)]: EBRT < 72 Gy	950		83			
Misrai 2008[162]	5 years	Biochemical disease-free survival rate[a] (ASTRO criteria: a rise in PSA of 2 ng/ml or more above the nadir PSA)						
Pe 2009[170]	5 years	Biochemical failure-free rate[a] (PSA failure defined by Phoenix criterion: PSA nadir + ≥ 2 ng/ml)	171		96.1			

HIFU			AS			EBRT			RP		
N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
804		80									
									100		91
						82		84			
						170		91			
						289		74			
						484		51	1034		81
119		30									
						189		94.8			

continued

TABLE 78 Cancer-related efficacy outcomes (*continued*)

			BT			CRYO		
Study ID	Timeline	Outcome	*N*	*n*	%	*N*	*n*	%
Pickles 2010[171]	5 years	Biochemical non-evidence of disease[a]	139		95.2			
Shah 2012,[182] Vicini 2011[201]	5 years	Disease-free survival[a] (absence of local recurrence, disease or death secondary to prostate cancer): African American	36		84.8			
Shah 2012,[182] Vicini 2011[201]	5 years	Disease-free survival[a] (absence of local recurrence, disease or death secondary to prostate cancer): white	504		90.7			
Sumitomo 2010[185]	5 years	Disease-free survival rate[a] (Phoenix definition: PSA nadir + 2 ng/ml): HIFU						
Sumitomo 2010[185]	5 years	Disease-free survival rate[a] (Phoenix definition: PSA nadir + 2 ng/ml): HIFU + TURP						
Vassil 2010,[200] Burdick 2009,[112] Ciezki 2004,[118] Kibel 2012,[144] Nepple 2013[165]	5 years	Biochemical recurrence-free survival[a] [failure defined as nadir + 2 ng/ml (BT and RT); PSA ≥ 0.4 ng/ml (RP)]: laparoscopic RP	256		89.5			
Vassil 2010,[200] Burdick 2009,[112] Ciezki 2004,[118] Kibel 2012,[144] Nepple 2013[165]	5 years	Biochemical recurrence-free survival[a] [failure defined as nadir + 2 ng/ml (BT and RT); PSA ≥ 0.4 ng/ml (RP)]: retropubic RP						
Wong 2009[205]	5 years	Biochemical no evidence of disease[a] (ASTRO – Phoenix definition: PSA nadir + < 2 ng/ml with no backdating): IMRT	225		94			
Zelefsky 1999[206]	5 years	Actuarial PSA relapse-free survival[a]	145		82			
Giberti 2009[49]	6 years	Biochemical disease-free survival rate[a]	85		91.7			
Mack 1997[158]	Mean 8.5 (range 6–18) years	No evidence of disease				66	25	37.9

HIFU			AS			EBRT			RP		
N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
						139		84.7			
						12		82			
						469		77.4			
65		61.3									
64		75.2									
						305		85.7	64		60.2
									354		79.9
						314		87			
						137		88			
									89		91

continued

TABLE 78 Cancer-related efficacy outcomes (*continued*)

Study ID	Timeline	Outcome	BT			CRYO		
			N	*n*	%	*N*	*n*	%
Chaussy 2003[116]	10 years	PSA stability rate[a] (ASTRO criterion): HIFU						
Reintervention								
Ahmed 2012[99]	After 6 months	Reintervention						
Ahmed 2011[98]	6–12 months	Reintervention						
Donnelly 2010,[125] Robinson 2009[179]	Within 6 months	Reintervention				117	14	12
Koch 2007[150]	Within 6 months	Reintervention: two treatments						
Koch 2007[150]	Within 6 months	Reintervention: three treatments						
Lindner 2009[155]	6 months	Reintervention						
Cytron 2003[122]	9 months (unclear)	Reintervention				22	1	4.5
Chaussy 2003[116]	Mean 10.9 (range 2.9–26.9) months	Reintervention: HIFU + TURP						
Ellis 2007[129]	Mean 15.2 (SD 7.4) months	Reintervention				60	11	18
Chaussy 2003[116]	Mean 18 (range 3–46.3) months	Reintervention: HIFU						
Chaussy 2003[116]		Reintervention: all patients (HIFU and HIFU + TURP)						
Mearini 2009[161]	Median 2 years (range 11.8–40.8 months)	Reintervention						
Pinthus 2012[173]	Median 24 (range 6–48) months	Reintervention						
Caso 2012,[114] Caso 2012,[115] Polascik 2007[175]	Median 2.3 (range 1–3.4) years	Reintervention				97	4	4.1
Lian 2011[154]	Median 2.5 years (range 9–56 months)	Reintervention				102	1	1
Wong 1997[204]	2.5 years	Reintervention				83	12	14.5
Inoue 2011[143]	Median 3 years (range 12–84 months)	Reintervention						
Onik 2008[166]	Median 4.2 years (range 24–105 months)	Reintervention				21	1	4.8

HIFU			AS			EBRT			RP		
N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
96		84.2									
41	4	10									
19	1	5.3									
						N/A	N/A	N/A			
20	10	50									
20	2	10									
175		7									
96		24									
271		31									
163	20	12.3									
402	12	3									
137	15	10.9									

continued

TABLE 78 Cancer-related efficacy outcomes (*continued*)

			BT			CRYO		
Study ID	Timeline	Outcome	*N*	*n*	%	*N*	*n*	%
Blana 2009[106]	Median 4.7 (range 2–10.9) years	Reintervention						
Poissonnier 2007[174]	5 years	Reintervention and watchful waiting						
Bahn 2002[102]	Median 5.43 years	Reintervention				75	32	42.7
Donnelly 2002,[124] Saliken 1999[180]	Median 5 years (range 35–85 months)	Reintervention: two treatments				76	10	13.1
Donnelly 2002,[124] Saliken 1999[180]	Median 5 years (range 35–85 months)	Reintervention: three treatments				76	1	1.3
El Fegoun 2011[127]	Median 10.6 (range 7.5–11.1) years	Reintervention						
Moved to other treatments								
Giberti 2009[49]	3 months	Additional treatments	85	7	8.3			
Ahmed 2012[99]	After 6 months	Moved to AS						
Ahmed 2011[98]	6–12 months	Moved to AS						
Donnelly 2010,[125] Robinson 2009[179]	Within 6 months	Moved to other treatments				117	16	13.7
Donnelly 2010,[125] Robinson 2009[179]	Within 6 months	Moved to other treatments: CRYO				N/A	N/A	N/A
Donnelly 2010,[125] Robinson 2009[179]	Within 6 months	Moved to other treatments: hormone therapy				117	13	11.1
Donnelly 2010,[125] Robinson 2009[179]	Within 6 months	Moved to other treatments: watchful waiting				117	3	2.6
Maestroni 2008[159]	After 6 months	Moved to other treatments: hormone therapy						
Bul 2013,[111] van den Bergh 2010[197]	1.6 years	Moved to other treatments						
Bul 2013,[111] van den Bergh 2010[197]	1.6 years	Moved to other treatments: RP						
Bul 2013,[111] van den Bergh 2010[197]	1.6 years	Moved to other treatments: radiotherapy						
Bul 2013,[111] van den Bergh 2010[197]	1.6 years	Moved to other treatments: hormone therapy						
Bul 2013,[111] van den Bergh 2010[197]	1.6 years	Moved to other treatments: HIFU						

HIFU			AS			EBRT			RP		
N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
285	43	15.1									
227	12	5.3									
12	1	8.3									
									89	8	9
41	5	12									
19	1	5.3									
						114	32	28.1			
						114	9	7.9			
						114	16	14			
						114	7	6.1			
25	4	16									
			2494	527	21.1						
			2494	253	10.1						
			2494	238	9.5						
			2494	8	0.32						
			2494	4	0.16						

continued

TABLE 78 Cancer-related efficacy outcomes (*continued*)

			BT			CRYO		
Study ID	Timeline	Outcome	*N*	*n*	%	*N*	*n*	%
Bul 2013,[111] van den Bergh 2010[197]	1.6 years	Moved to other treatments: unknown						
Pinthus 2012[173]	Median 2 years (range 6–48 months)	Moved to other treatments: RP						
Pinthus 2012[173]	Median 2 years (range 6–48 months)	Moved to other treatments: radiotherapy						
Pinthus 2012[173]	Median 2 years (range 6–48 months)	Moved to other treatments: hormone therapy						
Pinthus 2012[173]	Median 2 years (range 6–48 months)	Moved to other treatments: AS						
Pinthus 2012[173]	Median 2 years (range 6–48 months)	Moved to other treatments						
Caso 2012,[114] Caso 2012,[115] Polascik 2007[175]	Median 2.3 (range 1–3.4) years	Moved to other treatments				97	12	12.3
Caso 2012,[114] Caso 2012,[115] Polascik 2007[175]	Median 2.3 (range 1–3.4) years	Moved to other treatments: radiotherapy				97	3	3.1
Caso 2012,[114] Caso 2012,[115] Polascik 2007[175]	Median 2.3 (range 1–3.4) years	Moved to other treatments: hormone therapy				97	2	2.1
Caso 2012,[114] Caso 2012,[115] Polascik 2007[175]	Median 2.3 (range 1–3.4) years	Moved to other treatments: watchful waiting				97	1	1
Caso 2012,[114] Caso 2012,[115] Polascik 2007[175]	Median 2.3 (range 1–3.4) years	Moved to other treatments: chemotherapy				97	1	1
Mearini 2009[161]	Median 2 years (range 11.8–40.8 months)	Moved to other treatments: radiotherapy						
Tosoian 2011[187]	Median 2.7 (range 0.01–15.0) years	Moved to other treatments						
Hardie 2005[140]	Median 3.5 years (range 1–116 months)	Moved to other treatments						
Misrai 2008[162]	Median 3.8 (range 1–6.8) years	Moved to other treatments						
Misrai 2008[162]	Median 3.8 (range 1–6.8) years	Moved to other treatments: radiotherapy						

HIFU			AS			EBRT			RP		
N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
			2494	28	1.12						
402	6	1.5									
402	4	1									
402	4	1									
402	7	1.7									
402	28	7									
163	2	1.2									
			769	255	33.2						
			80	11	14						
119	22	18.5									
119	14	11.8									

continued

TABLE 78 Cancer-related efficacy outcomes (*continued*)

			BT			CRYO		
Study ID	Timeline	Outcome	*N*	*n*	%	*N*	*n*	%
Misrai 2008[162]	Median 3.8 (range 1–6.8) years	Moved to other treatments: hormone therapy						
Misrai 2008[162]	Median 3.8 (range 1–6.8) years	Moved to other treatments: RP						
Blana 2009[106]	Median 4.7 (range 2–10.9) years	Moved to other treatments: hormone therapy						
Blana 2009[106]	Median 4.7 (range 2–10.9) years	Moved to other treatments: radiotherapy						
Poissonnier 2007[174]	5 years	Moved to other treatments: radiotherapy						
Poissonnier 2007[174]	5 years	Moved to other treatments: hormone therapy						
Poissonnier 2007[174]	5 years	Moved to other treatments: EBRT + hormone therapy						
Pickles 2010[171]	5 years	Moved to other treatments: hormone therapy (actuarial use)	139	7	5			
Selvadurai 2013,[181] van As 2008[196]	Median 5.7 years	Moved to other treatments						
Selvadurai 2013,[181] van As 2008[196]	Median 5.7 years	Moved to other treatments: EBRT + hormone therapy						
Selvadurai 2013,[181] van As 2008[196]	Median 5.7 years	Moved to other treatments: RP						
Selvadurai 2013,[181] van As 2008[196]	Median 5.7 years	Moved to other treatments: BT						
Selvadurai 2013,[181] van As 2008[196]	Median 5.7 years	Moved to other treatments: HIFU						
Selvadurai 2013,[181] van As 2008[196]	Median 5.7 years	Moved to other treatments: hormone therapy						
Godtman 2013[134]	Median 6 (range 0.08–15.1) years	Moved to other treatments						
Godtman 2013[134]	Median 6 (range 0.08–15.1) years	Moved to other treatments: RP						
Godtman 2013[134]	Median 6 (range 0.08–15.1) years	Moved to other treatments: radiotherapy						

HIFU			AS			EBRT			RP		
N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
119	7	5.9									
119	1	0.8									
285	15	5.2									
285	7	2.5									
227	12	5.3									
227	3	1.3									
227	4	1.8									
						139	11	8			
			471	148	31.4						
			471	91	19.3						
			471	43	9.1						
			471	10	2.1						
			471	1	0.2						
			471	3	0.6						
			439	162	37						
			439	106	24.1						
			439	32	7.3						

continued

TABLE 78 Cancer-related efficacy outcomes (*continued*)

Study ID	Timeline	Outcome	BT			CRYO		
			N	*n*	%	*N*	*n*	%
Godtman 2013[134]	Median 6 (range 0.08–15.1) years	Moved to other treatments: hormone therapy						
Klotz 2010,[146] Klotz 2005,[148] Klotz 2012,[147] Loblaw 2010[157]	Median 6.8 (range 1–13) years	Moved to other treatments						
Klotz 2010,[146] Klotz 2005,[148] Klotz 2012,[147] Loblaw 2010[157]	Median 6.8 (range 1–13) years	Moved to other treatments: RP						
Klotz 2010,[146] Klotz 2005,[148] Klotz 2012,[147] Loblaw 2010[157]	Median 6.8 (range 1–13) years	Moved to other treatments: radiotherapy						
Klotz 2010,[146] Klotz 2005,[148] Klotz 2012,[147] Loblaw 2010[157]	Median 6.8 (range 1–13) years	Moved to other treatments: hormone therapy						
Sumitomo 2010[185]	12–93 months	Moved to other treatments: hormone therapy						
Sumitomo 2010[185]	12–93 months	Moved to other treatments: radiotherapy						
Sumitomo 2010[185]	12–93 months	Moved to other treatments: radiohormonal therapy						
Sumitomo 2010[185]	12–93 months	Moved to other treatments: chemotherapy						
Sumitomo 2010[185]	12–93 months	Moved to other treatments: RP						
Mack 1997[158]	Mean 8.5 years	Moved to other treatments: radiotherapy				66	20	30
Mack 1997[158]	Mean 8.5 years	Moved to other treatments: hormone therapy				66	27	41
El Fegoun 2011[127]	Median 10.6 (range 7.5–11.1) years	Moved to other treatments: hormone therapy						

ASTRO, American Society for Radiation Oncology; BT, brachytherapy; CRYO, cryotherapy; IQR, interquartile range; N/A, not applicable; N/R, not reported; OS, overall survival; PCSM, prostate cancer-specific mortality; RT, radiotherapy; SD, standard deviation; TURP, transurethral resection of the prostate.

a The percentages are Kaplan–Meier estimates, and thus the numbers at risk at each time point rather than *N* would be required to calculate *n*.

HIFU			AS			EBRT			RP		
N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
			439	24	5.5						
			450	135	30						
			450	35	7.7						
			450	90	20						
			450	10	2.3						
129	28	21.7									
129	2	1.5									
129	1	0.8									
129	1	0.8									
129	3	2.3									
12	4	33.3									

TABLE 78a All efficacy outcomes: laser

Study ID	Timeline	Outcome	*N*	*n*	%
Lindner 2009[155]	6 months	Reintervention	12	1	8.3

TABLE 78b All efficacy outcomes: PDT

Study ID	Timeline	Outcome	*N*	*n*	%
Barret 2013[103]	Median follow-up 9 (IQR 6–15) months		23	23	100

IQR, interquartile range.

TABLE 79 Urinary function dichotomous outcomes

			BT			CRYO			HIFU			EBRT			RP		
Study ID	**Timeline**	**Outcome**	***N***	***n***	**%**	***N***	***n***	**%**	***N***	***n***	**%**	***N***	***n***	**%**	***N***	***n***	**%**
Urinary continence																	
Ahmed 2012[99]	6 months	Urinary continence (pad free and no leak)/UCLA EPIC							41	37	90.2						
Ahmed 2011[98]	6 months	Urinary continence (pad free and no leak)							20	19	95						
Ahmed 2012[99]	12 months	Urinary continence (pad free and no leak)/UCLA EPIC							41	38	92.7						
Borchers 2004[109]	1 year	Urinary continence: EORTC-QLQ-PR30	52		13										42		62
Urinary incontinence (UI)																	
Bahn 2002[102]	6 months (average)	Any leakage (even a drop of urine) (definition 2)				533	23	4.3									
Ellis 2007[129]	6 months (more or equal) Mean follow-up 15.2 (SD 7.4) months	UI defined as drop of urine at any time				60	2	3.3									
Giberti 2009[49]	6 months	UI	100	0	0										100	16	16
Mohammed 2012,[164] Shah 2012,[182] Vicini 2011[201]	6 months (within 3–6 months)	UI: all patients	540	45	8.3							2190	188	8.6			
Borchers 2004[109]	1 year	Newly developed (UI) (EORTC-QLQ-PR30)	52	NR	40										42	NR	20
Caso 2012,[114] Caso 2012,[115] Polascik 2007[175]	Within 1 year	All incontinence				106	22	20.8									

continued

TABLE 79 Urinary function dichotomous outcomes (*continued*)

			BT			CRYO			HIFU			EBRT			RP		
Study ID	**Timeline**	**Outcome**	***N***	***n***	**%**	***N***	***n***	**%**	***N***	***n***	**%**	***N***	***n***	**%**	***N***	***n***	**%**
Han 2003[139]	1 year follow-up (reported as postoperative)	All incontinence				104	8	7.7									
Kirschner-Hermanns 2008[145]	1 year	UI (ICSmale)	33	17	52										61	40	66
Hubosky 2007[52]	1.1-year mean follow-up (range 1–32, median 11 months)	Incontinence defined as required pads because of leaking urine				89	2	2									
Pinkawa 2009[172]	Median 16 months (RT: range 12–21 months; BT: range 12–24 months)	Moderate/big problem from dripping or leaking urine (EPIC)	52	6	12							52	3	6			
Ward 2012[202]	1 year	UI (use of any pads)				1160	8	0.7									
Hale 2013[138]	Mean 1.6 years (range 2–52 months)	UI (use of any pads)				26	0	0									
Uchida 2005[191]	Median 1.7 years (range 2–24 months)	UI grade 1 Defined by Japanese version of National Cancer Institute-Common Toxicity Criteria version 2.0							72	1	1.4						
Buron 2007[113]	2 years	UI: EORTC-QLQ-PR25	308	39	12.7										127	25	19.7
Reeve 2012[176]	2 years	UI	41	13	31.7							169	67	39.6	72	32	44.4
Williams 2012[203]	2 years (within 5 years)	UI Assessed using self-assessment with validated instruments	9985	1116	11.2	943	182	19.3									
Lian 2011[154]	Median 2.5 years (range 9–56 months)	UI requiring 1–2 pads per day				102	4	3.9									

Study ID	Timeline	Outcome	BT			CRYO			HIFU			EBRT			RP		
			N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
Chen 2009[117]	3 years	UI (PCSI)	78	16	20.5							154	46	30	112	60	53.6
Smith 2009[184]	3 years	UI (use of any pads)	58	3	5.4							123	3	2.7	981	111	12.3
Onik 2008[166]	Median 4.2 years (range 24–105 months), reported as postoperative	UI				21	0	0									
Colombel 2006[120]	5 years	UI grade 1							242	23	9.5						
Crook 2011[121]	5 years	Any urinary leakage (EPIC)	101	14	13.9										67	27	40.3
Donnelly 2002[124]	Within 5 years	UI				76	1	1.3									
Giberti 2009[49]	5 years	UI	100	0	0										100	0	0
El Fegoun 2011[127]	Median 10.6 (range 7.5–11.1) years	UI (use of any pads)							12	0	0						
Urinary function																	
Ahmed 2011[98]	6 months	Any LUTS (I-PSS ordinal sum)							20	20	100						
Boettcher 2012[108]	6 months	Urgency frequency from OAB severity scale	33	14	42.4										66	10	15.2
Giberti 2009[49]	6 months	Irritative symptoms	100	68	68										100	4	4
Koch 2007[150]	6 months	Urinary dysfunction, I-PSS (mild: <8; moderate: 8–19; severe: 20–35) Decrease in score							19	12	63.2						
Koch 2007[150]	6 months	Urinary dysfunction, I-PSS (mild: <8; moderate: 8–19; severe: 20–35) No change in score							19	2	10.5						

continued

TABLE 79 Urinary function dichotomous outcomes (*continued*)

			BT			CRYO			HIFU			EBRT			RP		
Study ID	**Timeline**	**Outcome**	***N***	***n***	**%**	***N***	***n***	**%**	***N***	***n***	**%**	***N***	***n***	**%**	***N***	***n***	**%**
Koch 2007[150]	6 months	Urinary dysfunction, I-PSS (mild: < 8; moderate: 8–19; severe: 20–35)							19	5	26.3						
		Increase in score															
Poissonnier 2007[174]	6 months	Urgency							227	12	5						
Shah 2012,[182] Vicini 2011,[201] Mohammed 2012[164]	3–6 months	Frequency/urgency: all patients	540	295	54.6							2190	883	40.3			
Tsui 2005[189]	6 months	Urinary symptoms (median I-PSS > baseline)	86	67	77.9							N/R	N/R	N/R			
Tsui 2005[189]	6 months	Urinary symptoms (RTOG > 0)	N/R	N/R	N/R							76	4	5.3			
Ahmed 2011[98]	1 year	Any LUTS (I-PSS ordinal sum)							20	20	100						
Boettcher 2012[108]	1 year	Urgency frequency from OAB severity scale	33	11	33.5										66	8	12.1
Caso 2012,[114] Caso 2012,[115] Polascik 2007[175]	1 year	Worsening LUTS (urgency)				106	8	7.5									
Caso 2012,[114] Caso 2012,[115] Polascik 2007[175]	1 year	Splayed stream				106	2	1.8									
Kirschner-Hermanns 2008[145]	1 year	LUTS (ICSmale)	33	29	88										61	49	80
Kirschner-Hermanns 2008[145]	1 year	Bothersome LUTS ('quite a problem' or 'a serious problem') (ICSmale)	33	10	30										61	7	11
Kirschner-Hermanns 2008[145]	1 year	Urgency (ICSmale)	33	29	88										61	39	64

			BT			CRYO			HIFU			EBRT			RP		
Study ID	Timeline	Outcome	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
Kirschner-Hermanns 2008[145]	1 year	Bothersome urgency ('quite a problem' or 'a serious problem') (ICSmale)	33	7	21										61	1	2
Boettcher 2012[108]	2 years	Urgency frequency: OAB severity scale	33	12	36.6										66	8	12.1
Buron 2007[113]	2 years	Urinary urgency: EORTC-QLQ-PR25	308	76	24.7										127	14	11
Buron 2007[113]	2 years	Diurnal urinary frequency: EORTC-QLQ-PR25	308	74	24										127	8	6.3
Buron 2007[113]	2 years	Nocturnal urinary frequency: EORTC-QLQ-PR25	308	62	20.1										127	7.4	5.8
Boettcher 2012[108]	3 years	Urgency frequency: OAB severity scale	33	10	30										66	7	11
Chen 2009[117]	3 years	Urinary obstruction/irritation	75	27	36							152	101	66.4	107	53	49.5
Crook 2011[121]	5 years	Weak stream and incomplete emptying (EPIC)	101	39	38.6							67	21	31.3			
Giberti 2009[49]	5 years	Irritative symptoms	100	0	0										100	0	0
Inoue 2011[143]	7 years	Urgency in voiding							137	15	11						
Inoue 2011[143]	7 years	Difficult voiding							137	30	22						

BT, brachytherapy; CRYO, cryotherapy; EORTC-QLQ-PR25, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Prostate-25 items; EORTC-QLQ-PR30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Prostate-30 items; EPIC, Expanded Prostate Cancer Index Composite; ICSmale, International Continence Society-male questionnaire; LUTS, lower urinary tract symptoms; N/R, not reported; NR, number at risk (defined as number who were continent prior to treatment); OAB, overactive bladder; PCSI, Prostate Cancer Symptom Index; RT, radiotherapy; SD, standard deviation; UCLA EPIC, University of California, Los Angeles Expanded Prostate Cancer Index Composite.

TABLE 80 Urinary function continuous outcomes

			BT		CRYO		HIFU		EBRT		RP	
Study ID	Timeline	Outcome as reported/defined	*n*	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score
UI												
Truesdale 2010,[188] Lambert 2007[152]	6 months	Mean (SD) UI AUA Symptom Index score			30	8.9 (7.3)						
Talcott 2003[186]	1 year	Mean (SD) UI symptom index (urinary, bowel and sexual function scale)	80	4.6 (11.1)					182	9.2 (15.8)	129	23.9 (23.5)
Truesdale 2010,[188] Lambert 2007[152]	1 year	Mean (SD) UI AUA Symptom Index score			54	7.6 (6.3)						
Pinkawa 2009[172]	Median 1.3 years RT: range 12–21 months; BT: range 12–24 months	Mean, median (range) UI score (EPIC)	52	90, 100 (83–100)					52	90, 100 (90–100)		
Talcott 2003[186]	2 years	Mean (SD) UI symptom index (urinary, bowel and sexual function scale)	80	7.5 (15.1)					182	8.5 (15.7)	129	23.4 (23.9)
Ferrer 2008,[130] Pardo 2010,[167] Guedea 2009[137]	3 years	Mean UI EPIC domain-specific	155	88.7					100	89.7	109	N/R
Frank 2007[131]	3.5 years (BT); 4.7 years (EBRT); 4 years (RP)	Mean (SD) UI (EPIC)	74	85.9 (23)					135	85.5 (18.9)	234	73.4 (25.1)

Study ID	Timeline	Outcome as reported/defined	BT		CRYO		HIFU		EBRT		RP	
			n	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score
Urinary bother												
Kobuke 2009[149]	6 months	Urinary bother (UCLA-PCI)	36	77.1							37	86.6
Mohamed 2012[163]	6 months	Mean (SD) Urinary bother (AUA Symptom Index)	240	2.26 (1.12)					483	1.84 (0.9)	146	1.99 (1.08)
Kobuke 2009[149]	1 year	Urinary bother (UCLA-PCI)	36	86.6							37	87.8
Pinkawa 2009[172]	Median 1.3 years RT: range 12–21 months; BT: range 12–24 months	Mean, median (IQR) Urinary bother (EPIC)	52	82, 89 (68–100)					52	88, 93 (83–96)		
Pinkawa 2009[172]	Median 1.3 years RT: range 12–21 months; BT: range 12–24 months	Mean, median (IQR) UI bother (EPIC)	52	86, 100 (94–100)					52	92, 100 (100–100)		
Pinkawa 2009[172]	Median 1.3 years RT: range 12–21 months; BT: range 12–24 months	Mean, median (IQR) Urinary obstructive/irritative bother (EPIC)	52	82, 87 (66–100)					52	87, 90 (80–100)		
Smith 2009[184]	3 years	Mean (SD) Urinary bother Long-form UCLA-PCI: RP nerve sparing	58	84.4 (24.6)					123	81.4 (27.6)	494	84.8 (23.5)

continued

TABLE 80 Urinary function continuous outcomes (*continued*)

			BT		CRYO		HIFU		EBRT		RP	
Study ID	**Timeline**	**Outcome as reported/defined**	***n***	**Score**	***n***	**Score**	***n***	**Score**	***n***	**Score**	***n***	**Score**
Smith 2009[184]	3 years	Mean (SD) Urinary bother (Long-form UCLA-PCI): RP non-nerve sparing									476	83.1 (25.3)
Frank 2007[131]	Median 3.5 years (BT), median 4.7 years (EBRT), median 4 years (RP)	Mean (SD) Urinary bother (EPIC domain specific)	74	78 (19.6)					135	80.4 (18)	234	83.2 (16.1)
Urinary function *EPIC domain urinary function*												
Ferrer 2008,[130] Pardo 2010,[167] Guedea 2009[137]	6 months	Mean (SE) Urinary function domain (EPIC)	247	89.5 (0.9)					180	96.1 (0.7)	118	83.2 (1.5)
Ferrer 2008,[130] Pardo 2010,[167] Guedea 2009[137]	1 year	Mean (SE) Urinary domain (EPIC)	255	92.6 (0.8)					184	94.7 (0.8)	121	88.5 (1.2)
Ahmed 2012[99]	1 year	Median (IQR) Urinary function domain (EPIC)					41	100 (92.5, 100)				
Pinkawa 2009[172]	Median 1.3 years (RT: range 12–21 months; BT: range 12–24 months)	Mean, median (range) Urinary function (EPIC)	52	91, 100 (89–100)					52	94, 100 (94–100)		
Frank 2007[131]	Median 3.5 years (BT), median 4.7 years (EBRT), median 4 years (RP)	Mean (SD) Urinary function domain (EPIC)	74	85.8 (24.3)					135	90.1 (15.3)	234	83.7 (15.8)

Study ID	Timeline	Outcome as reported/defined	BT		CRYO		HIFU		EBRT		RP	
			n	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score
Frank 2007[131]	Median 3.5 years (BT), median 4.7 years (EBRT), median 4 years (RP)	Mean (SD) Urinary irritation domain (EPIC)	74	79.9 (19)					135	85.2 (12.8)	234	89.9 (11.6)
Crook 2011[121]	Median 5.2 years follow-up	Mean (SD) Urinary domain (EPIC): all participants	101	91.82 (8.53)							67	88.15 (11.47)
Crook 2011[121]	Median 5.2 years follow-up	Mean (SD) Urinary domain (EPIC): RCT patients	15	93.37 (3.36)							15	82.87 (12.05)
Crook 2011[121]	Median 5.2 years follow-up	Mean (SD) Urinary domain (EPIC): NRCS patients	86	91.54 (9.16)							52	89.83 (10.86)
I-PSS urinary function												
Giberti 2009[49]	6 months	Mean Urinary function (I-PSS)	85	15.2							89	4.9
Kobuke 2009[149]	6 months	Mean Urinary function (I-PSS)	36	12							37	8.4
Lindner 2009[155]	6 months	Mean Urinary function (I-PSS)										
Maestroni 2008[159]	6 months	Mean (range) Urinary function (I-PSS)					25	5.2 (1–14)				
Mearini 2009[161]	6 months	Median (range) Urinary function (I-PSS)					160	7 (5–12)				

continued

TABLE 80 Urinary function continuous outcomes (*continued*)

			BT		CRYO		HIFU		EBRT		RP	
Study ID	**Timeline**	**Outcome as reported/defined**	***n***	**Score**	***n***	**Score**	***n***	**Score**	***n***	**Score**	***n***	**Score**
Shoji 2010,[183] Uchida 2009[195]	6 months	Mean (SD)					326	9.28 (6.38)				
		Urinary function (I-PSS)										
Sumitomo 2010[185]	6 months	Mean (SD)					50	13.6 (3.6)				
		Urinary function (I-PSS): HIFU										
Sumitomo 2010[185]	6 months	Mean (SD)					60	7.7 (2.9)				
		Urinary function (I-PSS): HIFU + TURP										
Tsui 2005[189]	6 months	Median (range)	80	10 (1–32)								
		Urinary function (I-PSS)										
Ahmed 2012[99]	1 year	Median (IQR)					41	7 (3–12)				
		Urinary function (I-PSS)										
Giberti 2009[49]	1 year	Mean	85	10.1							89	4.7
		Urinary function (I-PSS)										
Kobuke 2009[149]	1 year	Mean	36	9.8							37	8.7
		Urinary function (I-PSS)										
Lee 2001[153]	1 year	Mean (SD)	44	10.4 (7.3)					23	8.5 (5.4)	23	5.5 (3.7)
		Urinary function (I-PSS)										
Shoji 2010,[183] Uchida 2009[195]	1 year	Mean (SD)					326	8.34 (7.14)				
		Urinary function (I-PSS)										
Sumitomo 2010[185]	1 year	Mean (SD)					50	14.1 (3.3)				
		Urinary function (I-PSS): HIFU										

			BT		CRYO		HIFU		EBRT		RP	
Study ID	Timeline	Outcome as reported/defined	*n*	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score
Sumitomo 2010[185]	1 year	Mean (SD)					60	8 (3.4)				
		Urinary function (I-PSS): HIFU + TURP										
Tsui 2005[189]	1 year	Median (range)	75	7 (0–23)								
		Urinary function (I-PSS)										
Uchida 2005[191]	1 year	Mean					24	9.1				
		Urinary symptom change score (I-PSS)										
Chaussy 2003[116]	Mean 1.6 (SD 1) years (range 3–46.3 months): HIFU	Mean (SD)					96	8.91 (10.89)				
		Urinary function (I-PSS): HIFU										
Chaussy 2003[116]	Mean 10.9 (SD 6.2) months (range 2.9–26.9 months): HIFU + TURP	Mean (SD)					175	3.37 (3.21)				
		Urinary function (I-PSS): HIFU + TURP										
Caso 2012,[114] Caso 2012,[115] Polascik 2007[175]	2 years	Median (range)			58	6 (2–10)						
		I-PSS										
Shoji 2010,[183] Uchida 2009[195]	2 years	Mean (SD)					326	8.8 (7.76)				
		Urinary function (I-PSS)										
Sumitomo 2010[185]	2 years	Mean (SD)					50	14.9 (3.6)				
		Urinary function (I-PSS): HIFU										
Sumitomo 2010[185]	2 years	Mean (SD)					60	7.9 (3.2)				
		Urinary function (I-PSS): HIFU + TURP										

continued

TABLE 80 Urinary function continuous outcomes (*continued*)

			BT		CRYO		HIFU		EBRT		RP	
Study ID	**Timeline**	**Outcome as reported/defined**	***n***	**Score**	***n***	**Score**	***n***	**Score**	***n***	**Score**	***n***	**Score**
Tsui 2005[189]	2 years	Median (range) Urinary function (I-PSS)	41	5.5 (0–25)								
Tsui 2005[189]	3 years	Median (range) Urinary function (I-PSS)	21	4 (1–19)								
Giberti 2009[49]	5 years	Mean Urinary function (I-PSS)	85	5.1							89	4.7
El Fegoun 2011[127]	Median 10.6 (range 7.5–11.1) years	Mean, median (range) I-PSS score					12	5.5, 6 (1–12)				
Other												
Boettcher 2012[108]	6 months	OAB severity scale (1–5) Urgence score	33	2.57							66	1.72
Giberti 2009[49]	6 months	Mean urinary symptoms EORTC-QLQ-PR25	85	36							89	17
Hubosky 2007[52]	6 months	AUA Symptom Index			46	6.43						
Hubosky 2007[52]	6 months	Urinary function (UCLA-PCI)			46	74						
Hubosky 2007[52]	6 months	% baseline score, urinary function (UCLA-PCI): open RP	122	92	46	99					135	80
Hubosky 2007[52]	6 months	% baseline score, urinary function (UCLA-PCI): robotic RP	122	92	46	99					135	69
Kobuke 2009[149]	6 months	Mean urinary function (UCLA-PCI)	36	87.5							37	78.2
Robinson 2009,[179] Donnelly 2010[125]	6 months	Mean urinary function (UCLA-PCI)			112	90.2			109	83.5		

			BT		CRYO		HIFU		EBRT		RP	
Study ID	Timeline	Outcome as reported/defined	*n*	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score
Smith 2009[184]	6 months	Mean (SD)	58	93.5 (14.3)					123	92.6 (15.2)	494	85.5 (17)
		Urinary function (UCLA-PCI): nerve sparing										
Smith 2009[184]	6 months	Mean (SD)	58	93.5 (14.3)					123	92.6 (15.2)	476	83.3 (19.2)
		Urinary function (UCLA-PCI): non-nerve sparing										
Boettcher 2012[108]	1 year	OAB severity scale (1–5)	33	2.56							66	1.85
		Urgency score										
Giberti 2009[49]	1 year	Mean urinary symptoms score (EORTC-QLQ-PR25)	85	15							89	10
Hubosky 2007[52]	1 year	Urinary function (AUA Symptom Index)			35	7.6						
Mohamed 2012[163]	1 year	Mean (SD)	240	2.36 (0.99)					483	1.85 (0.8)	146	1.17 (0.85)
		Urinary dysfunction (AUA Symptom Index)										
Mohamed 2012[163]	1 year	Mean (SD)	240	1.52 (0.99)					483	1.24 (0.58)	146	1.37 (0.74)
		Urinary limitation (AUA Symptom Index)										
Hubosky 2007[52]	1 year	Urinary function (UCLA-PCI)			35	87.6						
Malcolm 2010[160]	1 year	% baseline score	122	84.6	81	98.6					135	70.3
		Urinary function (UCLA-PCI): open RP										

continued

TABLE 80 Urinary function continuous outcomes (*continued*)

			BT		CRYO		HIFU		EBRT		RP	
Study ID	Timeline	Outcome as reported/defined	*n*	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score
Malcolm 2010[160]	1 year	Urinary function (UCLA-PCI): robotic RP									447	68.1
Kobuke 2009[149]	1 year	Mean urinary function (UCLA-PCI)	36	83.7							37	66.1
Robinson 2009,[179] Donnelly 2010[125]	1 year	Mean urinary function (UCLA-PCI)			112	88.7			105	88.4		
Talcott 2003[186]	1 year	Mean (SD)	80	19.3 (12.8)					182	13 (15.2)	129	19.3 (12.8)
		Urinary obstruction/irritation symptom index (urinary, bowel and sexual function scale)										
Hubosky 2007[52]	1.5 years	Urinary function (AUA Symptom Index)			25	7.4						
Hubosky 2007[52]	1.5 years	Urinary function (UCLA-PCI)			25	90.4						
Robinson 2009,[179] Donnelly 2010[125]	1.5 years	Mean urinary function score (UCLA-PCI)			111	91.6			100	90.2		
Boettcher 2012[108]	2 years	OAB severity scale (1–5)	33	2.57							66	1.7
		Urgency score										
Hubosky 2007[52]	2 years	Urinary function (AUA Symptom Index)			11	7.1						
Hubosky 2007[52]	2 years	Urinary function (UCLA-PCI)			11	88.4						
Malcolm 2010[160]	2 years	Urinary function (UCLA-PCI): open RP	122	81.0	81	94.9					135	74.8

Study ID	Timeline	Outcome as reported/defined	BT		CRYO		HIFU		EBRT		RP	
			n	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score
Malcolm 2010[160]	2 years	Urinary function (UCLA-PCI): robotic RP									47	70.0
Robinson 2009,[179] Donnelly 2010[125]	2 years	Mean urinary function score (UCLA-PCI)			108	90.6			106	89.6		
Talcott 2003[186]	2 years	Mean (SD)	80	18.8 (13.1)					182	12.1 (15.3)	129	18.8 (13.1)
		Urinary obstruction/irritation symptom index (urinary, bowel and sexual function scale)										
Boettcher 2012[108]	3 years	OAB severity scale (1–5)	33	2.18							66	1.85
		Urgency score										
Malcolm 2010[160]	3 years	Urinary function (UCLA-PCI): open RP	122	79.2	81	105.1					135	73.9
Malcolm 2010[160]	3 years	Urinary function (UCLA-PCI): robotic RP									447	71.8
Robinson 2009,[179] Donnelly 2010[125]	3 years	Mean urinary function score (UCLA-PCI)			105	93			105	88.6		
Giberti 2009[49]	5 years	Mean urinary symptoms score (EORTC-QLQ-PR25)	85	17							89	10

AUA, American Urological Association; BT, brachytherapy; CRYO, cryotherapy; EORTC-QLQ-PR25, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Prostate-25 items; EPIC, Expanded Prostate Cancer Index Composite; IQR, interquartile range; OAB, overactive bladder; RT, radiotherapy; SD, standard deviation; SE, standard error.

TABLE 80a Urinary function continuous outcomes: PDT

Study ID	Timeline	Outcome as reported/defined	*n*	Score
Barret 2013[103]	1 year	Median (IQR) urinary function score (I-PSS)	23	6 (3–10)
Barret 2013[103]	1 year	Median (IQR) urinary function score (I-PSS)	23	

IQR, interquartile range.

TABLE 81 Bowel function dichotomous outcomes

			BT			CRYO			HIFU			EBRT			RP		
Study ID	Timeline	Outcome as reported/defined	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
Bowel bother																	
Robinson 2009,[179] Donnelly 2010[125]	6 months	Moderate or big problem bowel bother (UCLA-PCI)				111	8	7.3				109	17	15.6			
Robinson 2009,[179] Donnelly 2010[125]	1 year	Moderate or big problem bowel bother (UCLA-PCI)				110	5	4.6				105	18	17.1			
Pinkawa 2009[172]	Median 1.3 years EBRT: range 12–21 months BT: range 12–24 months	Mean bowel function score (EPIC)	52	1	2.0							52	6	12.0			
Robinson 2009,[179] Donnelly 2010[125]	2 years	Moderate or big problem bowel bother (UCLA-PCI)				102	6	5.9				101	15	15.0			
Chen 2009[117]	3 years	Bowel problems (PCSI)	72	49	68.0							140	105	75.0	100	44	44.0
Robinson 2009,[179] Donnelly 2010[125]	3 years	Moderate or big problem bowel bother (UCLA-PCI)				98	7	7.2				97	10	10.3			
Smith 2009[184]	3 years	Moderate or big problem bowel bother (UCLA-PCI)	58	0	0.0							123	16	14.5	981	32	3.5

Study ID	Timeline	Outcome as reported/defined	BT			CRYO			HIFU			EBRT			RP		
			N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
Bowel symptoms																	
Tsui 2005[189]	6 months	Bowel symptoms (RTOG)	55	6	11							64	8	12.5			
Tsui 2005[189]	1 year	Bowel symptoms (RTOG)	61	2	3.3							76		12.1			
Tsui 2005[189]	2 years	Bowel symptoms (RTOG)	42	3	7.1							76		14.9			
Tsui 2005[189]	3 years	Bowel symptoms (RTOG)	21	4	19.0							76		4.5			
Faecal continence																	
Shah 2012,[182] Mohammed 2012,[164] Vicini 2011[201]	Median follow-up of 4.8 years	Grade ≥ 2 rectal incontinence (NCI-CTCAE v3.0)	417	1	0.3							1039	31	3.0			
Shah 2012,[182] Mohammed 2012,[164] Vicini 2011[201]	Median follow-up after 6 months: 4.8 years	Grade ≥ 3 rectal incontinence (NCI-CTCAE v3.0)	417	0	0.0							1039	4	0.4			
Borchers 2004[109]	1 year	Stool incontinence (Kelley questionnaire and EORTC-QLQ-C30)	52		20.0										42		4.0
Uchida 2005[191]	Median 1.2 years (range 2–24 months)	Grade 1 stool incontinence (Japanese NCI-CTCAE v2.0)							72	1	1.0						
Buron 2007[113]	2 years	Faecal incontinence (EORTC-QLQ-PR25)	200	18	8.9										52	1	2.0

BT, brachytherapy; CRYO, cryotherapy; EORTC-QLQ-PR25, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Prostate-25 items; EPIC, Expanded Prostate Cancer Index Composite; NCI-CTCAE v3.0, National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0; PCSI, Prostate Cancer Symptom Index.

TABLE 82 Bowel function continuous outcomes

			BT		CRYO		EBRT		RP	
Study ID	Timeline	Outcome as reported/defined	*n*	Score	*n*	Score	*n*	Score	*n*	Score
Bowel function (EPIC)										
Ferrer 2008,[130] Pardo 2010,[167] Guedea 2009[137]	6 months	Mean (SE) bowel function score (EPIC)	247	95.2 (0.6)			180	93.9 (1.0)	118	96.8 (0.9)
Ferrer 2008,[130] Pardo 2010,[167] Guedea 2009[137]	1 year	Mean (SE) bowel function score (EPIC)	255	96.8 (0.6)			184	94.6 (0.8)	121	97.4 (0.9)
Pinkawa 2009[172]	Median 1.3 years RT: range 12–21 months BT: range 12–24 months	Mean, median (IQR) bowel function score (EPIC)	52	93.0, 96.0 (92.0–100.0)			52	89.0, 82.0 (92.0–96.0)		
Ferrer 2008,[130] Pardo 2010,[167] Guedea 2009[137]	2 years	Mean (SE) bowel function score (EPIC)	240	97.9 (0.3)			179	94.5 (0.9)	122	97.9 (0.7)
Ferrer 2008,[130] Pardo 2010,[167] Guedea 2009[137]	3 years	Mean bowel function score (EPIC)	155	96.8			100	94.6	109	N/R
Frank 2007[131]	BT: 3.5 years; EBRT: 4.7 years; RP: 4 years	Mean (SD) bowel function score (EPIC)	74	89.4 (11.5)			135	85.8 (14.2)	234	93.0 (9.0)
Crook 2011[121]	Median 5.2 years	Mean (SD) bowel domain score (EPIC)	101	93.0 (11.6)					67	94.4 (8.9)
Bowel function (UCLA-PCI)										
Hubosky 2007[52]	6 months	Mean bowel function score (UCLA-PCI)			46	77.0				
Kobuke 2009[149]	6 months	Bowel function score (UCLA-PCI)	36	90.7					37	90.5
Litwin 2004[156]	6 months	Mean (SE) bowel function score (UCLA-PCI)	209	79 (2.1)			99	75 (2.2)	1276	84 (1.2)

Study ID	Timeline	Outcome as reported/defined	BT		CRYO		EBRT		RP	
			n	Score	*n*	Score	*n*	Score	*n*	Score
Malcolm 2012[160]	6 months	Bowel function score (UCLA-PCI)	122	85.0	81	82.0			Open: 135	Open: 89.0
									Robotic: 447	Robotic: 90.0
Donnelly 2010,[125] Robinson 2009[179]	6 months	Bowel function score (UCLA-PCI)			112	80.0	109	87.5		
Hubosky 2007[52]	1 year	Mean bowel function score (UCLA-PCI)			35	92.8				
Kobuke 2009[149]	1 year	Bowel function score (UCLA-PCI)	36	86.1					37	92.1
Litwin 2004[156]	1 year	Mean (SE) bowel function score (UCLA-PCI)	209	78.0 (2.3)			99	76.0 (2.3)	1276	85.0 (1.3)
Malcolm 2012[160]	1 year	Bowel function score (UCLA-PCI)	122	87.0	81	91.0			Open: 135	Open: 89.0
									Robotic: 447	Robotic: 91.0
Donnelly 2010,[125] Robinson 2009[179]	1 year	Bowel function score (UCLA-PCI)			112	84.3	105	89.8		
Hubosky 2007[52]	2 years	Mean bowel function score (UCLA-PCI)			11	86.0				
Litwin 2004[156]	2 years	Mean (SE) bowel function score (UCLA-PCI)	209	80.0 (3.3)			99	78.0 (2.8)	1276	84.0 (1.4)
Malcolm 2012[160]	2 years	Bowel function score (UCLA-PCI)	122	92.0	81	90.0			Open: 135	Open: 90.0
									Robotic: 447	Robotic: 89.0
Donnelly 2010,[125] Robinson 2009[179]	2 years	Bowel function score (UCLA-PCI)			108	85.2	106	89.0		
Malcolm 2012[160]	3 years	Bowel function score (UCLA-PCI)	122	90.0	81	90.0			Open: 135	Open: 88.0
									Robotic: 447	Robotic: 90.0
Donnelly 2010,[125] Robinson 2009[179]	3 years	Bowel function score (UCLA-PCI)			105	88.1	105	84.1		

continued

TABLE 82 Bowel function continuous outcomes (*continued*)

			BT		CRYO		EBRT		RP	
Study ID	**Timeline**	**Outcome as reported/defined**	***n***	**Score**	***n***	**Score**	***n***	**Score**	***n***	**Score**
Smith 2009[184]	3 years	Mean (SD) bowel function score (UCLA-PCI)	58	88.8 (11.5)				84.5 (15.8)	Nerve sparing: 494 Non-nerve sparing: 476	Nerve sparing: 88.1 (13.9) Non-nerve sparing: 88.5 (12.3)
Bowel bother (EPIC)										
Pinkawa 2009[172]	Median 1.3 years RT: range 12–21 months BT: range 12–24 months	Mean, median (IQR) bowel bother score (EPIC)	52	93.0, 100.0 (93.0–100.0)			52	87.0, 79.0 (96.0–100.0)		
Frank 2007[131]	BT: median 3.5 years EBRT: median 4.7 years RP: median 4 years	Mean (SD) bowel bother score (EPIC)	74	86.4 (16.8)			135	85.1 (19.8)	234	94.6 (10.4)
Bowel bother (EORTC-QLQ-PR25)										
Giberti 2009[49]	6 months	Mean bowel symptoms score (EORTC-QLQ-PR25)	85	6.0					89	3.0
Giberti 2009[49]	1 year	Mean bowel symptoms score (EORTC-QLQ-PR25)	85	4.0					89	2.0
Giberti 2009[49]	5 years	Mean bowel symptoms score (EORTC-QLQ-PR25)	85	5.0					89	2.0
Bowel bother (Symptom Index)										
Talcott 2003[186]	1 year	Mean (SD) bowel problems score (Symptom Index)	80	7.2 (7.1)			182	9.8 (9.8)	129	4.4 (5.9)
Talcott 2003[186]	2 years	Mean (SD) bowel problems score (Symptom Index)	80	7.2 (8.5)			182	8.9 (9.4)	129	4.8 (6.0)

Study ID	Timeline	Outcome as reported/defined	BT		CRYO		EBRT		RP	
			n	Score	*n*	Score	*n*	Score	*n*	Score
Bowel bother (UCLA-PCI)										
Hubosky 2007[52]	6 months	Mean bowel bother score (UCLA-PCI)			46	73.0				
Kobuke 2009[149]	6 months	Bowel bother score (UCLA-PCI)	36	88.8					37	92.1
Litwin 2004[156]	6 months	Mean (SE) bowel bother score (UCLA-PCI)	209	75.0 (3.0)			99	70.0 (3.1)	1276	84.0 (1.8)
Malcolm 2012[160]	6 months	Bowel bother score (UCLA-PCI)	122	86.0	81	89.0			Open: 135	Open: 94.0
									Robotic: 447	Robotic: 94.0
Hubosky 2007[52]	1 year	Mean bowel bother score (UCLA-PCI)			35	80.0				
Kobuke 2009[149]	1 year	Bowel bother score (UCLA-PCI)	36	85.3					37	92.6
Litwin 2004[156]	1 year	Mean (SE) bowel bother score (UCLA-PCI)	209	78.0 (3.2)			99	72.0 (3.2)	1276	84.0 (1.8)
Malcolm 2012[160]	1 year	Bowel bother score (UCLA-PCI)	122	99.0	81	92.0			Open: 135	Open: 91.0
									Robotic: 447	Robotic: 94.0
Hubosky 2007[52]	2 years	Mean bowel bother score (UCLA-PCI)			11	66.0				
Litwin 2004[156]	2 years	Mean (SE) bowel bother score (UCLA-PCI)	209	80.0 (4.7)			99	73.0 (3.9)	1276	83.0 (2.0)
Malcolm 2012[160]	2 years	Bowel bother score (UCLA-PCI)	122	89.0	81	93.0			Open: 135	Open: 94.0
									Robotic: 447	Robotic: 91.0
Smith 2009[184]	3 years	Mean (SD) Moderate or big bowel problems (UCLA-PCI)	58	91.1 (14.6)			123	79.8 (28.2)	Nerve sparing: 494	Nerve sparing: 90.0 (20.9)
									Non-nerve sparing: 476	Non-nerve sparing: 90.5 (18.7)

BT, brachytherapy; CRYO, cryotherapy; EORTC-QLQ-PR25, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Prostate-25 items; EPIC, Expanded Prostate Cancer Index Composite; IQR, interquartile range; N/R, not reported; RT, radiotherapy; SD, standard deviation; SE, standard error.

TABLE 83 Sexual function dichotomous outcomes

			BT			CRYO			HIFU			AS			EBRT			RP		
Study ID	**Timeline**	**Outcome**	***N***	***n***	**%**	***N***	***n***	**%**	***N***	***n***	**%**	***N***	***n***	**%**	***N***	***n***	**%**	***N***	***n***	**%**
Erectile dysfunction (ED)																				
Buron 2007[113]	6 months	ED (only for sexually active patients) (EORTC-QLQ-PR25)	308	122	39.6													127	63	49.6
Ellis 2007[129]	6 months	ED/impotence				60	22	36.7												
Koch 2007[150]	6 months	New onset severe ED (IIEF < 8)							20	4	20									
Ellis 2007[129]	1 year	ED/impotence				60	24	40												
Han 2003[139]	1 year	ED/impotence				104	83	79.8												
Sumitomo 2010[185]	1 year	ED (IIEF – 5 > 7)							129	36	27.9									
Ward 2012[202]	1 year	New-onset ED				1160	122	10.5												
Uchida 2005[191]	1.2 years	ED grade 3							72	12	16.7									
Hilton 2012[141]	1–1.5 years	Sexual activity: inactive										427	64	15						
Buron 2007[113]	1.5 years	ED (only for sexually active patients) (EORTC-QLQ-PR25)	308	85	27.6													127	42	33.1
Polascik 2007,[175] Caso 2012,[114] Caso 2012[115]	Median 1.5 years (range 3–43 months)	ED/impotence				50	3	6												
Hale 2013[138]	Mean 1.6 years (range 2–52 months)	Impotence				26	0	0												
Alemozaffar 2011[100]	2 years	ED (Expanded Prostate Cancer Index Composite, EPIC-26)	247	140	57										229	145	63	511	334	65

			BT			CRYO			HIFU			AS			EBRT			RP		
Study ID	Timeline	Outcome	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
Alemozaffar 2013[100]	2 years	ED: of those potent prior to treatment (EPIC-26)	158	59	37										121	51	42	414	248	60
Shoji 2010,[183] Uchida 2009[195]	Median 2 years (range 2–88 months)	ED							517	33	6.4									
Williams 2012[203]	Within 2 years	ED assessed using self-assessment with validated instruments	9985	2102	21.1	943	331	35.1												
Zelefsky 1999[206]	BT: median 2 years (range 12–109 months) EBRT: median 3 years (range 6–103 months)		145	28	19.3										137	32	23.4			
Poissonnier 2007[174]	Mean 2.3 years (SD 20, range 12–107 months)	Impotence (a patient is unable to penetrate his partner without pharmacological support)							227	24	10.6									
Lian 2011[154]	Median 2.5 years (range 9–56 months)	ED/impotence (IIEF)				102	25	24.5												
Chen 2009[117]	3 years	Sexual dysfunction (PCSI): intermediate and poor	75	61	81.3										150	140	93.3	105	101	96
Inoue 2011[143]	Median 3 (range 1–7) years	ED (IIEF) (defined as a score of ≤ 7 for patients who had a pretreatment IIEF-5 score of > 7)							137	22	16.1									
Smith 2009[184]	3 years	Impotence (defined as being unable to obtain an erection sufficient for sexual intercourse) (UCLA-PCI)	58	20	36.4										123	72	67.9	981	695	77.4

continued

TABLE 83 Sexual function dichotomous outcomes (*continued*)

			BT			CRYO			HIFU			AS			EBRT			RP		
Study ID	**Timeline**	**Outcome**	***N***	***n***	**%**	***N***	***n***	**%**	***N***	***n***	**%**	***N***	***n***	**%**	***N***	***n***	**%**	***N***	***n***	**%**
Onik 2008[166]	Mean 4.2 (range 2–8.8) years	ED/impotence				21	4	19												
Crook 2011[121]	5 years	Quality of erections (EPIC)	99	49	49.5													67	47	70
		None at all + not firm enough for any sexual activity + firm enough for masturbation and foreplay only																		
Mack 1997[158]	Mean 8.5 years	ED/impotence				66	6	9												
Potency																				
Ahmed 2012[99]	6 months	Erections satisfactory for penetration (IIEF)							41	29	70.7									
Giberti 2009[49]	6 months	Good erectile function (mean IIEF score of > 22)	100	49	49										100	36	36			
Robinson 2009,[179] Donnelly 2010[125]	6 months	Assisted and unassisted intercourse (UCLA-PCI)				51	5	9.8							56	24	42.9			
Tsui 2005[189]	6 months	Potency (oncologist's description)	86	23	26.7										76	11	14.5			
Maestroni 2008[159]	6–12 months	Number potent (IIEF-5: high erectile deficit score of 6–10							25	0	0									
van den Bergh 2012[198]	6 months	'Yes' response to the question 'Were you sexually active (e.g. masturbation, sexual intercourse) during the last 2 weeks?'										107	73	68	29	11	37	8	3	35
Ahmed 2012[99]	1 year	Erections satisfactory for penetration (IIEF)							41	31	75.6									

			BT			CRYO			HIFU			AS			EBRT			RP		
Study ID	Timeline	Outcome	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
Ahmed 2011[98]	1 year	Erections satisfactory for penetration (IIEF)							20	19	95									
Giberti 2009[49]	1 year	Good erectile function (mean IIEF score of > 22)	100	66	66										100	61	61			
Hilton 2012[141]	1–1.5 years	Sexual activity: intercourse										427	330	77						
Robinson 2009,[179] Donnelly 2010[125]	1 year	Assisted and unassisted intercourse (UCLA-PCI)				51	9	17.7							54	24	44.4			
Tsui 2005[189]	1 year	Potency (oncologist's description)	86	23	26.7										76	11	14.5			
van den Bergh 2012[198]	1 year	'Yes' response to the question 'Were you sexually active (e.g. masturbation, sexual intercourse) during the last 2 weeks?'										58	38	65	31	11	36	9	3	36
Pinkawa 2009[172]	Mean 1.3 years (range 12–21 months)	Erections sufficient for sexual intercourse (EPIC)	52	35	67										52	32	61			
Robinson 2009,[179] Donnelly 2010[125]	1.5 years	Assisted and unassisted intercourse (UCLA-PCI)				51	9	17.7							48	23	47.9			
Tsui 2005[189]	1.5 years	Potency (oncologist's description)	86	21	24.4										76	9	11.8			
Robinson 2009,[179] Donnelly 2010[125]	2 years	Assisted and unassisted intercourse (UCLA-PCI)				47	10	21.3							51	21	41.2			
Tsui 2005[189]	2 years	Potency (oncologist's description)	86	24	27.9										76	11	14.5			
Poissonnier 2007[174]	Mean 2.3 years (SD 20, range 12–107 months)	Potency implies a patient is able to penetrate his partner without pharmacological support							227	43	18.9									

continued

TABLE 83 Sexual function dichotomous outcomes (*continued*)

			BT			CRYO			HIFU			AS			EBRT			RP		
Study ID	Timeline	Outcome	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
Lian 2011[154]	Median 2.5 years (range 9–56 months)	Erectile function/potency (IIEF)				102	14	13.7												
Chen 2009[117]	3 years	Sexual function (PCSI): normal	75	14	19										150	12	8			
Robinson 2009,[179] Donnelly 2010[125]	3 years	Assisted and unassisted intercourse (UCLA-PCI)				45	10	22.2							50	18	36			
Tsui 2005[189]	3 years	Potency (oncologist's description)	86	9	10.5										76	9	11.8			
Colombel 2006[120]	5 years	Potency (IIEF)							242	73	30									
Crook 2011[121]	5 years	Quality of erections (EPIC) enough for intercourse	99	51	51.22													67	20	30.08
Donnelly 2002[124]	5 years	Resumption of sexual activity among the patients capable of unassisted intercourse				76	18	23.7												
Giberti 2009[49]	5 years	Good erectile function (mean IIEF score of > 22)	100	58	58										100	58	58			
Zelefsky 2011[207]	Median 6.4 (range 1–11) years	The ability to achieve an erection sufficient for sexual intercourse	448	123	27.5										281	81	28.8			

BT, brachytherapy; CRYO, cryotherapy; EORTC-QLQ-PR25, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Prostate-25 items; EPIC-26, Expanded Prostate Cancer Index Composite-26 items; PCSI, Prostate Cancer Symptom Index; SD, standard deviation.

TABLE 84 Sexual function continuous outcomes

Study ID	Timeline	Outcome as reported/defined	BT		CRYO		HIFU		Laser		AS		EBRT		RP	
			n	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score
Erectile dysfunction																
IIEF																
Ahmed 2011[98]	6 months	Mean erectile function domain (IIEF-15)					20	21.7								
Ahmed 2011[98]	6 months	Mean orgasmic function domain (IIEF-15)					20	7.1								
Ahmed 2011[98]	6 months	Mean sexual desire domain (IIEF-15)					20	6.9								
Ahmed 2011[98]	6 months	Mean intercourse satisfaction domain (IIEF-15)					20	8.5								
Ahmed 2011[98]	6 months	Mean overall satisfaction domain (IIEF-15)					20	7.4								
Lindner 2009[155]	6 months	IIEF							12	23.1						
Maestroni 2008[159]	6 months	Mean IIEF-5					3	2.75								
Mearini 2009[161]	6 months	IIEF, median (range)					160	12 (6–20)								
Shoji 2010,[183] Uchida 2009[195]	6 months	Mean (SD) IIEF (non-neoadjuvant therapy patients)					112	4 (2.65)								
Truesdale 2010,[188] Lambert 2007[152]	6 months	Mean (SD) erectile dysfunction/impotence			23	33 (20.9)										
Ahmed 2011[98]	1 year	Mean erectile function domain (IIEF-15)					20	21.8								
Ahmed 2011[98]	1 year	Mean intercourse satisfaction domain (IIEF-15)					20	7.6								
Ahmed 2011[98]	1 year	Mean orgasmic function domain (IIEF-15)					20	7.1								

continued

TABLE 84 Sexual function continuous outcomes (*continued*)

Study ID	Timeline	Outcome as reported/defined	BT		CRYO		HIFU		Laser		AS		EBRT		RP	
			n	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score
Ahmed 2011[98]	1 year	Mean sexual desire domain (IIEF-15)					20	7								
Ahmed 2011[98]	1 year	Mean overall satisfaction domain (IIEF-15)					20	7								
Ahmed 2012[99]	1 year	Median (IQR) sexual function (IIEF-15)					41	47 (29.5–63.3)								
Ahmed 2012[99]	1 year	Median (IQR) erectile function domain (IIEF-15)					41	21 (10.3–27.3)								
Ahmed 2012[99]	1 year	Median (IQR) intercourse satisfaction domain (IIEF-15)					41	8 (0–11)								
Ahmed 2012[99]	1 year	Median (IQR) orgasmic function domain (IIEF-15)					41	7 (5–8.5)								
Ahmed 2012[99]	1 year	Median (IQR) sexual desire domain (IIEF-15)					41	7 (5–8)								
Ahmed 2012[99]	1 year	Median (IQR) overall satisfaction domain (IIEF-15)					41	8 (8–9)								
Barret 2013[103]	1 year	Median (IQR) sexual function (IIEF-5)	12	14 (8–24)	50	14 (8–25)	21	14 (8–25)								
Shoji 2010,[183] Uchida 2009[195]	1 year	Mean (SD) IIEF (non-neoadjuvant therapy patients)					112	6.36 (5.37)								
Truesdale 2010,[188] Lambert 2007[152]	1 year	Mean (SD) ED			51	34 (22.6)										
Vasarainen 2012[199]	1 year	Mean (IQR) erectile function (IIEF-5)									48	19.5 (10–29)				
Shoji 2010,[183] Uchida 2009[195]	2 years	Mean (SD) IIEF (non-neoadjuvant therapy patients)					112	4.4 (5.08)								

Study ID	Timeline	Outcome as reported/defined	BT		CRYO		HIFU		Laser		AS		EBRT		RP	
			n	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score
SHIM																
Hilton 2012[141]	1–1.5 years	Mean (95% CI)										17.7 (16.9 to 18.5)				
Caso 2012,[114] Caso 2012,[115] Polascik 2007[175]	2 years	Median (range)			58	2 (1–6)										
EPIC																
Ferrer 2008,[130] Pardo 2010,[167] Guedea 2009[137]	6 months	Mean (SE) sexual domain	247	47.1 (1.7)									180	45.5 (2)	118	23.7 (1.6)
Ferrer 2008,[130] Pardo 2010,[167] Guedea 2009[137]	1 year	Mean (SE) sexual domain	255	50.5 (1.6)									184	44.1 (1.9)	121	33.8 (2.1)
Pinkawa 2009[172]	Median 1.3 years RT: range 12–21 months BT: range 12–24 months	Mean sexual function	52	61									52	60		
Ferrer 2008,[130] Pardo 2010,[167] Guedea 2009[137]	2 years	Mean (SE) sexual domain	240	49.8 (1.6)									179	43.5 (1.9)	122	33.1 (2.1)
Ferrer 2008,[130] Pardo 2010,[167] Guedea 2009[137]	3 years	Mean sexual domain	155	46									100	43.5	N/R	N/R

continued

TABLE 84 Sexual function continuous outcomes (*continued*)

Study ID	Timeline	Outcome as reported/defined	BT		CRYO		HIFU		Laser		AS		EBRT		RP	
			n	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score
Frank 2007[131]	BT: median 3.5 years EBRT: median 4.7 years RP: median 4 years	Mean (SD) sexual function	74	37.8 (27.2)									135	28 (27.9)	234	25.1 (24.5)
Crook 2011[121]	Median 5.2 years	Mean (SD) sexual domain: all patients	101	52.54 (24.06)											67	39.22 (25.35)
Crook 2011[121]	Median 5.2 years	Mean (SD) sexual domain: randomised patients	15	61.1 (25.72)											15	38.54 (28.86)
Crook 2011[121]	Median 5.2 years	Mean (SD) sexual domain: NRCS patients	84	50.91 (23.55)											52	39.43 (24.44)
EORTC-QLQ-PR25																
Giberti 2009[49]	6 months	Mean sexual function domain	85	10											89	9
Giberti 2009[49]	6 months	Mean sexual activity domain	85	11											89	10
Giberti 2009[49]	1 year	Mean sexual function domain	85	7											89	7
Giberti 2009[49]	1 year	Mean sexual activity domain	85	8											89	8
Giberti 2009[49]	2 years	Mean sexual function domain	85	8											89	7
Giberti 2009[49]	2 years	Mean sexual activity domain	85	8											89	8

Study ID	Timeline	Outcome as reported/defined	BT		CRYO		HIFU		Laser		AS		EBRT		RP	
			n	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score
UCLA-PCI score																
Hubosky 2007[52]	6 months	Sexual function domain			46	5.7										
Kobuke 2009[149]	6 months	Sexual function domain	36	33.2											37	5.5
Malcolm 2010[160]	6 months	Sexual function domain: open RP	122	49.3	81	19.2									135	27.4
Malcolm 2010[160]	6 months	Sexual function domain: robotic RP													447	24.1
Robinson 2009,[179] Donnelly 2010[125]	6 months	Sexual function domain			112	36							109	10.4		
Hubosky 2007[52]	1 year	Sexual function domain			35	5.2										
Kobuke 2009[149]	1 year	Sexual function domain (UCLA-PCI)	36	38.3											37	9.5
Malcolm 2010[160]	1 year	Sexual function domain: open RP	122	45.4	81	18.0									135	31.8
Malcolm 2010[160]	1 year	Sexual function: robotic RP													447	29.2
Robinson 2009,[179] Donnelly 2010[125]	1 year	Sexual function domain			112	35.8							105	13.5		
Robinson 2009,[179] Donnelly 2010[125]	1.5 years	Sexual function domain			111	38.6							100	16.3		
Malcolm 2010[160]	2 years	Sexual function domain: open RP	122	47.4	81	21.6									135	34.0
Malcolm 2010[160]	2 years	Sexual function domain: robotic RP													447	32.9
Robinson 2009,[179] Donnelly 2010[125]	2 years	Sexual function domain			108	38.3							106	13.9		

continued

TABLE 84 Sexual function continuous outcomes (*continued*)

Study ID	Timeline	Outcome as reported/defined	BT		CRYO		HIFU		Laser		AS		EBRT		RP	
			n	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score
Malcolm 2010[160]	3 years	Sexual function domain: open RP	122	46.7	81	16.2									135	35.5
Malcolm 2010[160]	3 years	Sexual function domain: robotic RP	122	73	81	27									447	33.6
Robinson 2009,[179] Donnelly 2010[125]	3 years	Sexual function domain			105	16							105	36.7		
Smith 2009[184]	3 years	Mean (SD) sexual function domain: nerve sparing	58	54 (25.7)									123	32 (29)	494	34.7 (27.7)
Smith 2009[184]	3 years	Mean (SD) sexual function domain: non-nerve sparing	58	54 (25.7)									123	32 (29)	476	22 (23.6)
Other																
Mohamed 2012[163]	6 months	Mean (SD) SAQ: sexual dysfunction	240	2.86 (1.07)									483	2.84 (1.02)	146	2.93 (0.73)
Talcott 2003[186]	1 year	Mean (SD) sexual function symptom index (urinary, bowel and sexual function scale)	80	42.4 (35.6)									182	65.8 (32)	129	73.7 (25.4)
Talcott 2003[186]	2 years	Mean (SD) sexual function symptom index (urinary, bowel and sexual function scale)	80	45 (33.1)									182	69.2 (32.3)	129	68.5 (27.4)
Sexual bother *UCLA-PCI score*																
Hubosky 2007[52]	6 months	Sexual bother			46	16.0										
Kobuke 2009[149]	6 months	Sexual bother	36	71.2											37	50.9
Malcolm 2010[160]	6 months	Sexual bother: open RP	122	56.0	81	48.0									135	24.1

Study ID	Timeline	Outcome as reported/defined	BT		CRYO		HIFU		Laser		AS		EBRT		RP	
			n	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score
Malcolm 2010[160]	6 months	Sexual bother (UCLA-PCI): robotic RP													447	35.3
Hubosky 2007[52]	1 year	Sexual bother			35	21.8										
Kobuke 2009[149]	1 year	Sexual bother	36	76.1											37	62.7
Malcolm 2010[160]	1 year	Sexual bother: open RP	122	50.4	81	47.2									135	34.4
Malcolm 2010[160]	1 year	Sexual bother: robotic RP													447	39.5
Malcolm 2010[160]	2 years	Sexual bother: open RP	122	62.4	81	48.8									135	44.7
Malcolm 2010[160]	2 years	Sexual bother: robotic RP													447	40.3
Malcolm 2010[160]	3 years	Sexual bother: open RP	122	68	81	40									135	49.9
Malcolm 2010[160]	3 years	Sexual bother: robotic RP													447	37.8
Smith 2009[184]	3 years	Mean (SD) sexual bother (UCLA-PCI): nerve sparing	58	66.8 (32.7)									123	57.6 (41.9)	494	34.7 (27.7)
Smith 2009[184]	3 years	Mean (SD) sexual bother (UCLA-PCI): non-nerve sparing	58	66.8 (32.7)									123	57.6 (41.9)	476	52.2 (39.7)
SAQ																
Mohamed 2012[163]	6 months	Mean (SD) SAQ: sexual bother	240	2.67 (1.25)									483	2.53 (1.21)	146	3.35 (1.16)

continued

TABLE 84 Sexual function continuous outcomes (*continued*)

Study ID	Timeline	Outcome as reported/defined	BT		CRYO		HIFU		Laser		AS		EBRT		RP	
			n	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score	*n*	Score
EPIC																
Pinkawa 2009[172]	Median 1.3 years RT: range 12–21 months BT: range 12–24 months	Mean sexual function score	52	61									52	60		
Frank 2007[131]	BT: median 3.5 years EBRT: median 4.7 years RP: median 4 years	Mean (SD) sexual bother	74	49.4 (31.9)									135	50.2 (36.7)	234	44.7 (31.8)

BT, brachytherapy; CRYO, cryotherapy; EORTC-QLQ-PR25, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Prostate-25 items; EPIC, Expanded Prostate Cancer Index Composite; IIEF, International Index of Erectile Function; N/R, not reported; RT, radiotherapy; SAQ, sexual adjustment questionnaire; SD, standard deviation; SE, standard error; SHIM, Sexual Health Inventory for Men.

TABLE 84a Sexual function continuous outcomes: laser

Study ID	Timeline	Outcome as reported/defined	*n*	Score
Lindner 2009[155]	6 months	Mean IIEF-15	12	23.1

TABLE 84b Sexual function continuous outcomes: PDT

Study ID	Timeline	Outcome as reported/defined	*n*	Score
Barret 2013[103]	1 year	Median (IQR) sexual function (IIEF-5)	23	13 (7–25)

TABLE 85 Summary of outcomes of the primary review: bowel function (dichotomous data)

Study ID	Timeline	Outcome as reported/defined	BT			CRYO			HIFU			EBRT			RP			Notes
			N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	
Bowel bother																		
Donnelly 2010[125,179]	6 months	Moderate or big problem bowel bother (UCLA-PCI)				111	8	7.3				109	17	15.6				
Donnelly 2010[125,179]	1 year	Moderate or big problem bowel bother (UCLA-PCI)				110	5	4.6				105	18	17.1				
Pinkawa 2009[172]	Median: 1.3 years EBRT: range 12–21 months BT: range 12–24 months	Mean bowel function score (EPIC)	52	1	2.0							52	6	12.0				
Donnelly 2010[125,179]	2 years	Moderate or big problem bowel bother (UCLA-PCI)				102	6	5.9				101	15	15.0				
Chen 2009[117]	3 years	Bowel problems (PCSI)	72	49	68.0							140	105	75.0	100	44	44.0	
Donnelly 2010[125,179]	3 years	Moderate or big problem bowel bother (UCLA-PCI)				98	7	7.2				97	10	10.3				
Smith 2009[184]	3 years	Moderate or big problem bowel bother (UCLA-PCI)	58	0	0.0							123	16	14.5	981	32	3.5	

Study ID	Timeline	Outcome as reported/defined	BT			CRYO			HIFU			EBRT			RP			Notes
			N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	
Bowel symptoms																		
Tsui 2005[189]	6 months	Bowel symptoms (RTOG)	55	6	11							64	8	12.5				
Tsui 2005[189]	1 year	Bowel symptoms (RTOG)	61	2	3.3							66	8	12.1				
Tsui 2005[189]	2 years	Bowel symptoms (RTOG)	42	3	7.1							67	10	14.9				
Tsui 2005[189]	3 years	Bowel symptoms (RTOG)	21	4	19.0							44	2	4.5				
Faecal continence																		
Shah 2012[164,182,201]	Median follow-up of 4.8 years	Grade ≥ 2 rectal incontinence (NCI-CTCAE v3.0)	417	1	0.3							1039	31	3.0				
Shah 2012[164,182,201]	Median follow-up after 6 months: 4.8 years	Grade ≥ 3 rectal incontinence (NCI-CTCAE v3.0)	417	0	0.0							1039	4	0.4				
Borchers 2004[109]	1 year	Stool incontinence (Kelley questionnaire and EORTC-QLQ-C30)	52		20.0										42		4.0	21% loss to follow-up (not stratified by intervention groups)
Uchida 2005[191]	Median 1.2 years (range 2–24 months)	Grade 1 stool incontinence (Japanese NCI-CTCAE v2.0)							72	1	1.0							
Buron 2007[113]	2 years	Faecal incontinence (EORTC-QLQ-PR25)	200	18	8.9										52	1	2.0	

BT, brachytherapy; CRYO, cryotherapy; EORTC-QLQ-PR25, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Prostate-25 items; EPIC, Expanded Prostate Cancer Index Composite; NCI-CTCAE v3.0, National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0; PCSI, Prostate Cancer Symptom Index.

TABLE 86 Summary of outcomes of the primary review: bowel function (continuous data)

Study ID	Timeline	Outcome as reported/defined	BT		CRYO		EBRT		RP		Notes
			n	Score	*n*	Score	*n*	Score	*n*	Score	
Bowel function (EPIC)											
Ferrer 2008[130]	6 months	Mean (SE) bowel function score (EPIC)	247	95.2 (0.6)			180	93.9 (1.0)	118	96.8 (0.9)	
Ferrer 2008[130]	1 year	Mean (SE) bowel function score (EPIC)	255	96.8 (0.6)			184	94.6 (0.8)	121	97.4 (0.9)	
Pinkawa 2009[172]	Median: 1.3 years RT: range 12–21 months BT: range 12–24 months	Mean, median (IQR) bowel function score (EPIC)	52	93.0, 96.0 (92.0–100.0)			52	89.0, 92.0 (82.0–96.0)			
Ferrer 2008[130]	2 years	Mean (SE) bowel function score (EPIC)	240	97.9 (0.3)			179	94.5 (0.9)	122	97.9 (0.7)	
Ferrer 2008[130]	3 years	Mean bowel function score (EPIC)	155	96.8			100	94.6	109	N/R	
Frank 2007[131]	BT: 3.5 years EBRT: 4.7 years RP: 4 years	Mean (SD) bowel function score (EPIC)	74	89.4 (11.5)			135	85.8 (14.2)	234	93.0 (9.0)	
Crook 2011[121]	Median 5.2 years	Mean (SD) bowel domain score (EPIC)	101	93.0 (11.6)					67	94.4 (8.9)	

Study ID	Timeline	Outcome as reported/defined	BT		CRYO		EBRT		RP		Notes
			n	Score	*n*	Score	*n*	Score	*n*	Score	
Bowel function (UCLA-PCI)											
Hubosky 2007[52]	6 months	Mean bowel function score (UCLA-PCI)			46	77.0					
Kobuke 2009[149]	6 months	Bowel function (UCLA-PCI)	36	90.7					37	90.5	
Litwin 2004[156]	6 months	Mean (SE) bowel function (UCLA-PCI)	209	79 (2.1)			99	75 (2.2)	1276	84 (1.2)	
Malcolm 2010[160]	6 months	Bowel function score (UCLA-PCI)	122	85.0	81	82.0			Open: 135 Robotic: 447	Open: 89.0 Robotic: 90.0	Of the total study population, 80% returned a follow-up questionnaire at least 12 months after treatment, 60% after at least 24 months and 40% after 36 months
Donnelly 2010[125,179]	6 months	Bowel function score (UCLA-PCI)			112	80.0	109	87.5			
Hubosky 2007[52]	1 year	Mean bowel function score (UCLA-PCI)			35	92.0					
Kobuke 2009[149]	1 year	Bowel function score (UCLA-PCI)	36	86.1					37	92.1	
Litwin 2004[156]	1 year	Mean (SE) bowel function score (UCLA-PCI)	209	78.0 (2.3)			99	76.0 (2.3)	1276	85.0 (1.3)	
Malcolm 2010[160]	1 year	Bowel function score (UCLA-PCI)	122	87.0	81	91.0			Open: 135 Robotic: 447	Open: 89.0 Robotic: 91.0	Of the total study population, 80% returned a follow-up questionnaire at least 12 months after treatment, 60% after at least 24 months and 40% after 36 months

continued

TABLE 86 Summary of outcomes of the primary review: bowel function (continuous data) (*continued*)

Study ID	Timeline	Outcome as reported/defined	BT		CRYO		EBRT		RP		Notes
			n	Score	*n*	Score	*n*	Score	*n*	Score	
Donnelly 2010[125,179]	1 year	Bowel function score (UCLA-PCI)			112	84.3	105	89.8			
Hubosky 2007[52]	2 years	Mean bowel function score (UCLA-PCI)			11	86.0					
Litwin 2004[156]	2 years	Mean (SE) bowel function score (UCLA-PCI)	209	80.0 (3.3)			99	78.0 (2.8)	1276	84.0 (1.4)	
Malcolm 2010[160]	2 years	Bowel function score (UCLA-PCI)	122	92.0	81	90.0			Open: 135 Robotic: 447	Open: 90.0 Robotic: 89.0	Of the total study population, 80% returned a follow-up questionnaire at least 12 months after treatment, 60% after at least 24 months and 40% after 36 months
Donnelly 2010[125,179]	2 years	Bowel function score (UCLA-PCI)			108	85.2	106	89.0			
Malcolm 2010[160]	3 years	Bowel function score (UCLA-PCI)	122	90.0	81	90.0			Open: 135 Robotic: 447	Open: 88.0 Robotic: 90.0	Of the total study population, 80% returned a follow-up questionnaire at least 12 months after treatment, 60% after at least 24 months and 40% after 36 months
Donnelly 2010[125,179]	3 years	Bowel function score (UCLA-PCI)			105	88.1	105	84.1			
Smith 2009[184]	3 years	Mean (SD) bowel function score (UCLA-PCI)	58	88.8 (11.5)				84.5 (15.8)	Nerve sparing: 494 Non-nerve sparing: 476	Nerve sparing: 88.1 (13.9) Non-nerve sparing: 88.5 (12.3)	

Study ID	Timeline	Outcome as reported/defined	BT		CRYO		EBRT		RP		Notes
			n	Score	*n*	Score	*n*	Score	*n*	Score	
Bowel bother (EPIC)											
Pinkawa 2009[172]	Median 1.3 years RT: range 12–21 months BT: range 12–24 months	Mean, median (IQR) bowel bother score (EPIC)	52	93.0, 100.0 (93.0–100.0)			52	87.0, 96.0 (79.0–100.0)			
Frank 2007[131]	BT: median 3.5 years EBRT: median 4.7 years RP: median 4 years	Mean (SD) bowel bother score (EPIC)	74	86.4 (16.8)			135	85.1 (19.8)	234	94.6 (10.4)	
Bowel bother (EORTC-QLQ-PR25)											
Giberti 2009[49]	6 months	Mean bowel symptoms score (EORTC-QLQ-PR25)	85	6.0					89	3.0	
Giberti 2009[49]	1 year	Mean bowel symptoms score (EORTC-QLQ-PR25)	85	4.0					89	2.0	
Giberti 2009[49]	5 years	Mean bowel symptoms score (EORTC-QLQ-PR25)	85	5.0					89	2.0	
Bowel bother (Symptom Index)											
Talcott 2003[186]	1 year	Mean (SD) bowel problems score (Symptom Index)	80	7.2 (7.1)			182	9.8 (9.8)	129	4.4 (5.9)	
Talcott 2003[186]	2 years	Mean (SD) bowel problems score (Symptom Index)	80	7.2 (8.5)			182	8.9 (9.4)	129	4.8 (6.0)	

continued

TABLE 86 Summary of outcomes of the primary review: bowel function (continuous data) (*continued*)

Study ID	Timeline	Outcome as reported/defined	BT		CRYO		EBRT		RP		Notes
			n	Score	*n*	Score	*n*	Score	*n*	Score	
Bowel bother (UCLA-PCI)											
Hubosky 2007[52]	6 months	Mean bowel bother score (UCLA-PCI)			46	73.0					
Kobuke 2009[149]	6 months	Bowel bother score (UCLA-PCI)	36	88.8					37	92.1	
Litwin 2004[156]	6 months	Mean (SE) bowel bother score (UCLA-PCI)	209	75.0 (3.0)			99	70.0 (3.1)	1276	84.0 (1.8)	
Malcolm 2010[160]	6 months	Bowel bother score (UCLA-PCI)	122	86.0	81	89.0			Open: 135 Robotic: 447	Open: 94.0 Robotic: 94.0	Of the total study population, 80% returned a follow-up questionnaire at least 12 months after treatment, 60% after at least 24 months and 40% after 36 months
Hubosky 2007[52]	1 year	Mean bowel bother score (UCLA-PCI)			35	80.0					
Kobuke 2009[149]	1 year	Bowel bother score (UCLA-PCI)	36	85.3					37	92.6	
Litwin 2004[156]	1 year	Mean (SE) bowel bother score (UCLA-PCI)	209	78.0 (3.2)			99	72.0 (3.2)	1276	84.0 (1.8)	
Malcolm 2010[160]	1 year	Bowel bother score (UCLA-PCI)	122	99.0	81	92.0			Open: 135 Robotic: 447	Open: 91.0 Robotic: 94.0	Of the total study population, 80% returned a follow-up questionnaire at least 12 months after treatment, 60% after at least 24 months and 40% after 36 months

Study ID	Timeline	Outcome as reported/defined	BT		CRYO		EBRT		RP		Notes
			n	Score	*n*	Score	*n*	Score	*n*	Score	
Hubosky 2007[52]	2 years	Mean bowel bother score (UCLA-PCI)			11	66.0					
Litwin 2004[156]	2 years	Mean (SE) bowel bother score (UCLA-PCI)	209	80.0 (4.7)			99	73.0 (3.9)	1276	83.0 (2.0)	
Malcolm 2010[160]	2 years	Bowel bother score (UCLA-PCI)	122	89.0	81	93.0			Open: 135 Robotic: 447	Open: 94.0 Robotic: 91.0	The number of returned questionnaires was not stratified by the intervention group At 12 months: 80% At 24 months: 60% At 36 months: 40%
Smith 2009[184]	3 years	Mean (SD) moderate or big bowel problems (UCLA-PCI)	58	91.1 (14.6)			123	79.8 (28.2)	Nerve sparing: 494 Non-nerve sparing: 476	Nerve sparing: 90.0 (20.9) Non-nerve sparing: 90.5 (18.7)	

BT, brachytherapy; CRYO, cryotherapy; EORTC-QLQ-PR25, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Prostate-25 items; EPIC, Expanded Prostate Cancer Index Composite; N/R, not reported; RT, radiotherapy; SD, standard deviation; SE, standard error.

TABLE 87 Summary of outcomes of the primary review: adverse events

		BT			CRYO			HIFU			EBRT			RP		
Study ID	Outcomes as reported	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
Acute genitourinary toxicity grade 3 or 4																
Eade 2008[126]	Grade 3 acute genitourinary toxicity (modified RTOG)	158	6	3.8							216	3	1.4			
Pickles 2010[171]	Grade 3 acute genitourinary toxicity (modified RTOG)	139	4	2.9							139	1	0.7			
Shah 2012[164,182,201]	Grade 3 acute genitourinary toxicity (NCI-CTCAE v3.0)	417	33	8.0							1039	42	4.0			
Wong 2009[205]	Grade 3 acute genitourinary toxicity (Mayo Clinic Arizona modification of the RTOG)	225	14	6.0							584	4	1.0			
Zelefsky 1999[206]	Grade 4 acute genitourinary toxicity (RTOG)	145	0	0.0							137	0	0.0			
Acute gastrointestinal toxicity grade 3 or 4																
Eade 2008[126]	Grade 3 acute gastrointestinal toxicity (RTOG)	158	0	0.0							216	0	0.0			
Pickles 2010[171]	Grade 3 acute gastrointestinal toxicity (RTOG)	139	0	0.0							139	0	0.0			
Shah 2012[164,182,201]	Grade $\geq$3 acute gastrointestinal toxicity (NCI-CTCAE v3.0)	417	1	0.2							1039	5	0.5			
Wong 2009[205]	Grade 3 acute gastrointestinal toxicity (Mayo Clinic Arizona modification of the RTOG)	225	0	0.0							584	3	1.0			
Bladder contracture, bladder spasm																
Koch 2007[150]	Bladder spasm							20	1	5.0						
Wong 1997[204]	Bladder contracture				71	1	1.0									
Bladder neck contracture, bladder neck stenosis																
Colombel 2006[120]	Bladder neck stenosis							242	34	14.0						
Eade 2008[126]	Bladder neck contracture	158	1	0.6												
Koch 2007[150]	Bladder neck contracture							20	0	0.0						
Sumitomo 2010[185]	Bladder neck contracture							129	13	10.1						
Wong 1997[204]	Bladder neck contracture				71	8	11.0									

Study ID	Outcomes as reported	BT			CRYO			HIFU			EBRT			RP		
		N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
Dysuria																
Shah 2012[164,182,201]	Dysuria	417	42	10.0							1039	83	8.0			
Ahmed 2011[98]	Dysuria							20	6	30.0						
Ahmed 2012[99]	Self-resolving mild–moderate dysuria							41	9	22.0						
Buron 2007[113]	Percentage of patients with increase in urinary pain over time relative to baseline	262	167	63.7										91	17	18.4
Caso 2012[114,115,175]	Dysuria				106	2	2.0									
Crook 2011[121]	Pain and burning with urination	101	5	4.9										67	1	1.6
Maestroni 2008[159]	Transient dysuria							25	3	12.0						
Pinkawa 2009[172]	Moderate or big problem from pain on urination	52	19	37.0							52	14	26.0			
Infection/inflammation																
Ahmed 2012[99]	Urinary tract infection							41	7	17.1						
Caso 2012[114,115,175]	Genitourinary infections				106	6	6.0									
Chaussy 2003[116]	Urinary tract infection							271	66	24.4						
Donnelly 2002[124]	Testicular abscess				76	1	1.3									
El Fegoun 2011[127]	Genitourinary infections							12	2	16.7						
Hale 2012[138]	Urinary tract infection				26	1	4.0									
Hubosky 2007[52]	Prostatic cavitation/persistent urinary tract infection				89	1	1.0									
Illing 2006[142]	Genitourinary infections							34	4	11.8						
Koch 2007[150]	Genitourinary infections							20	9	45.0						
Maestroni 2008[159]	Urinary tract infection							25	3	12.0						
Mearini 2009[161]	Urinary tract infection							163	1	0.6						

continued

TABLE 87 Summary of outcomes of the primary review: adverse events (*continued*)

		BT			CRYO			HIFU			EBRT			RP		
Study ID	Outcomes as reported	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
Sumitomo 2010[185]	Epididymitis							129	11	8.5						
Uchida 2005[191]	Genitourinary infections							72	11	15.3						
Williams 2012[203]	Cystitis	9985	237	2.4												
Rectal bleeding																
Buron 2007[113]	Rectal bleeding (percentage of patients with morbidity increase over time relative to baseline)	200	30	15.1										52	0	0.0
Caso 2012[114,115,175]	Blood per rectum				106	1	1.0									
Maestroni 2008[159]	Haemorrhoidal crisis							25	1	4.0						
Pinkawa 2009[172]	Bloody stools	52	6	12.0							52	7	14.0			
Shah 2012[164,182,201]	Bleeding	417	0	0.0							1039	33	3.2			
Williams 2012[203]	Rectal injury/ulcer	9985	200	2.0	943	12	1.3									
Zelefsky 1999[206]	Rectal bleeding	145	6	4.0							137	10	6.0			
Zelefsky 2011[207]	Rectal bleeding	448	23	5.1							281	4	1.4			
Rectal pain																
Caso 2012[114,115,175]	Rectal pain				160	2	1.8									
Eade 2008[126]	Proctitis	158	1	0.7							216	0	0.0			
Maestroni 2008[159]	Referred painful tenesmus caused by rectosigmoiditis							25	3	12.0						
Pinkawa 2009[172]	Painful bowel movements	52	14	27.0							52	27	52.0			
Shah 2012[164,182,201]	Proctitis or tenesmus	417	5	1.0							1039	223	21.0			
Truesdale 2010[152,188]	Rectal pain				25	0	0.0									
Williams 2012[203]	Proctitis/haemorrhage	9985	1867	18.7	943	111	11.8									

Study ID	Outcomes as reported	BT			CRYO			HIFU			EBRT			RP		
		N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
Urethral or vesical fistula																
Ahmed 2011[98]	Rectourethral fistula							20	0	0.0						
Bahn 2002[102]	Fistula				590	2	0.3									
Barrett 2013[103]	Rectourethral fistula				50	1	2.0									
Caso 2012[114,115,175]	Fistula				50	0	0.0									
Ellis 2007[129]	Rectal fistula				60	0	0.0									
Hale 2013[138]	Rectal fistula				26	0	0.0									
Han 2003[139]	Fistula				104	0	0.0									
Hubosky 2007[52]	Rectourethral fistula				89	1	1.0									
Inoue 2011[143]	Rectourethral fistula							137	0	0.0						
Koch 2007[150]	Rectourethral fistula							20	1	5.0						
Lian 2011[154]	Fistula				102	0	0.0									
Mack 2007[158]	Fistula				66	4	6.0									
Maestroni 2008[159]	Low-flow rectovesical fistula							25	1	4.0						
Mearini 2009[161]	Rectourethral fistula							163	1	0.6						
Onik 2008[166]	Fistula				21	0	0.0									
Sumitomo 2010[185]	Rectourethral fistula							129	2	1.5						
Truesdale 2010[152,188]	Fistula				25	0	0.0									
Ward 2012[202]	Fistula				1160	1	0.1									
Williams 2012[203]	Urethral fistula	9985	27	0.3												
Wong 1997[204]	Fistula				71	0	0.0									

continued

TABLE 87 Summary of outcomes of the primary review: adverse events (*continued*)

		BT			CRYO			HIFU			EBRT			RP		
Study ID	Outcomes as reported	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
Urethral sloughing																
Ahmed 2012[99]	Urinary debris							41	14	34.0						
Caso 2012[114,115,175]	Urethral sloughing				106	17	16.0									
Colombel 2006[120]	Postoperative sloughing of necrotic tissue in the prostatic fossa							242	10	4.0						
Donnelly 2002[124]	Urethral sloughing				76	3	3.9									
Hale 2013[138]	Urethral sloughing				26	0	0.0									
Han 2003[139]	Urethral sloughing				102	5	5.0									
Hubosky 2007[52]	Urethral sloughing				89	2	2.0									
Lian 2011[154]	Urethral sloughing				102	5	4.9									
Poissonnier 2007[174]	Urethral sloughing							227	20	8.8						
Wong 1997[204]	Urethral sloughing				71	27	38.0									
Urethral stricture, anastomotic urethral stricture, meatal stenosis, bladder neck stenosis																
Ahmed 2011[98]	Presphincteric stricture							20	1	5.0						
Barrett 2013[103]	Urethral stricture				50	1	2.0									
Caso 2012[114,115,175]	Meatal stenosis				106	1	1.0									
Eade 2008[126]	Urethral stricture	158	11	7.0							216	0	0.0			
El Fegoun 2011[127]	Urethral stricture							12	0	0.0						
Elliott 2007[128]	Urethral stricture	799	14	1.8	199	5	2.5				645	11	1.7	3310	277	8.4
Giberti 2009[49]	Anastomotic urethral stricture	85	2	2.0										89	6	6.5
Han 2003[139]	Urethral stricture				104	0	0.0									
Inoue 2011[143]	Grade 3b urethral stricture (Japanese NCI-CTCAE v2.0)							137	14	10.0						
Koch 2007[150]	Urethral stricture							20	0	0.0						

Study ID	Outcomes as reported	BT			CRYO			HIFU			EBRT			RP		
		N	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%
Lian 2011[154]	Urethral stricture				102	0	0.0									
Maestroni 2008[159]	Urethral stenosis							25	0	0.0						
Poissonnier 2007[174]	Bladder neck stenosis/urethral stricture							227	27	12.0						
Shah 2012[164,182,201]	Urethral stricture	417	29	7.0							1039	42	4.0			
Sumitomo 2010[185]	Urethral stricture							129	23	17.8						
Uchida 2005[191]	Urethral stricture							72	13	18.0						
Williams 2012[203]	Urethral stricture	9985	371	3.7	943	49	5.2									
Zelefsky 1999[206]	Urethral stricture	145	10	7.0							137	2	1.0			
Urinary retention																
Truesdale 2010[152,188]	Retention				25	1	4.0									
Ahmed 2012[99]	Acute urinary retention							41	1	2.0						
Barret 2013[103]	Grade 1 acute urinary retention (Clavien–Dindo)				50	4	8.0	21	5	24.0						
Caso 2012[114,115,175]	Retention/suprapubic catheter				106	4	3.7									
El Fegoun 2011[127]	Acute urinary retention							12	1	8.3						
Giberti 2009[49]	Urinary retention	85	9	10.0										89	0	0.0
Hale 2013[138]	Urinary retention				26	1	4.0									
Hubosky 2007[52]	Prolonged retention				89	4	4.0									
Koch 2007[150]	Urinary retention > 30 days							20	2	10.0						
Lian 2011[154]	Retention				102	0	0.0									
Maestroni 2008[159]	Acute urinary retention							25	2	8.0						
Shah 2012[164,182,201]	Acute urinary retention	417	63	15.0							1039	69	6.6			

continued

TABLE 87 Summary of outcomes of the primary review: adverse events (*continued*)

		BT			CRYO			HIFU			EBRT			RP		
Study ID	**Outcomes as reported**	***N***	***n***	**%**	***N***	***n***	**%**	***N***	***n***	**%**	***N***	***n***	**%**	***N***	***n***	**%**
Sumitomo 2010[185]	Grade 2 acute urinary retention (NCI-CTCAE v4.0)							129	19	14.7						
Uchida 2009[183,195]	Acute urinary retention > 14 days							326	43	13.2						
Ward 2012[202]	Retention				518	6	1.2									
Williams 2012[203]	Urinary retention	9985	831	8.3	943	198	21.0									
Zelefsky 1999[206]	Grade 3 acute urinary retention (RTOG)	145	5	3.0							137	0	0.0			

BT, brachytherapy; CRYO, cryotherapy; NCI-CTCAE v3.0, National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

TABLE 88 Summary of outcomes of the primary review: quality of life

		BT		CRYO		HIFU		AS			EBRT		RP	
Study ID	Time	*n*	Score	*n*	Score	*n*	Score	*n*	Score	SD	*n*	Score	*n*	Score
EORTC-QLQ-PR25														
Giberti 2009[49]	1 year	85	9.0										89	9.0
Giberti 2009[49]	5 years	85	8.0										89	8.0
EORTC-QLQ-C30 score														
Global health														
Borchers 2004[109]	1 year		66.0											70.0
Giberti 2009[49]	1 year	85	81.0										89	78.0
Kirschner-Hermanns 2008[145]	1 year		61.0											70.0
Giberti 2009[49]	5 years	85	82.0										89	78.0
Emotional functioning														
Borchers 2004[109]	1 year		76.0											78.0
Giberti 2009[49]	1 year	85	84.0										89	86.0
Kirschner-Hermanns 2008[145]	1 year	33	66.0										61	83.0
Robinson 2009[179]	1 year		88.3									86.8		
Robinson 2009[179]	2 years		87.3									86.3		
Robinson 2009[179]	3 years		87.3									87.3		
Giberti 2009[49]	5 years	85	82.0										89	84.0
Physical function														
Borchers 2004[109]	1 year		90.0											91.0
Giberti 2009[49]	1 year	85	90.0										89	86.0
Robinson 2009[179]	1 year		96.3									96.3		
Robinson 2009[179]	2 years		90.0									96.6		
Robinson 2009[179]	3 years		90.9									96.5		
Giberti 2009[49]	5 years	85	94.0										89	90.0
Role function														
Borchers 2004[109]	1 year		90.0											87.0
Giberti 2009[49]	1 year	85	93.0										89	90.0
Robinson 2009[179]	1 year		98.7									94.4		
Robinson 2009[179]	2 years		95.7									89.5		
Robinson 2009[179]	3 years		92.0									91.4		
Giberti 2009[49]	5 years	85	94.0										89	90.0

continued

TABLE 88 Summary of outcomes of the primary review: quality of life (*continued*)

		BT		CRYO		HIFU		AS			EBRT		RP	
Study ID	Time	*n*	Score	*n*	Score	*n*	Score	*n*	Score	SD	*n*	Score	*n*	Score
Cognitive function														
Borchers 2004[109]	1 year		86.0											86.0
Giberti 2009[49]	1 year	85	88.0										89	90.0
Robinson 2009[179]	1 year		83.6									86.6		
Robinson 2009[179]	2 years		84.3									88.2		
Robinson 2009[179]	3 years		83.4									87.0		
Giberti 2009[49]	5 years	85	88.0										89	90.0
Social function														
Borchers 2004[109]	1 year		77.0											74.0
Giberti 2009[49]	1 year	85	93.0										89	89.0
Robinson 2009[179]	1 year		87.6									89.1		
Robinson 2009[179]	2 years		87.5									87.0		
Robinson 2009[179]	3 years		87.5									88.0		
Giberti 2009[49]	5 years	85	94.0										89	89.0
Sexual function														
Borchers 2004[109]	1 year		53.0											42.0
Health function														
Robinson 2009[179]	1 year		76.9									81.1		
Robinson 2009[179]	2 years		78.3									81.3		
Robinson 2009[179]	3 years		80.9									80.3		
Fatigue score														
Giberti 2009[49]	1 year	85	19.0										89	18.0
Robinson 2009[179]	1 year		21.3									14.0		
Robinson 2009[179]	2 years		20.1									12.8		
Robinson 2009[179]	3 years		20.1									13.4		
Giberti 2009[49]	5 years	85	18.0										89	18.0
Nausea and vomiting														
Giberti 2009[49]	1 year	85	2.0										89	1.0
Robinson 2009[179]	1 year		1.2									1.2		
Robinson 2009[179]	2 years		1.4									1.4		
Robinson 2009[179]	3 years		1.0									1.0		
Giberti 2009[49]	5 years	85	1.0										89	1.0

TABLE 88 Summary of outcomes of the primary review: quality of life (*continued*)

		BT		CRYO		HIFU		AS			EBRT		RP	
Study ID	Time	*n*	Score	*n*	Score	*n*	Score	*n*	Score	SD	*n*	Score	*n*	Score
Pain score														
Giberti 2009[49]	1 year	85	8.0										89	9.0
Robinson 2009[179]	1 year		11.4									7.2		
Robinson 2009[179]	2 years		15.0									6.6		
Robinson 2009[179]	3 years		10.1									7.9		
Giberti 2009[49]	5 years	85	8.0										89	9.0
Dyspnoea score														
Giberti 2009[49]	1 year	85	10.0										89	8.0
Giberti 2009[49]	5 years	85	11.0										89	8.0
Insomnia score														
Giberti 2009[49]	1 year	85	20.0										89	23.0
Giberti 2009[49]	5 years	85	20.0										89	22.0
Appetite loss score														
Giberti 2009[49]	1 year	85	4.0										89	4.0
Giberti 2009[49]	5 years	85	4.0										89	3.0
Constipation score														
Giberti 2009[49]	1 year	85	1.0										89	4.0
Giberti 2009[49]	5 years	85	0.0										89	3.0
Diarrhoea score														
Giberti 2009[49]	1 year	85	8.0										89	6.0
Giberti 2009[49]	5 years	85	6.0										89	5.0
Financial problems score														
Giberti 2009[49]	1 year	85	2.0										89	3.0
Giberti 2009[49]	5 years	85	2.0										89	3.0
EPIC														
Hormonal domain														
Crook 2011[121]	5 years	101	93.5										67	90.0
Hormonal function score														
Ferrer 2008[130,137,167]	1 year	255	95.5								184	92.9	121	93.3
Pinkawa 2009[172]	2 years	52	92.0								52	91.0		
Ferrer 2008[130,137,167]	2 years	240	95.5								179	93.7	122	93.7
Ferrer 2008[130,137,167]	3 years	155	93.5								100	90.7	109	N/R
Hormonal bother score														
Pinkawa 2009[172]	2 years	52	92.0								52	87.0		
Patient satisfaction score														
Crook 2011[121]	5 years	101	93.6										67	76.9

continued

TABLE 88 Summary of outcomes of the primary review: quality of life (*continued*)

		BT		CRYO		HIFU		AS			EBRT		RP	
Study ID	Time	*n*	Score	*n*	Score	*n*	Score	*n*	Score	SD	*n*	Score	*n*	Score
FACT-G *Composite score*														
Ahmed 2012[99]	1 year					41	102.0							
Ahmed 2011[98]	1 year					20	101.3							
Ferrer 2008[130,137,167]	1 year	255	81.1								184	80.6	121	79.8
Lee 2001[153]	1 year	44	102.2								23	101.0	23	101.9
Uchida 2009[183,195]	1 year					326	92.6							
Uchida 2005[191]	1 year					29	46.2							
Ferrer 2008[130,137,167]	2 years	240	82.5								179	77.5	122	76.6
Uchida 2009[183,195]	2 years					326	93.5							
Physical														
Ferrer 2008[130,137,167]	1 year	255	27.2								184	26.7	121	26.1
Uchida 2009[183,195]	1 year					326	26.9							
Lee 2001[153]	1 year	44	25.3								23	25.1	23	26.3
Ferrer 2008[130,137,167]	2 years	240	26.7								179	26.1	122	25.9
Uchida 2009[183,195]	2 years					326	26.3							
Functional														
Ferrer 2008[130,137,167]	1 year	255	17.2								184	16.7	121	17.2
Uchida 2009[183,195]	1 year					326	22.9							
Lee 2001[153]	1 year	44	24.1								23	23.2	23	23.3
Ferrer 2008[130,137,167]	2 years	240	16.6								179	16.3	122	15.8
Uchida 2009[183,195]	2 years					326	23.4							
Emotional														
Ferrer 2008[130,137,167]	1 year	255	20.1								184	20.4	121	19.6
Uchida 2009[183,195]	1 year					326	22.9							
Lee 2001[153]	1 year	44	22.3								23	21.9	23	21.7
Ferrer 2008[130,137,167]	2 years	240	19.7								179	20.0	122	19.6
Uchida 2009[183,195]	2 years					326	23.4							
Social/family														
Ferrer 2008[130,137,167]	1 year	255	18.5								184	17.7	121	17.7
Uchida 2009[183,195]	1 year					326	25.9							
Lee 2001[153]	1 year	44	22.7								23	23.1	23	22.8
Ferrer 2008[130,137,167]	2 years	240	17.1								179	16.6	122	16.3
Uchida 2009[183,195]	2 years					326	25.3							
Doctor/patient relationship														
Lee 2001[153]	1 year	44	7.8								23	7.7	23	7.7

TABLE 88 Summary of outcomes of the primary review: quality of life (*continued*)

		BT		CRYO		HIFU		AS			EBRT		RP	
Study ID	Time	*n*	Score	*n*	Score	*n*	Score	*n*	Score	SD	*n*	Score	*n*	Score
FACT-P														
Composite score														
Ahmed 2012[99]	1 year					41	145.3							
Ahmed 2011[98]	1 year					20	144.2							
Ferrer 2008[130,137,167]	1 year	255	39.5								184	38.7	121	37.9
Donnelly 2002[124,177,178,180]	1 year			75	135.8									
Lee 2001[153]	1 year	44	138.5								23	136.9	23	140.4
Uchida 2009[183,195]	1 year					326	37.2							
Ferrer 2008[130,137,167]	2 years	240	38.9								179	37.5	122	37.2
Donnelly 2002[124,177,178,180]	2 years			75	140.0									
Uchida 2009[183,195]	2 years					326	35.9							
Donnelly 2002[124,177,178,180]	3 years			75	138.9									
Physical well-being														
Ahmed 2011[98]	1 year					20	27.2							
Donnelly 2002[124,177,178,180]	1 year			75	26.1									
Donnelly 2002[124,177,178,180]	2 years			75	27.0									
Donnelly 2002[124,177,178,180]	3 years			75	26.2									
Social/family well-being														
Ahmed 2011[98]	1 year					20	26.2							
Donnelly 2002[124,177,178,180]	1 year			75	23.4									
Donnelly 2002[124,177,178,180]	2 years			75	23.1									
Donnelly 2002[124,177,178,180]	3 years			75	21.7									
Emotional well-being														
Ahmed 2011[98]	1 year					20	22.6							
Donnelly 2002[124,177,178,180]	1 year			75	17.9									
Donnelly 2002[124,177,178,180]	2 years			75	18.3									
Donnelly 2002[124,177,178,180]	3 years			75	18.1									

continued

TABLE 88 Summary of outcomes of the primary review: quality of life (*continued*)

		BT		CRYO		HIFU		AS			EBRT		RP	
Study ID	Time	*n*	Score	*n*	Score	*n*	Score	*n*	Score	SD	*n*	Score	*n*	Score
Functional well-being														
Ahmed 2011[98]	1 year					20	25.5							
Donnelly 2002[124,177,178,180]	1 year			75	24.1									
Donnelly 2002[124,177,178,180]	2 years			75	25.0									
Donnelly 2002[124,177,178,180]	3 years			75	24.7									
Doctor relationship														
Donnelly 2002[124,177,178,180]	1 year			75	7.4									
Donnelly 2002[124,177,178,180]	2 years			75	7.4									
Donnelly 2002[124,177,178,180]	3 years			75	7.5									
Additional concerns (total)														
Donnelly 2002[124,177,178,180]	1 year			75	37.2									
Donnelly 2002[124,177,178,180]	2 years			75	37.6									
Donnelly 2002[124,177,178,180]	3 years			75	37.2									
FACT-P Trial Outcome Index														
Ahmed 2012[99]	1 year					41	97.5							
Prostate cancer subscale														
Ahmed 2011[98]	1 year					20	43.2							
Lee 2001[153]	1 year	44	36.3								23	35.8	23	38.6
SF-12 *Mental component*														
van den Bergh 2012[198]	1 year										70	54.8	67	55.3
Crook 2011[121]	5 years	101	44.7										67	43.2
Physical component														
van den Bergh 2012[198]	1 year										70	47.3	67	51.2
Crook 2011[121]	5 years	101	55.9										67	55.4
SF-36 *Physical component summary*														
Ferrer 2008[130,137,167]	1 year	255	52.2								184	50.9	121	52.5
Ferrer 2008[130,137,167]	2 years	240	50.9								179	49.2	122	50.6

TABLE 88 Summary of outcomes of the primary review: quality of life (*continued*)

		BT		CRYO		HIFU		AS			EBRT		RP	
Study ID	Time	*n*	Score	*n*	Score	*n*	Score	*n*	Score	SD	*n*	Score	*n*	Score
Physical function														
Ferrer 2008[130,137,167]	1 year	255	91.9								184	89.9	121	91.2
Kobuke 2009[149]	1 year	36	87.9										37	93.5
Ferrer 2008[130,137,167]	2 years	240	88.8								179	85.1	122	85.7
Role physical														
Ferrer 2008[130,137,167]	1 year	255	96.3								184	94.4	121	93.1
Kobuke 2009[149]	1 year	36	84.6										37	88.0
Ferrer 2008[130,137,167]	2 years	240	93.1								179	91.2	122	89.6
Bodily pain														
Ferrer 2008[130,137,167]	1 year	255	87.9								184	84.2	121	86.5
Kobuke 2009[149]	1 year	36	81.8										37	88.7
Ferrer 2008[130,137,167]	2 years	240	85.9								179	81.6	122	82.1
General health														
Ferrer 2008[130,137,167]	1 year	255	72.8								184	71.6	121	70.8
Kobuke 2009[149]	1 year	36	57.3										37	67.7
Ferrer 2008[130,137,167]	2 years	240	69.3								179	67.9	122	68.8
Mental component summary														
Ferrer 2008[130,137,167]	1 year	255	56.5								184	56.3	121	55.3
Ferrer 2008[130,137,167]	2 years	240	56.3								179	56.3	122	54.9
Vitality														
Ferrer 2008[130,137,167]	1 year	255	85.8								184	83.3	121	85.3
Kobuke 2009[149]	1 year	36	66.5										37	74.8
Ferrer 2008[130,137,167]	2 years	240	83.0								179	81.0	122	80.0
Social function														
Ferrer 2008[130,137,167]	1 year	255	98.0								184	96.9	121	96.0
Kobuke 2009[149]	1 year	36	84.2										37	91.6
Ferrer 2008[130,137,167]	2 years	240	98.0								179	96.5	122	95.8
Mental health														
Ferrer 2008[130,137,167]	1 year	255	88.1								184	87.5	121	87.0
Kobuke 2009[149]	1 year	36	75.7										37	82.3
Ferrer 2008[130,137,167]	2 years	240	87.0								179	85.9	122	83.6
Role emotional														
Ferrer 2008[130,137,167]	1 year	255	96.3								184	96.6	121	94.6
Kobuke 2009[149]	1 year	36	83.9										37	88.5
Ferrer 2008[130,137,167]	2 years	240	94.6								179	94.9	122	93.8

continued

TABLE 88 Summary of outcomes of the primary review: quality of life (*continued*)

		BT		CRYO		HIFU		AS			EBRT		RP	
Study ID	Time	*n*	Score	*n*	Score	*n*	Score	*n*	Score	SD	*n*	Score	*n*	Score
I-PSS-QoL														
Ahmed 2012[99]	1 year					41	1.0							
Ahmed 2011[98]	1 year					20	1.0							
Quality of life index														
Uchida 2009[183,195]	1 year					326	2.2							
Uchida 2009[183,195]	2 years					326	2.3							
Trial outcome index														
Lee 2001[153]	1 year	44	85.8								23	84.1	23	88.2
CES-D														
van den Bergh 2012[198]	1 year							129	5.4			70.0	67	7.3
STAI general anxiety measure														
van den Bergh 2012[198]	1 year							129	34.8			70.0	67	32.0
RAND-36														
Physical functioning														
Vasarainen 2012[199]	1 year							75	90.0	12.9				
Role physical														
Vasarainen 2012[199]	1 year							75	89.0	25.7				
Role emotional														
Vasarainen 2012[199]	1 year							75	88.0	29.0				
Vitality														
Vasarainen 2012[199]	1 year							75	76.0	16.0				
Mental health														
Vasarainen 2012[199]	1 year							75	81.0	14.1				
Social functioning														
Vasarainen 2012[199]	1 year							75	93.0	14.0				
Body pain														
Vasarainen 2012[199]	1 year							75	87.0	18.7				
General health														
Vasarainen 2012[199]	1 year							75	65.0	16.3				

BT, brachytherapy; CES-D, Center for Epidemiologic Studies Depression scale; CRYO, cryotherapy; EORTC-QLQ-PR25, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Prostate-25 items; EPIC, Expanded Prostate Cancer Index Composite; FACT-G, Functional Assessment of Cancer Therapy – General; FACT-P, Functional Assessment of Cancer Therapy – Prostate; I-PSS-QoL, I-PSS – quality of life; SD, standard deviation; SF-12, Short Form questionnaire-12 items; STAI, State–Trait Anxiety Inventory.

TABLE 89 Summary of outcomes of the primary review: quality of life (change score from baseline)

Study ID	Time	Outcome as reported/defined	BT		RP	
			n	Change score	*n*	Change score
EORTC-QLQ-C30 score						
Buron 2007[113]	1 year	Global health change score from baseline	194	−0.6	60	4.3
Buron 2007[113]	2 years	Global health change score from baseline	200	0.8	52	7.7
Buron 2007[113]	1 year	Emotional functioning change score from baseline	194	7	60	8.5
Buron 2007[113]	2 years	Emotional functioning change score from baseline	200	9.3	52	12.1

BT, brachytherapy.

TABLE 90 Summary of outcomes of the primary review: quality of life (change score between intervention groups)

Study ID	Time	Outcome as reported/defined	*n*	Change score (range)
AUA-SS				
Bradley 2004[110]	2 years	Total score difference between intervention groups	BT = 102 RP = 60	−3.32 (−6.67 to 0.03)

AUA-SS, American Urological Association Score; BT, brachytherapy.

Appendix 11 Data tables of the salvage review

TABLE 91 Summary of outcomes of the salvage review: efficacy

Study ID	Time	Outcome as reported/defined	Salvage CRYO			Salvage RP		
			N	*n*	%	*N*	*n*	%
Biochemical disease-free survival								
[a]Chin 2001[208]	1 year	PSA ≤ 2 ng/ml	118		71.0			
van der Poel 2008[215]	1 year	PSA ≤ 0.1 ng/ml				32		89.0
[a]Chin 2001[208]	2 years	PSA ≤ 2 ng/ml	118		61.0			
[a]van der Poel 2008[215]	2 years	PSA ≤ 0.1 ng/ml				32		79.0
[a]Chin 2001[208]	3 years	PSA ≤ 2 ng/ml	118		55.0			
[a]van der Poel 2008[215]	3 years	PSA ≤ 0.1 ng/ml				32		61.0
[a]Chin 2001[208]	4 years	PSA ≤ 2 ng/ml	118		54.0			
[a]van der Poel 2008[215]	4 years	PSA ≤ 0.1 ng/ml				32		54.0
[a]van der Poel 2008[215]	5 years	PSA ≤ 0.1 ng/ml				32		48.0
[a]van der Poel 2008[215]	6 years	PSA ≤ 0.1 ng/ml				32		37.0
[a]van der Poel 2008[215]	7 years	PSA ≤ 0.1 ng/ml				32		30.0
[a]van der Poel 2008[215]	8 years	PSA ≤ 0.1 ng/ml				32		18.0
[a]van der Poel 2008[215]	9 years	PSA ≤ 0.1 ng/ml				32		12.0
[a]van der Poel 2008[215]	10 years	PSA ≤ 0.1 ng/ml				32		12.0
[a]van der Poel 2008[215]	11 years	PSA ≤ 0.1 ng/ml				32		12.0
[a]van der Poel 2008[215]	12 years	PSA ≤ 0.1 ng/ml				32		12.0
[a]van der Poel 2008[215]	13 years	PSA ≤ 0.1 ng/ml				32		12.0
Biochemical failure								
van der Poel 2008[215]	10 years	PSA > 0.1 ng/ml				32	22	69.0
Biochemical control								
Robinson 2006[212]	1 year	PSA < 0.3 ng/ml	39	25	64.1			
Chin 2001[208]	2 years	PSA ≤ 2 ng/ml	118	65	55.0			
Robinson 2006[212]	2 years	PSA < 0.3 ng/ml	31	16	51.6			
Seabra 2009[213]	2 years	PSA < 0.2 ng/ml				38	29	76.0
Gheiler 1998[210]	3 years	PSA ≤ 4 ng/ml				30	15	50.0
Tefilli 1998[214]	3 years	PSA < 0.4 ng/ml				24	12	50.0

continued

TABLE 91 Summary of outcomes of the salvage review: efficacy (*continued*)

Study ID	Time	Outcome as reported/defined	Salvage CRYO			Salvage RP		
			N	*n*	%	*N*	*n*	%
Overall survival								
Robinson 2006[212]	2 years	Overall survival	46	43	93			
Darras 2006[209]	7 years	Overall survival				11	10	91.0
Cancer-specific death								
Neerhut 1998[211]	2 years	Cancer-specific death				16	0	0.0
Robinson 2006[212]	2 years	Cancer-specific death	46	1	2.0			
Gheiler 1998[210]	3 years	Cancer-specific death				30	0	0.0
van der Poel 2008[215]	5 years	Cancer-specific death				32	0	0.0
Darras 2006[209]	7 years	Cancer-specific death				11	1	9.0
van der Poel 2008[215]	10 years	Cancer-specific death				32	2	6.0
Reintervention								
Chin 2001[208]	2 years	Repeat cryoablation	118	7	6.0			
Robinson 2006[212]	2 years	Androgen deprivation therapy	46	7	15.2			
Darras 2006[209]	3 years	Antiandrogen monotherapy				11	1	9.0
Darras 2006[209]	3 years	Hormonal therapy and chemotherapy				11	3	27.0

CRYO, cryotherapy.
a Data were abstracted from Kaplan–Meier curves using Engauge Digitizer version 4.1 (http://digitizer.sourceforge.net/). The numbers at risk at each time point rather than *N* would be required to calculate *n*.

TABLE 92 Summary of outcomes of the salvage review: functional (dichotomous data)

Study ID	Time	Outcome as reported/defined	Salvage CRYO			Salvage HIFU			Salvage RP		
			N	*n*	%	*N*	*n*	%	*N*	*n*	%
Bowel function											
Robinson 2006[212]	12 months	Moderate or big problem with sexual function	39	13	32.3						
Robinson 2006[212]	24 months	Moderate or big problem with sexual function	31	9	29.0						
Sexual dysfunction *12 months*											
Robinson 2006[212]	12 months	Moderate or big problem with sexual function	39	27	68.8						
van der Poel 2008[215]	12 months	Erections insufficient for coitus							32	26	81.0

TABLE 92 Summary of outcomes of the salvage review: functional (dichotomous data) (*continued*)

Study ID	Time	Outcome as reported/defined	Salvage CRYO			Salvage HIFU			Salvage RP		
			N	*n*	%	*N*	*n*	%	*N*	*n*	%
24 months											
Robinson 2006[212]	24 months	Moderate or big problem with sexual function	31	16	51.9						
Seabra 2009[213]	Median 18 (range 1–36) months	ED (undefined)							42	31	74.0
Sexual function											
Robinson 2006[212]	24 months	Unassisted intercourse	46	1	2.0						
Tefilli 1998[214]	37 months	Sexually potent without any kind of treatment							24	1	4.2
Urinary continence											
van der Poel 2008[215]	12 months	Continent (no pads)							32	14	44.0
Gheiler 1998[210]	36.1 months	Continent (no pads)							30	15	50.0
Darras 2006[209]	Mean 6.9, median 5.2 years (range 27–158 months)	Complete continence (no pads)							11	5	45.0
Urinary incontinence											
12 months											
Colombel 2006[120]	15 months	Incontinence				71	5	7.0			
24 months											
Chin 2001[208]	Median 18.6 (range 3–54) months	Incontinence	118	24	20.0						
Neerhut 1998[211]	Median 20 (range 3–39) months	Persistent incontinence							16	4	25.0
Seabra 2009[213]	Median 18 (range 1–36) months	Incontinence (≥ 2 pads/day)							42	30	72.0
36 months											
Gheiler 1998[210]	36.1 months	Incontinence (use of pads)							30	15	50.0
Tefilli 1998[214]	Mean 37 months	Complete incontinence							21	9	42.9
84 months											
Darras 2006[209]	Mean 6.9, median 5.2 years (range 27–158 months)	Incontinence							11	6	55.0
Urinary function											
Robinson 2006[212]	12 months	Moderate or big problem with urinary function	39	6	14.6						
Robinson 2006[212]	24 months	Moderate or big problem with urinary function	31	3	9.7						

CRYO, cryotherapy.

TABLE 93 Summary of outcomes of the salvage review: functional (continuous data)

Study ID	Outcome as reported/defined	Time	Salvage CRYO		Salvage HIFU		Salvage RP	
			n	Score	*n*	Score	*n*	Score
Bowel function								
Robinson 2006[212]	UCLA-PCI bowel function score	12 months	39	86.0				
Robinson 2006[212]	UCLA-PCI bowel function score	24 months	31	82.0				
Sexual function								
Robinson 2006[212]	UCLA-PCI sexual function score	12 months	39	6.0				
Robinson 2006[212]	UCLA-PCI sexual function score	24 months	31	8.0				
Urinary function								
Robinson 2006[212]	UCLA-PCI urinary function score	12 months	39	55.0				
Robinson 2006[212]	UCLA-PCI urinary function score	24 months	31	58.0				

CRYO, cryotherapy.

TABLE 94 Summary of outcomes of the salvage review: adverse events

Study ID	Time	Outcome as reported/defined	Salvage CRYO			Salvage HIFU			Salvage RP		
			N	*n*	%	*N*	*n*	%	*N*	*n*	%
Anastomotic stricture/urethral and bladder neck strictures											
van der Poel 2008[215]	1 year	Urethral and bladder neck strictures							32	1	3.0
Neerhut 1998[211]	Median 20 (range 3–39) months	Anastomotic stricture							16	4	25.0
Darras 2006[209]	Mean 6.9, median 5.2 years (range 27–158 months)	Anastomotic stricture							11	2	18.0
Bladder neck contracture, bladder neck stenosis											
Colombel 2006[120]	15 months	Bladder neck stenosis				71	12	17.0			
Gheiler 1998[210]	36.1 months	Bladder neck contracture							30	5	17.0
Chin 2001[208]	Median 18.6 (range 3–54) months	Bladder neck contracture	118	2	2.0						
Darras 2006[209]	Mean 6.9, median 5.2 years (range 27–158 months)	Bladder neck contracture							11	2	18.0
Operative death											
Neerhut 1988[211]	Median 20 (range 3–39) months	Operative death							16	0	0.0
Debris sloughing											
Chin 2001[208]	Median 18.6 (range 3–54) months	Debris sloughing	118	6	5.0						
Deep-vein thrombosis											
Gheiler 1998[210]	36.1 months	Deep-vein thrombosis							30	1	3.0

TABLE 94 Summary of outcomes of the salvage review: adverse events (*continued*)

Study ID	Time	Outcome as reported/defined	Salvage CRYO			Salvage HIFU			Salvage RP		
			N	*n*	%	*N*	*n*	%	*N*	*n*	%
Grade 3 rectal complaints											
van der Poel 2008[215]	> 1 year	Grade 3 rectal complaints							32	1	3.0
Grade 4 rectal complaints											
van der Poel 2008[215]	> 1 year	Grade 4 rectal complaints							32	1	3.0
Mild acute tubular necrosis											
Neerhut 1988[211]	Median 20 (range 3–39) months	Mild acute tubular necrosis							16	1	6.0
Prolonged leakage of urine from the anastomotic site											
Neerhut 1988[211]	Median 20 (range 3–39) months	Prolonged leakage of urine from the anastomotic site							16	3	19.0
Prolonged postoperative ileus											
Gheiler 1998[210]	36.1 months	Prolonged postoperative ileus							30	1	3.0
Rectourethral fistula, rectovesical fistula											
Colombel 2006[120]	15 months	Rectourethral fistula				71	4	6.0			
Seabra 2009[213]	Median 18 (range 1–36) months	Rectovesical fistula							42	2	4.8
Chin 2001[208]	Median 18.6 (range 3–54) months	Rectourethral fistula	118	4	3.0						
Neerhut 1988[211]	Median 20 (range 3–39) months	Rectovesical fistula							16	1	6.0
Gheiler 1998[210]	36.1 months	Rectovesical fistula							30	1	3.0
Rectal injury											
Neerhut 1988[211]	Median 20 (range 3–39) months	Rectal injury							16	3	19.0
Vesico-urethral fistula beyond external sphincter											
Chin 2001[208]	Median 18.6 (range 3–54) months	Vesico-urethral fistula beyond external sphincter	118	1	1.0						
Ureteral fistula											
Gheiler 1998[210]	36.1 months	Ureteral fistula							30	1	3.0
Ureteral transection											
Neerhut 1988[211]	Median 20 (range 3–39) months	Ureteral transection							16	1	6.0
Uretero–vesical junction stricture and hydronephrosis											
Neerhut 1988[211]	Median 20 (range 3–39) months	Uretero–vesical junction stricture and hydronephrosis							16	1	6.0

CRYO, cryotherapy.

TABLE 95 Summary of outcomes of the salvage review: quality of life

Study ID	Time	Outcome as reported/defined	Salvage CRYO			Salvage RP		
			n	Score	SD	*n*	Score	SD
EORTC-QLQ-PR25								
Robinson 2006[212]	12 months	Cognitive function score	39	90.0				
Robinson 2006[212]	24 months	Cognitive function score	31	89.0				
Robinson 2006[212]	12 months	Emotional function score	39	87.0				
Robinson 2006[212]	24 months	Emotional function score	31	89.0				
Robinson 2006[212]	12 months	Fatigue score	39	17.0				
Robinson 2006[212]	24 months	Fatigue score	31	17.0				
Robinson 2006[212]	12 months	Health function score	39	78.0				
Robinson 2006[212]	24 months	Health function score	31	82.0				
Robinson 2006[212]	12 months	Nausea/vomiting score	39	4.0				
Robinson 2006[212]	24 months	Nausea/vomiting score	31	2.0				
Robinson 2006[212]	12 months	Pain score	39	17.0				
Robinson 2006[212]	24 months	Pain score	31	13.0				
Robinson 2006[212]	12 months	Physical function score	39	95.0				
Robinson 2006[212]	24 months	Physical function score	31	96.0				
Robinson 2006[212]	12 months	Role function score	39	94.0				
Robinson 2006[212]	24 months	Role function score	31	98.0				
Robinson 2006[212]	12 months	Social function score	39	85.0				
Robinson 2006[212]	24 months	Social function score	31	89.0				
FACT-G								
Tefilli 1998[214]	37 months	Physical well-being				24	21.9	5.0
Tefilli 1998[214]	37 months	Social/family well-being				24	22.6	3.6
Tefilli 1998[214]	37 months	Emotional well-being				24	16.4	2.9
Tefilli 1998[214]	37 months	Functional well-being				24	20.7	5.0
Tefilli 1998[214]	37 months	Relationship with doctor				24	7.0	1.3
Tefilli 1998[214]	37 months	FACT-G total				24	88.7	14.2

TABLE 95 Summary of outcomes of the salvage review: quality of life (*continued*)

			Salvage CRYO			Salvage RP		
Study ID	**Time**	**Outcome as reported/defined**	***n***	**Score**	**SD**	***n***	**Score**	**SD**
FACT-P								
Tefilli 1998[214]	37 months	FACT-P				24	33.3	6.4
FAIT-U								
Tefilli 1998[214]	37 months	FAIT-U				24	24.0	9.6
FACT-Total								
Tefilli 1998[214]	37 months	FACT-G total + FACT-P				24	122.0	19.2
Tefilli 1998[214]	37 months	FACT-G total + FAIT-U				24	112.7	20.5
TOI-P								
Tefilli 1998[214]	37 months	TOI-P = PWB + FWB + FACT-P				24	75.8	14.7
TOI-U								
Tefilli 1998[214]	37 months	TOI-U = PWB + FWB + FAIT-U				24	66.6	16.6

CRYO, cryotherapy; EORTC-QLQ-PR25, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Prostate-25 items; FACT-G, Functional Assessment of Cancer Therapy – General; FACT-P, Functional Assessment of Cancer Therapy – Prostate; FAIT-U, Functional Assessment of Incontinence Therapy; FWB, functional well-being; PWB, physical well-being; SD, standard deviation; TOI-P, Trial Outcome Index using FACT-P; TOI-U, Trial Outcome Index using FAIT-U.

Appendix 12 Utility table

Paper	Aims	Methods	Sample	Results
Sommers 2007[249] Decision analysis using individual patient preferences to determine optimal treatment for localised prostate cancer	Decision model for four treatments: RP, BT, EBRT and WW	TTO and 10 years of life as maximum trade-off for the following health states: ED, urinary problems, bowel problems, metastatic prostate cancer and additional four health states from a combination of first three. Side effects observed at 6, 12 and 24 months	156 people with prostate cancer of low (46.8%), medium (39.1%), high (9.6%) or unknown (4.5%) risk, who had not yet undergone treatment	*Average QALYs (figures in parentheses are 10th and 90th centiles):* UI = 0.905 (0.735–1), ED = 0.92 (0.7–1), bowel = 0.859 (0.5–1), ED plus urinary = 0.874 (0.6–1), ED plus bowel = 0.842 (0.5–1), bowel plus urinary = 0.835 (0.5–1), ED, bowel and urinary = 0.8 (0.5–1), metastatic prostate cancer = 0.65 (0.2–1)
Bayoumi 2000[244] Cost-effectiveness of androgen suppression therapies in advanced prostate cancer	Estimated cost-effectiveness of six different antiandrogen therapies for advanced prostate cancer and specified utility weights	Review of quality of life literature from the perspectives of patients and physicians. Markov model based on formal meta-analysis and literature review of economic data. Four health states: local recurrence of prostate cancer, asymptomatic distant metastases, symptomatic distant metastases, death	Base case in 65-year-old individual with clinically evident local recurrence of prostate cancer using a societal perspective over 20 years	*Utility weight (range) for quality of life:* Local recurrent disease: 0.92 (0.8–1) Distant asymptomatic disease: 0.9 (0.8–1) Distant symptomatic disease, hormone responsive: 0.8 (0.4–0.9) Distant symptomatic disease, hormone resistant: 0.4 (0.1–0.7) Adjustment for living with mild side effect: 0.85 (0.5–1)
Sandblom 2004[246] A population-based study of pain and quality of life during the year before death in people with prostate cancer	To estimate quality of life in the year before death for hormone-refractory prostate cancer	EQ-5D	To analyse quality of life in 1442 people who had died within year that the EQ-5D was distributed	Time of death (0–4 months): mean EQ-5D 0.46, VAS score of 0.45 Time of death (4–8 months): mean EQ-5D 0.52, VAS score of 0.53 Time of death (8–12 months): mean EQ-5D 0.58, VAS score of 0.57 Average (0–12 months): mean EQ-5D 0.538 (95% CI 0.461 to 0.615), VAS score of 0.54

Paper	Aims	Methods	Sample	Results
Hummel 2010[245] Intensity-modulated radiotherapy for the treatment of prostate cancer: a systematic review and economic evaluation	To determine cost-effectiveness of either IMRT or 3D-CRT for patients undergoing radical treatment for prostate cancer	Utilities calculated and adjusted from previous studies	Patients undergoing radical treatment for prostate cancer with either IMRT or 3D-CRT	Baseline utility scores for people aged 60, 70 and 80 years were 0.850, 0.813 and 0.771 respectively. These values also applied to patients who had PSA failure but no clinical progression *Utility scores for people aged 70 years:* Post radical treatment, no adverse events 0.813 Post radical treatment, GI toxicity 0.727 Clinical failure (on hormone treatment) 0.734 Hormone-refractory cancer 0.641
Ito 2010[250] Cost-effectiveness of fracture prevention in people who receive ADT for localised prostate cancer	To assess the cost-effectiveness of measuring bone mineral density before initiating ADT followed by alendronate (Fosamax®, Merck) therapy in people with localised prostate cancer via a Markov model simulating the progression of prostate cancer and the incidence of hip fracture	Utilities from previous literature	Hypothetical cohort of people aged 70 years with localised advanced or high-risk localised prostate cancer (T2c to T4N0) starting a 2-year course of ADT after radiation therapy	*Utilities for prostate cancer:* Localised disease 0.840 (range 0.630–1) from Kattan *et al.* (1997)[294] Rising PSA 0.8 (range 0.6–1) assumed value Non-castrate metastasis 0.440 (range 0.33–0.55) from Kattan *et al.* (1997)[294] Castrate metastasis 0.130 (range 0.0998–0.163) from Kattan *et al.* (1997)[294]
Kobayashi 2007[247] Prostate cancer screening strategies with rescreening interval determined by individual baseline PSA values are cost-effective	To determine whether or not prostate cancer screening strategies with rescreening intervals determined by individual baseline PSA values are cost-effective	Utilities taken from previous studies		*Utility (range):* Curable disease 0.9 (0.6–0.9) Metastatic disease 0.5 (0.3–0.6) Recurrent disease 0.7 (0.5–0.8)

Paper	Aims	Methods	Sample	Results
Korfage 2005[239] 5-year follow-up of HRQoL after primary treatment of localised prostate cancer	To determine HRQoL in people with localised prostate cancer up to 5 years after primary treatment with RP or EBRT	EQ-5D at 1 month before treatment and 6, 12 and 52 months after treatment	Followed newly diagnosed people with localised disease from 1 month until 5 years after RP ($n = 127$) or EBRT ($n = 187$)	*Mean value (SD) pre treatment and 6, 12 and 52 months after treatment* RP: 0.89 (0.15); 0.91 (0.16); 0.9 (0.17); 0.88 (0.18) EBRT: 0.81 (0.20); 0.83 (0.21); 0.82 (0.20); 0.76 (0.23)
Kattan 1997[294] A decision analysis for the treatment of clinically localized prostate cancer	To compare WW and RP for localised prostate cancer. Markov model where all patients have localised prostate cancer with no evidence of metastasis and are treated by WW or RP. Every 6 months, a percentage of patients progress to hormonal therapy-controlled metastatic disease. In subsequent 6 months, a percentage progress to hormone-refractory disease and eventual death from prostate cancer	Utilities were obtained from a previous study using TTO for living with prostate cancer managed by WW, living with metastatic prostate cancer responsive or refractory to hormonal therapy, post-treatment impotence and severe incontinence	31 people, 55–75 years of age, none of whom had been diagnosed with prostate cancer	*Utilities:* No recurrence (RP) 0.84 Living with prostate cancer (WW) 0.72 Impotence 0.69 Incontinence 0.57 Metastatic cancer 0.42 Refractory cancer 0.13
Ramsay 2012[218] Systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of laparoscopic surgery and robotic surgery for removal of the prostate in people with localised prostate cancer	This study aimed to determine the relative clinical effectiveness and cost-effectiveness of robotic RP compared with laparoscopic RP in the treatment of localised prostate cancer within the UK NHS	Utility values taken from the literature	People with clinically localised prostate cancer (cT1 or cT2)	*Utilities:* General states surveillance: Post-operative 1 year 0.9 Further cancer treatment: Biochemical recurrence 0.730 Localised recurrence 0.82 Systemic recurrence 0.420 Long-term adverse event: Bladder neck contracture 0.72 UI 0.830 ED 0.84

Paper	Aims	Methods	Sample	Results
Shimizu 2008[238] Factors associated with variation in utility scores among patients with prostate cancer	To assess the effects of age, comorbidity and disease-specific functions on utility scores derived from three methods on prostate cancer	TTO and EQ-5D	323 prostate cancer outpatients in three institutions in Japan. Patients receiving RP, EBRT, BT, primary hormonal therapy, WW or a combination of these for localised prostate cancer and patients with hormone-refractory prostate cancer were included in the study	Utility value for all patients with prostate cancer: 0.9 (SD 0.15)
Svatek 2008[295] Cost-effectiveness of prostate cancer chemoprevention: a quality of life-years analysis	To evaluate the cost-effectiveness of chemoprevention utilising a quality-of-life adjustment	Utilities taken from previous studies	People with and without prostate cancer	*Utility (SD):* Lower urinary tract symptoms after treatment 0.05 Post prostatectomy NED: Gleason score of 2–5: 0.16 (0.06) Gleason score of 6: 0.18 (0.06) Gleason score of 7: 0.19 (0.06) Gleason score of 8–10: 0.29 (0.06) PSA recurrence (asymptomatic metastases) 0.33 (0.06) Symptomatic metastases 0.75 (0.06) Impotence 0.11 (0.10) Incontinence 0.17 (0.10)

Paper	Aims	Methods	Sample	Results
Stewart 2005[240] Utilities for prostate cancer health states in people aged 60 and older	To elicit utilities for health states associated with prostate cancer and its treatment	Standard gamble for 19 health states associated with prostate cancer or its treatment. The 19 health states were then combined and used to assess four main health states	162 people aged 60 years and older (including 52% with prostate cancer)	*Utilities:* Cancer with 20% chance of spread: 0.84 Cancer with 40% chance of spread: 0.81 Cancer with 75% chance of spread: 0.71 Spread asymptomatic: 0.67 Metastatic cancer: 0.25
Zeliadt 2005[241] Lifetime implications and cost-effectiveness of using finasteride to prevent prostate cancer	To estimate the lifetime implications of daily treatment with finasteride (Propecia®, Merck) following the results of the PCPT	Previous studies using the health utilities index	A cohort of people aged 55 years who initiate preventative treatment with finasteride	Prostate cancer (all grades): disutility 0.055
Krahn 1994[242] Screening for prostate cancer: a decision-analytic view	To determine the clinical and economic effects of screening for prostate cancer with PSA, TRUS and DRE	Utilities for chronic health states were elicited for scenarios describing impotence, incontinence and metastatic disease using TTO	Utilities were elicited from a group of 10 physicians, including urologists, radiation oncologists and internists	*Utilities:* Complete impotence 0.92 Partial impotence 0.95 Complete incontinence 0.61 Partial incontinence 0.81 Urethral obstruction 0.80 Metastatic disease 0.58

ADT, androgen deprivation therapy; BT, brachytherapy; GI, gastrointestinal; NED, no evidence of disease; PCPT, Prostate Cancer Prevention Trial; SD, standard deviation; TTO, time trade-off; VAS, visual analogue scale; WW, watchful waiting.

Appendix 13 Detailed breakdown of costs

TABLE 96 Intensity-modulated radiotherapy

IMRT	Resource description	Resource use per patient	Time (hours)	Hourly rate (£)	Cost per patient (£)
1	Patient referred to clinical oncology outpatient appointment	Consultant-led outpatient appointment		159	159
2	Scheduling	Radiographer – band 6	0.4	18.49	4.62
	Appointment	Administrator – band 2	0.4	9.37	2.34
3	Imaging				
	CT scanner	CT scan			92
		Radiographer – band 5	0.3	14.72	4.91
		Radiographer – band 6	0.3	18.49	6.16
	MRI scanner	MRI scan			199
		Radiographer – band 5	0.5	14.72	7.36
		Radiographer – band 6	0.5	18.49	9.25
4	Pre-planning preparation				
	Data preparation	Dosimetrist – band 5	0.4	14.72	3.68
	Volume and organ at risk definition	Dosimetrist – band 7	0.75	22.17	16.63
5	Plan development and administration	Dosimetrist – band 6	2	18.49	36.98
6	Plan data checking	Dosimetrist – band 6	0.75	18.49	13.87
7	Plan acceptance	Consultant clinical oncologist	0.5	157	78.5
8	Patient-specific QA				
	Plan transfer to phantom	Physicist – band 7	0.5	22.17	11.09
	Measurement on linear accelerator	Physicist – band 7	0.6	22.17	14.63
	Analysis of results	Physicist – band 7	0.5	22.17	11.09
	Independent MU calculation	Dosimetrist – band 6	0.3	18.49	6.16
9	Final preparation of data	Radiographer – band 6	0.4	18.49	4.62
	Linear accelerator-based preparation	Radiographer – band 6	0.16	18.49	3.08
		Radiographer – band 6	0.16	18.49	3.08
10	Initial verification session	Radiographer – band 6	0.5	18.49	9.25
		Radiographer – band 5	0.5	14.72	7.36
	Course of treatment – 37 treatments				
11	Patient set up	Radiographer – band 5	3.1	14.72	45.63
		Radiographer – band 6	3.1	18.49	57.32

continued

TABLE 96 Intensity-modulated radiotherapy (*continued*)

IMRT	Resource description	Resource use per patient	Time (hours)	Hourly rate (£)	Cost per patient (£)
12	Imaging of patient	Radiographer – band 6	3.1	18.49	57.32
		Radiographer – band 6	3.1	18.49	57.32
13	Image analysis	Radiographer – band 6	3.1	18.49	57.32
		Radiographer – band 6	3.1	18.49	57.32
14	Treatment delivery	Radiographer – band 5	3.1	14.72	45.63
		Radiographer – band 6	3.1	18.49	57.32
15	Offline image analysis	Radiographer – band 6	3.1	18.49	57.32
16	Treatment outpatient clinics	Follow-up outpatient appointments	3 per course	113	339
17	Treatment administration over course of treatment	Radiographer – band 6	2.5	18.49	46.23
18	Completion of course administration	Administrator – band 3	0.16	10.88	1.74
		Administrator – band 2	0.4	9.37	3.75
19	Capital costs				
	OMS		per course		6.66
	OMS maintenance contract		per course		1.86
	TPS		per course		14.39
	TPS maintenance contract		per course		1.65
	Linear accelerator		per course		852.85
	Linear accelerator maintenance contract		per course		43.29
Total					2508.58

CT, computerised tomography; MU, monitor unit; OMS, oncology management system; QA, quality assessment; TPS, treatment planning system.

TABLE 97 Intensity-modulated radiotherapy: adjuvant + salvage

IMRT: adjuvant + salvage	Resource description	Resource use per patient	Time (hours)	Hourly rate (£)	Cost per patient (£)
1	Patient referred to clinical oncology outpatient appointment	Consultant-led outpatient appointment		159	159
2	Scheduling	Radiographer – band 6	0.4	18.49	4.62
	Appointment	Administrator – band 2	0.4	9.37	2.34
3	Imaging				
	CT scanner	CT scan			92
		Radiographer – band 5	0.3	14.72	4.91
		Radiographer – band 6	0.3	18.49	6.16
	MRI scanner	MRI scan			199
		Radiographer – band 5	0.5	14.72	7.36
		Radiographer – band 6	0.5	18.49	9.25
4	Pre-planning preparation				
	Data preparation	Dosimetrist – band 5	0.4	14.72	3.68
	Volume and organ at risk definition	Dosimetrist – band 7	0.75	22.17	16.63
5	Plan development and administration	Dosimetrist – band 6	2	18.49	36.98
6	Plan data checking	Dosimetrist – band 6	0.75	18.49	13.87
7	Plan acceptance	Consultant clinical oncologist	0.5	157	78.5
8	Patient-specific QA				
	Plan transfer to phantom	Physicist – band 7	0.5	22.17	11.09
	Measurement on linear accelerator	Physicist – band 7	0.6	22.17	14.63
	Analysis of results	Physicist – band 7	0.5	22.17	11.09
	Independent MU calculation	Dosimetrist – band 6	0.3	18.49	6.16
9	Final preparation of data	Radiographer – band 6	0.4	18.49	4.62
	Linear accelerator-based preparation	Radiographer – band 6	0.16	18.49	3.08
		Radiographer – band 6	0.16	18.49	3.08
10	Initial verification session	Radiographer – band 6	0.5	18.49	9.25
		Radiographer – band 5	0.5	14.72	7.36
	Course of treatment – 33 treatments				
11	Patient set up	Radiographer – band 5	2.75	14.72	40.48
		Radiographer – band 6	2.75	18.49	50.85
12	Imaging of patient	Radiographer – band 6	2.75	18.49	50.85
		Radiographer – band 6	2.75	18.49	50.85

continued

TABLE 97 Intensity-modulated radiotherapy: adjuvant + salvage (*continued*)

IMRT: adjuvant + salvage	Resource description	Resource use per patient	Time (hours)	Hourly rate (£)	Cost per patient (£)
13	Image analysis	Radiographer – band 6	2.75	18.49	50.85
		Radiographer – band 6	2.75	18.49	50.85
14	Treatment delivery	Radiographer – band 5	2.75	14.72	40.48
		Radiographer – band 6	2.75	18.49	50.85
15	Offline image analysis	Radiographer – band 6	2.75	18.49	50.85
16	Treatment outpatient clinics	Follow-up outpatient appointments	3 per course	113	339
17	Treatment administration over course of treatment	Radiographer – band 6	2.5	18.49	46.23
18	Completion of course administration	Administrator – band 3	0.16	10.88	1.74
		Administrator – band 2	0.4	9.37	3.75
19	Capital costs				
	OMS		per course		6.66
	OMS maintenance contract		per course		1.86
	TPS		per course		14.39
	TPS maintenance contract		per course		1.65
	Linear accelerator		per course		761
	Linear accelerator maintenance contract		per course		38.61
Total					2356.46

CT, computerised tomography; OMS, oncology management system; QA, quality assessment; TPS, treatment planning system.

TABLE 98 Brachytherapy

Brachytherapy	Resource description	Resource use per patient	Time (hours)	Hourly rate (£)	Cost per patient (£)
1	Pre treatment				
	Clinical oncologist outpatient appointment	Clinical oncologist outpatient clinic			159
	Urinary flow study and transrectal ultrasound	Urology outpatient clinic – nurse led			104
2	Planning session. Formal theatre volume study – day case	Theatre session			258
		Urologist	1	172	172
		Oncologist	1	157	157
		Physicist – band 8a	2	26.44	52.88
3	Prostate brachytherapy plan created	Consultant urologist	0.4	172	43
		Physicist – band 8a	0.4	26.44	6.61
		Physicist – band 8a	2	26.44	52.88

TABLE 98 Brachytherapy (*continued*)

Brachytherapy	Resource description	Resource use per patient	Time (hours)	Hourly rate (£)	Cost per patient (£)
4	Implantation procedure	2 × brachytherapy physicist technicians – band 7	2	22.17	44.34
		I-125 seeds (Eckert and Ziegler BEBIG GmbH, Berlin)			3088
		Needles: £402 per box of 50, and 28 per patient			225
		Brachyballoon			44.5
		Brachydrape			15.5
		Brachy grid			78
		18Fr three-way catheters			6.34
		Theatre session			516
		Urologist	2	172	344
		Oncologist	2	157	314
		2 × medical physicist brachytherapy technicians – band 7	4	22.17	88.68
		Radiographer – band 7	2	22.17	44.34
5	Postimplant MRI and CT scan	1-night length of stay			321
		CT scan			92
		Radiographer – band 6	0.5	18.49	9.25
		MRI scan			199
		Radiographer – band 6	0.5	18.49	9.25
6	Quality assessment post implant	Dosimetrist – band 6	0.5	18.49	9.245
		Physicist – band 8a	1	26.44	26.44
		Consultant oncologist	0.4	157	39.25
		Physicist – band 8a	0.4	26.44	6.61
7	Outpatient follow-up	Outpatient clinical 6 weeks following implant			94
		PSA test			6.56
8	Capital costs	Ultrasound scanner			106.18
		Ultrasound probe			
		Isocord® needle rack (Eckert and Ziegler BEBIG GmbH, Berlin)			
		Isostrand® cutting fixture (Eckert and Ziegler BEBIG GmbH, Berlin)			
		TPS (VariSeed™ 8.0.2 TPS)			
		VariSeed™ module image fusion/coregistration			
		Electrometer			
		Chamber			
		TPS maintenance cost			23.76
Total					6756.615

CT, computerised tomography; TPS, treatment planning system.

TABLE 99 Cryotherapy

Cryotherapy	Resource description	Resource use per patient	Cost item required	Time (hours)	Hourly rate (£)	Cost per patient (£)
1	Pre treatment	Consultant-led urology outpatient	Outpatient appointment			129
		Nurse-led urology outpatient				47
		Bowel preparation	Sodium picosulphate (Picolax®, Ferring Pharmaceuticals) – two sachets			3.39
2	Procedure	Prostate ice rods	Prostate ice rods			4000
		Argon × 2	Argon × 2			87
		Helium × 1	Helium × 1			234
		Leg bag × 1	Leg bag × 1			6
		Suprapubic catheter	Suprapubic catheter			13.21
		Suture	Suture			2.5
		Dressings × 3	Dressings × 3			3.5
		Sensor wire	Sensor wire			20
		Bladder syringe	Bladder syringe			0.6
		Catheter bag	Catheter bag			1.25
		Brachyballoon	Brachyballoon			35
		Methylene	Methylene			14
		Saline bag	Saline bag			2.5
		Camera drape	Camera drape			2.49
		Cystoscopy tray	Cysto tray			4.15
		Urology tray	Urology tray			6.08
		12° lens	12° lens			3.95
		Consultant oncologist	Consultant oncologist (1.5 hours)	1.5	157	235.5
		Theatre session				904.7
3	Post procedure	Length of stay: 2 nights	2 nights, £250 per night			500
4	Post discharge	District nurse visit				38
		Consultant-led urology outpatient				94
5	Capital costs	Cryo machine (200 patients)				19.48
Total						6407.3

TABLE 100 High-intensity focused ultrasound

HIFU	Resource description	Resource use per patient	Time (hours)	Hourly rate (£)	Cost per patient (£)
1	Staff costs	Consultant urologist (international trainer and expert)	3	150	450
		Senior registrar (in theatre)	3	40	120
		Specialist registrar (ward review)	0.5	40	20
		Senior house officer (ward review)	0.5	30	15
		Clinical nurse specialist (teach CISC, remove SPC)	1	30	30
2	Theatre costs	HIFU	2	895.6275	1791.26
		Cystoscopy and SPC insertion	0.25	895.6275	223.91
3	Ward stay costs	Length of stay 1 night based on 20% of patients			78.56
4	Consumables costs	Swabs			
		Mepore® dressing (Molnlycke Health Care Limited, Bedfordshire)			
		Urethral and suprapubic catheter			
		Suprapubic trocar			
		50-ml syringe			
		Catheter bag			
		Leg bag			
		Flip-flow valve			
		Self-catheterisation catheter supplies			
		HIFU water			
		HIFU compressed gas			
		Total consumables costs			200
5	Capital costs	Maintenance costs	1	454.6690625	454.67
		Cost of Visual-Ice® cryoablation system			199
		% overheads			288.34
6	Imaging costs	MRI		199	199
		Radiographer – band 6	0.5	18.49	9.24
		TRUS		199	199
Total					4277.98

CISC, clean, intermittent self-catheterisation; SPC, suprapubic catheter.

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