

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

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Scientific summary

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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:

- primary ablative treatment of localised prostate cancer compared with AS, RP or EBRT
- 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 (NRCs) (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.

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