Partial ablation versus radical prostatectomy in intermediate-risk prostate cancer: the PART feasibility RCT

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Scientific summary

The PART feasibility RCT

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Scientific summary

Prostate cancer prevalence and incidence in the UK

Prostate cancer (PCa) is the most common cancer in men in the UK and the second most common cause of cancer deaths in males (accounting for 13% of such deaths) after lung cancer. In 2014, 46,690 new cases of PCa were diagnosed and 11,287 men died from the disease. The lifetime risk of men being diagnosed with PCa is one in eight. Incidence is increasing with wider use of prostate-specific antigen (PSA) testing in asymptomatic men in the community setting and an ageing UK population.

Diagnosis of prostate cancer

Prostate cancer is currently diagnosed following serum PSA testing, imaging in the form of multiparametric magnetic resonance imaging (mpMRI) scans and prostate biopsies.

Although PCa can be lethal, most men who are diagnosed with PCa will not suffer clinically significant consequences from the disease during their lifetime. Currently, opportunistic PSA testing leads to overdetection and overtreatment and places an increasing burden on the NHS.

Treatment options for localised prostate cancer

A number of conventional treatment options are available to men with clinically localised PCa, including active monitoring (AM) (also known as active surveillance), radical prostatectomy (RP), radical radiotherapy and brachytherapy. Localised PCa is stratified into low-, intermediate- and high-risk PCa depending on its potential to progress and metastasise with lethal outcomes. The stratification is determined by grading, staging and PSA values, but remains imperfect because of emerging knowledge of the genomic diversity of the disease. It is, however, accepted clinical practice, recommended by the National Institute for Health and Care Excellence (NICE) and most international guidelines, that most men with low-risk, low-volume disease be offered an AM programme as first-line treatment, whereas men with intermediate- and high-risk PCa are usually offered active radical therapeutic options.

The recently published National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme-funded ProtecT (Prostate testing for cancer and Treatment) trial investigated the treatment effectiveness of the three conventional treatment options for men with localised PCa. The trial randomised 1643 men with localised PCa to AM ($n = 545$), RP ($n = 553$) or radiotherapy ($n = 545$) and 10-year median follow-up data are available. No significant difference was found between these treatment options in terms of prostate-cancer-specific or all-cause mortality. However, radical treatments reduced progression to metastases or locally advanced disease by approximately 50% compared with AM. Patient-reported outcome measures (PROMs) showed consistent side-effect patterns related to radical treatments (effects on erectile function, urinary incontinence associated with surgery and bowel symptoms associated with radiotherapy), substantiated by further recent observational studies that explored contemporary radical treatments such as robot-assisted laparoscopic RP, intensity-modulated radiation therapy (IMRT) and brachytherapy.

Much of the decision-making process that currently governs PCa treatment is, therefore, largely based on the 'trade-off' that patients need to make between the oncological benefits of interventions and the side effects of radical treatments. The only randomised controlled trial (RCT) of focal therapy compared vascular-targeted photodynamic therapy (VTP) with AM in men with low-risk PCa, and found a reduction in positive biopsies in the treated men compared with the men who received AM. However, it could be argued that these men did not require active treatment in the first place and that the study cohort was not

optimal because it excluded intermediate-risk PCa. To our knowledge, there have been no RCTs comparing the treatment effectiveness of partial prostate ablation in unilateral, clinically localised intermediate-risk PCa with that of the current default position, which is for these men to be offered radical treatments that carry substantial side effects, as demonstrated by the ProtecT trial and contemporary observational studies. It is therefore imperative to investigate whether or not alternative treatment options with fewer side effects can offer similar oncological outcomes in men with intermediate-risk, clinically localised PCa; this is the rationale for this feasibility study with a view to proceed to a full RCT.

Alternatives to conventional treatments

Alternative, minimally invasive interventions (MIIs) [partial ablation (PA) or focal therapy] have been developed in an attempt to reduce the treatment burden associated with radical treatment and thereby improve the quality of life (QoL) of patients, while retaining at least equivalent cancer control. MIIs aim to reduce morbidity by lowering the chance of damage to the neurovascular bundles responsible for erectile function, and to the urinary continence mechanism, and may help to avoid the psychological morbidity and anxieties associated with surveillance, which often drive men to select radical treatments inappropriately. With the increasing incidence of clinically localised PCa, demand for these less aggressive, organ-sparing treatments is expected to increase, but robust validation through high-quality RCTs is needed to determine their comparative clinical effectiveness and cost-effectiveness before adoption in routine NHS clinical practice.

Examples of alternative technologies include high-intensity focused ultrasound (HIFU), cryotherapy, VTP, radiofrequency interstitial tumour ablation (RITA), laser photocoagulation and irreversible electroporation. These technologies are at different stages in their evaluation and application to clinical practice and are subject to rapid evolution, with frequent new developments to improve energy delivery, targeting, safety and imaging. Use of PA depends on accurately assessing the location and grade of the disease in the prostate using imaging and biopsies.

Using alternative technologies to target and treat all clinically significant prostate cancers focally, with careful follow-up and repeat treatments as necessary, may obviate the need for any radical therapies and is an attractive option for men with localised PCa. These technologies are now being used as primary ablative therapy in several centres worldwide, without robust Phase III RCT validation. Timely new evidence from the NIHR HTA PROstate MRI Imaging Study (PROMIS) investigating mpMRI in the diagnostic pathway for PCa will now allow accurate assessment of the location and grade of PCa using imaging and biopsies.

Implications for research

The demand for and use of PA in clinically significant prostate cancer is expanding but this is not supported by high-quality evidence of clinical effectiveness or cost-effectiveness because of a lack of relevant RCTs. A number of systematic reviews conclude that these alternative technologies have not been evaluated with sufficient reliability to inform their utilisation within the NHS. The lack of RCT-based evidence means that the true clinical effectiveness and cost-effectiveness of these treatments have not been established in order for NICE and other similar bodies globally to make robust recommendations, and highlights the urgent need for primary research. Efforts should focus on conducting rigorous, high-quality, randomised studies comparing partial and radical treatments, with long-term follow-up. Outcomes should include assessment of cancer-specific dysfunction and patient-reported measures of health-related quality of life (HRQoL), as well as economic evaluations to inform economic modelling.

The NIHR HTA feasibility study reported here was therefore developed and conducted in order to inform a full, definitive RCT. RP was selected in the radical treatment arm to allow comparisons of radiological and pathological staging accuracy in the randomised cohort and ease of determination of treatment failure. HIFU was selected as the most practicable PA comparator in the feasibility stage. At the time of the

design of this study, a HTA synthesis review suggested that HIFU was also the most likely treatment to be considered cost-effective when assessed against threshold values for a cost per quality-adjusted life-year (QALY) that society might be willing to pay.

This feasibility study set out to assess recruitment and randomisation rates and test trial processes and data capture methods. The potential barriers to recruitment are particularly pronounced in surgical trials in which the treatments offered are markedly different in terms of short- to medium-term side-effect profiles and of unknown benefit in terms of recurrence and long-term overall and cancer-specific mortality; therefore, a QuinteT Recruitment Intervention (QRI) was included in the study design to systematically identify and address barriers to recruitment.

Objectives

- To assess the feasibility of a RCT of HIFU versus RP for intermediate-risk, clinically localised PCa by recruiting and randomising 80 patients.
- To undertake a QRI to understand recruitment challenges for this trial and inform optimal recruitment strategies for a main RCT.
- To collect data on QoL and resource use to inform power calculations for the proposed main trial.
- To explore data capture methods and the feasibility of such methods to inform power calculations and a health economic evaluation for a main RCT.

Methods

Design

A prospective, non-blinded, multicentre, feasibility study was conducted to inform the design and conduct of a future RCT, involving a QRI to understand recruitment challenges.

Setting

Five secondary and tertiary NHS referral centres in England, representing large hospitals with specialist urology clinics.

Participants

Men referred to the clinics from community screening, a general practitioner or another health-care professional and subsequently diagnosed with unilateral, intermediate-risk, clinically localised PCa and who are fit for intervention with RP or PA of the prostate using HIFU.

Inclusion criteria

- Men with unilateral clinically significant intermediate-risk PCa or dominant unilateral clinically significant intermediate-risk and small contralateral low-risk disease:
  - Gleason score of 7 (3 + 4 or 4 + 3)
  - high-volume Gleason score of 6 (> 4-mm cancer core length)
  - PSA level of $\leq$ 20 ng/ml
  - clinical stage $\leq$ T2b disease.
- Life expectancy of $\geq$ 10 years.
- Fit, eligible and normally destined for radical surgery.
- No concomitant cancer.
- No previous treatment of their PCa.
- An understanding of the English language sufficient to receive written and verbal information about the trial, its consent process and the study questionnaires.

Exclusion criteria

- Unfit for radical surgery.
- Significant bilateral disease.
- Low-risk disease (Gleason score of ≤ 6, PSA level of 10 ng/ml).
- High-risk disease (Gleason score of ≥ 8, PSA level of > 20 ng/ml).
- Clinical T3 disease (extracapsular PCa).
- Men who have received previous active therapy for PCa.
- Men with evidence of extraprostatic disease.
- Men with an inability to tolerate a transrectal ultrasound.
- Men with a latex allergy.
- Men who have undergone a transurethral resection of the prostate (TURP) for symptomatic lower urinary tract symptoms during the previous 6 months.
- Metal implants/stents in the urethra.
- Prostatic calcification and cysts that interfere with effective delivery of HIFU.
- Men with renal impairment and a glomerular filtration rate (GFR) of < 35 ml/minute/1.73 m^2.
- Unable to give consent to participate in the trial, as judged by the attending clinicians.

Interventions

Participants received either (1) RP involving open, laparoscopic or robot-assisted surgery to remove the entire prostate gland and seminal vesicles or (2) HIFU using ultrasound energy focused by an acoustic lens to cause focal tissue damage as a result of thermal coagulative necrosis and acoustic cavitation. HIFU is delivered via a transrectal approach and is the ablative technology used for the partial ablation arm of this feasibility study.

Participants were randomised on a 1 : 1 basis, stratified by age, baseline Gleason score, PSA level and whether or not they had unilateral clinically significant intermediate-risk PCa or dominant unilateral clinically significant intermediate-risk and small contralateral low-risk PCa.

Key outcome measures

- Recruitment and randomisation of men to RP or HIFU (the target was set at 80 randomised participants).
- Findings of the QRI.
- Assessment of data capture methods, including collection and completeness of case report forms (CRFs), PROMs and resource use diaries at baseline and at 3, 6, 9, 12, 18, 24, 30 and 36 months, in line with routine clinical follow-up schedules.

Results

Five centres were opened to recruitment between January and November 2015: (1) Churchill Hospital, Oxford; (2) Royal Hallamshire Hospital, Sheffield; (3) Southampton General Hospital, Southampton; (4) Basingstoke and North Hampshire Hospital, Basingstoke; and (5) University College Hospital, London.

The QRI identified aspects of good practice, in relation to organisational challenges, that would improve recruitment. Particular challenges were raised regarding the availability of HIFU in some centres and strong patient treatment preferences. Clinicians' initial concerns about eligibility and equipoise also needed to be addressed and 'tips' were provided about ways to discuss randomisation and patient preferences. The recruitment rate increased from 1.4 patients per month during the period of January to November 2015 to 4.5 patients per month during the period of December 2015 to March 2017, with target recruitment achieved in all but one centre. There was evidence of changes in how recruiters discussed the study with patients, as suggested by the QRI, although it is difficult to identify the particular impact of the QRI on improving recruitment as distinct from other contributions.

Eighty-seven patients consented to participate by 31 March 2017 and 82 participants were randomised by 4 May 2017. Of the 82 participants randomised, 41 were allocated to RP and 41 were allocated to HIFU. At the time of data extraction on 10 October 2017, full treatment data were available for 71 participants. Participant characteristics were similar at baseline.

The most common reason for declining participation in the trial was strong treatment preference. RP was the most common treatment preference: 51 patients (22% of screened eligible patients) declined to participate in the trial and chose RP. Twenty-seven patients (11%) opted for AM, 11 (5%) opted for brachytherapy, 21 (9%) opted for radiotherapy, one (0.4%) opted for cryotherapy and 25 (10.5%) opted for HIFU. Only one participant withdrew consent after randomisation.

The return rate of the clinical CRFs and PROMs was 95% and 90.5%, respectively (excluding the patient resource use diaries). Analyses of EuroQol-5 Dimensions, five-level version (EQ-5D-5L), utility scores were limited by small numbers but highlight potential health gains for participants receiving HIFU compared with RP, with evidence suggesting that HIFU is unlikely to result in a loss in health benefit relative to RP.

Health-related quality of life outcomes relating to urinary and sexual functions were better in the HIFU group than in the RP group, but no significant differences were observed in overall HRQoL between the two groups.

In terms of safety, five serious adverse events (SAEs) were reported, two of which were suspected unexpected SAEs, and all of which were reported to the sponsor and the Research Ethics Committee (REC).

Conclusions

This study has demonstrated that it is feasible to recruit and retain participants in a trial of HIFU compared with RP, and that barriers to recruitment can be overcome. The QRI highlighted the need for training and support for recruiters and identified a number of key lessons that are likely to be important for recruitment if the study progresses to a main trial.

Although not powered to assess the clinical effectiveness of HIFU treatment compared with RP, because the Partial prostate Ablation versus Radical prosTatectomy (PART) trial was a feasibility study, the HRQoL outcomes are concordant with previous observational studies that suggest that, over the short to medium term, HRQoL outcomes are better in patients treated with HIFU than in those treated with RP. An indication of a trend towards better HRQoL and utility with PA adds to the clear need to undertake a full RCT to determine clinical effectiveness and cost-effectiveness.

There is a continuing lack of evidence to inform any clear recommendations on the use of PA therapies in current clinical practice. A full, definitive RCT comparing radical treatment with PA in clinically localised intermediate-risk PCa, incorporating a range of PA therapies that adequately reflects the treatment options offered throughout the NHS, is now more relevant and urgent than ever to address this substantial unmet need in the management of this increasingly common disease.

Trial registration

This trial is registered as ISRCTN99760303.

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