Active monitoring, radical prostatectomy and radical radiotherapy in PSA-detected clinically localised prostate cancer: the ProtecT three-arm RCT

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Declared competing interests of authors: Malcolm Mason reports personal fees from Sanofi (Paris, France), Bayer (Leverkusen, Germany) and Janssen Pharmaceutica (Beerse, Belgium) outside the submitted work. Derek Rosario reports grants from Bayer and personal fees from Ferring Pharmaceuticals (Saint-Prex, Switzerland) outside the submitted work. Jane Blazeby was a member of the following during the project: National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Clinical Trials and Evaluation Committee (2009–2013), HTA NIHR Obesity (2010–2012), Commissioning Board for HTA Surgery Themed Call Board and the NIHR Clinical Trials Unit (CTU) Standing Advisory Committee (2015–2019). Jenny Donovan was a member of the following during the project: HTA Commissioning Board (2006–12), Rapid Trials and Add-on Studies Board (2012), NIHR Senior Investigator panel (2009–12) and NIHR Health Services and Delivery Research board (Deputy Chairperson) (2010–11). Freddie C Hamdy was a member of the following during the project: HTA Commissioning Board (2007–12) and HTA Surgery Themed Call Board (2012–13). J Athene Lane was a member of the following during the project: CTUs funded by NIHR (2017 to present). Chris Metcalfe was a member of the following during the project: CTUs funded by NIHR (2010 to present). Tim Peters was a member of the following during the project: HTA Medicines for Children Themed Call (2005–6) and NIHR CTU Standing Advisory Committee (2008–14). John Staffurth reports support for travel to conferences and attendance on an advisory board from Bayer. Emma L Turner reports grants from Cancer Research UK (London, UK) during the conduct of the study.

Published August 2020
DOI: 10.3310/hta24370

Scientific summary

The ProtecT three-arm RCT

Health Technology Assessment 2020; Vol. 24: No. 37
DOI: 10.3310/hta24370

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Prostate cancer is the most common cancer among men in the UK. In 2014, there were 46,610 new cases of prostate cancer and 11,287 men died from the disease. Incidence rates are projected to rise by 12% between 2014 and 2035, to 233 cases per 100,000 males by 2035. Men's lifetime risk of prostate cancer is one in eight, and, although it is often overtreated, many men are undertreated. It is estimated that there were 330,000 men living with prostate cancer in the UK in 2015, expected to rise to around 830,000 by 2040.

Although prostate cancer can be lethal, the majority of men diagnosed through prostate-specific antigen testing will not suffer significant consequences during their lifetime, and evidence that treating such men improves survival or quality of life is weak. Consequently, there are concerns that increasing prostate-specific antigen testing results in overdetection, overtreatment and an increasing burden on the NHS. Prostate cancer continues to be under-researched and a limited number of studies are addressing the issues of screening and long-term comparison of treatment modalities. There have been few studies of the longer-term impact on quality of life of the major treatments for localised prostate cancer.

Conventional treatment options are available for clinically localised prostate cancer, including active monitoring/active surveillance, radical prostatectomy, radical radiotherapy and brachytherapy. A man trying to decide whether or not to be tested for prostate cancer needs information to answer the following critical questions:

- Is he at risk of harbouring aggressive prostate cancer, and will the prostate-specific antigen test help him to find out?
- Does he need immediate radical treatment, or can he receive active monitoring safely?
- If he needs radical treatment, what is the most suitable intervention, and what is the impact of each treatment on immediate and long-term quality of life?
- If he develops progressive disease, what is the long-term 'trade-off' between the benefits of treatments in preventing progression but greater short- and medium-term side effects of the radical interventions compared with active monitoring, and the longer-term impact on quality of life of treatments for progressing disease, or freedom from treatment?

The Prostate testing for cancer and Treatment (ProtecT) study has set out to address these questions.

Objectives

- To evaluate the comparative treatment effectiveness of the three conventional options for men with clinically localised prostate cancer (i.e. active monitoring, radical prostatectomy and radical radiotherapy).
- To assess quality-of-life measures and patient-reported outcomes related to the three treatment options.
- To inform patients, clinicians and policy-makers about the optimal management of patients with clinically localised prostate cancer.
- To develop a comprehensive biorepository of biobanked material donated by patients, associated with an electronic clinic-pathological database for conducting effective translational prostate cancer research.

Design

This research involved a prospective programme of prostate-specific antigen testing in primary care, with prostate check clinics run by research nurses. Men with a raised prostate-specific antigen level of ≥ 3 ng/ml were invited to secondary care and offered a transrectal ultrasound-guided biopsy protocol. Men with clinically localised prostate cancer were offered randomisation to active monitoring, radical prostatectomy or radical radiotherapy. Patient-reported outcomes were measured at baseline and follow-up. End points at the 10-year median follow-up were reported as clinical outcomes and 6-year full patient-reported outcome measures. All men diagnosed with prostate cancer were followed up in an extended comprehensive cohort design.

Setting

A total of 337 primary care centres were randomised to the Prostate testing for cancer and Treatment (ProtecT) trial in nine major cities in the UK; urology departments managed men with the diagnosis of prostate cancer, offered randomisation to those eligible with clinically localised disease and provided their allocated or selected treatment.

Participants

The participants were men aged 50–69 years: 228,966 were invited, 82,849 were recruited, 8846 received biopsies, 2896 were diagnosed with prostate cancer, 2664 were eligible and 1643 with clinically localised prostate cancer were randomised.

Clinical outcome measures and statistical analysis

The primary outcome measure was definite or probable prostate cancer mortality, including intervention-related deaths, at a median follow-up point of 10 years.

Secondary outcomes included all-cause mortality, metastases (by imaging or prostate-specific antigen levels of > 100 µg/l), clinical disease progression (metastases, T3/T4 disease, initiation of long-term androgen deprivation therapy, ureteric obstruction, rectal fistulae and the need for a urinary catheter owing to local tumour growth), primary treatment failure and treatment complications. Primary treatment failure following radical prostatectomy was defined as a prostate-specific antigen level of ≥ 0.2 µg/l 3 months post surgery; following radical radiotherapy, radical radiotherapy OG-ASTRO (Radiation Therapy Oncology Group – American Society for Radiation Oncology) Phoenix Consensus Conference recommendations were used.

A prespecified statistical analysis plan was developed. The primary outcome of mortality due to prostate cancer or its treatment was compared between the three allocated treatment groups on an intention-to-treat basis using Cox's proportional hazards regression adjusted for study centre, age at baseline, Gleason score and prostate-specific antigen level at baseline. The prostate cancer-specific mortality rate was presented with 95% confidence intervals for each allocated treatment group, and pairwise significance tests were planned if a test of an equal 10-year disease-specific mortality risk across all three groups yielded a p-value of < 0.05. This conditional approach keeps the overall false positive rate at 5%.

Patient-reported outcome measures and statistical analysis

Patient-reported outcome measures were prespecified secondary outcomes, collected by validated patient-reported outcome measures in four key domains:

1. urinary function and quality-of-life impact, including urinary incontinence and lower urinary tract symptoms, measured using the International Consultation on Incontinence Questionnaire, International Continence Society male Short-Form and Expanded Prostate Cancer Index Composite
2. sexual function and quality-of-life impact, including erectile function, measured using the Expanded Prostate Cancer Index Composite
3. bowel function and quality-of-life impact, including loose/bloody stools and incontinence, measured using the Expanded Prostate Cancer Index Composite
4. health-related quality of life, comprising –

    i. generic health status, measured using the Short Form questionnaire-12 items
    ii. anxiety/depression, measured using the Hospital Anxiety and Depression Scale
    iii. cancer-related quality of life, measured using the EORTC-QLQ Q30 (European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30 module).

Study questionnaires were completed at baseline (at biopsy, before knowledge of diagnosis), at 6 and 12 months after randomisation and annually thereafter. The International Continence Society male Short-Form, Short Form questionnaire-12 items and Hospital Anxiety and Depression Scale were included throughout; the International Consultation on Incontinence Questionnaire was added from 2001 and the Expanded Prostate Cancer Index Composite was added from 2005. As it concerned cancer-related quality of life, the EORTC-QLQ Q30 (European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30 module) was included at year 5 only. Patient-reported outcome measures were scored and analysed as recommended by the authors of the assessments, with key items identified to aid interpretation of clinical relevance.

Analyses were by intention to treat, with summary statistics and 95% confidence intervals by randomised group. Multilevel models were employed to accommodate correlations between repeated measurements and to test for treatment differences in follow-up assessments, and included covariates for the variables stratified by or minimised in the random allocation: age at baseline, prostate-specific antigen level at baseline, Gleason score and study centre. Baseline patient-reported outcome measures were not included as a covariate as Expanded Prostate Cancer Index Composite and International Consultation on Incontinence Questionnaire scores were not available for all men at baseline. Patient-reported outcome measure data indicated that the allocated groups were comparable at baseline.

Results

Of 1643 men randomised, 545 were allocated to active monitoring, 553 were allocated to radical prostatectomy and 545 were allocated to radical radiotherapy. Following randomisation, 482 men (88%) assigned to active monitoring, 391 (71%) to radical prostatectomy and 405 (74%) to radical radiotherapy received the allocated treatment within 9 months. Over 85% of men assigned to radical radiotherapy or radical prostatectomy received a radical intervention. Of the 545 men assigned to active monitoring, 290 received a radical treatment by the end of November 2015 (Kaplan–Meier estimate 54.6%, 95% confidence interval 50.2% to 59.2%). Of those 290 men, 142 (49%) received radical prostatectomy (37 within 9 months of allocation), 97 (33%) received radiotherapy as per protocol (17 within 9 months of allocation), 22 (8%) received brachytherapy (two within 9 months of allocation), 26 (9%) received non-protocol radiotherapy and three (1%) received high-intensity focused ultrasound beyond 9 months from allocation.

Of the 391 men who underwent radical prostatectomy within 9 months of allocation, nine (2%) had a prostate-specific antigen level of 0.2 µg/l or higher between 31 and 183 days following surgery; five of those men received salvage radical radiotherapy and one received long-term androgen deprivation therapy within 1 year of surgery. A further nine men received adjuvant radical radiotherapy within 1 year of surgery because of pT3 disease ($n = 8$) or positive surgical margins ($n = 7$). pT3 disease was present in 114 of the 391 men (29%), and 93 (24%) had a positive surgical margin. Four of 280 patients (1%) who received lymphadenectomy had lymph node involvement. Of the 405 men who started radical radiotherapy within 9 months of allocation, 55 (14%) had a prostate-specific antigen level increase of ≥ 2 ng/ml above the nadir following radical radiotherapy. Of those 55 men, three received salvage radical prostatectomy, 14 started long-term androgen deprivation therapy and one underwent high-intensity focused ultrasound.

Prostate cancer and all-cause mortality

There were seven definite prostate cancer-specific deaths and one probable prostate cancer-specific death in the active monitoring group, three definite and two probable prostate cancer-specific deaths in the radical prostatectomy group and four definite prostate cancer-specific deaths in the radical radiotherapy group. Prostate cancer-specific survival was > 98.8% in all groups, and there was no difference between the three randomised groups (log-rank test $p = 0.48$). The hazard ratio of prostate cancer-specific mortality for the radical radiotherapy group was 0.45 (95% confidence interval 0.14 to 1.47) compared with the active monitoring group and 0.80 (95% confidence interval 0.22 to 2.99) compared with the radical prostatectomy group; the hazard ratio of prostate cancer-specific mortality for the radical prostatectomy group compared with active monitoring was 0.56 (95% confidence interval 0.19 to 1.67). Subgroup analyses showed no evidence of any subgroup modifying the relative effectiveness of the three treatments in terms of prostate cancer mortality. All-cause deaths were evenly distributed across the treatment groups (likelihood ratio test $p = 0.87$).

Disease progression

A total of 204 men showed progression including distant metastases, which was higher in the active monitoring group than in the radical prostatectomy and radical radiotherapy groups (active monitoring = 112, radical prostatectomy = 46 and radical radiotherapy = 46; $p < 0.001$). Evidence of disease progression included the presence of metastases (active monitoring = 33, radical prostatectomy = 13 and radical radiotherapy = 16; $p = 0.004$), or clinical T3 or T4 disease (active monitoring = 79, radical prostatectomy = 24 and radical radiotherapy = 21), or initiation of long-term androgen deprivation therapy (active monitoring = 47, radical prostatectomy = 26 and radical radiotherapy = 30), with evidence of more than one criterion for some men.

Treatment complications

There were no deaths related to radical prostatectomy; nine men suffered thromboembolic or cardiovascular events, 14 required more than 3 units of blood transfused, one suffered a rectal injury and nine required intervention for anastomotic problems. There were three deaths unrelated to prostate cancer within 90 days of completing radical radiotherapy and no cases of radiation toxicity requiring major intervention.

Numbers needed to treat

From these data, compared with active monitoring, 178 and 137 men would need to be treated with radical prostatectomy and radical radiotherapy, respectively, in order to avoid one prostate cancer death; 27 and 33 men would need to be treated with radical prostatectomy and radical radiotherapy, respectively, to avoid one patient progressing to metastases; and nine men would need to be treated by either radical prostatectomy or radical radiotherapy to avoid one patient developing clinical disease progression.

Patient-reported outcomes

Follow-up response rates were > 80% for all patient-reported outcome measures, without decline over time.

Domain A: urinary function and quality-of-life impact

All measures of urinary incontinence showed the greatest impact in the radical prostatectomy group at 6 months, with some recovery, although urinary incontinence remained worse in the radical prostatectomy group than in the radical radiotherapy and active monitoring groups at all time points. Urinary incontinence rates were similar and little affected in the radical radiotherapy and active monitoring groups, with a worsening in the active monitoring group over time. Pad use increased from 1% at baseline to 47% in the radical prostatectomy group, compared with 4% in the active monitoring group and 5% in the radical radiotherapy group at 6 months. By year 6, 18% of men in the radical prostatectomy group used pads, compared with 10% in the active monitoring group and 3% in the radical radiotherapy group. There was a greater impact on quality of life in the radical prostatectomy group for 2 years, but this improved to become similar to active monitoring and radical radiotherapy. Levels of voiding lower urinary tract symptoms were a little worse in the radical radiotherapy group at 6 months, but then returned to be close to baseline levels and became similar to levels in the radical prostatectomy and active monitoring groups. Urinary frequency remained similar across the groups, with nocturia increasing in all groups at 6 months, particularly in the radical radiotherapy group, but recovering and returning closest to baseline in the radical prostatectomy group.

Domain B: sexual function and quality-of-life impact (including erectile function)

Erectile function reduced for all men at 6 months, with clear differences between the groups ($p < 0.001$). At baseline, 67% of participants reported erections firm enough for intercourse, but by 6 months this reduced to 50% in the active monitoring group, 24% in the radical radiotherapy group and 11% in the radical prostatectomy group. Erectile function remained worse in the radical prostatectomy group at all time points, with some recovery over 2 years but further decline to 15% at 6 years, compared with recovery followed by decline to 29% in the radical radiotherapy group and a gradual year-on-year decline in the active monitoring group.

Domain C: bowel function and quality-of-life impact

Bowel function and bother and the impact of bowel habits on quality of life were unchanged in the radical prostatectomy and active monitoring groups, but were worse in the radical radiotherapy group, particularly at 6 months (see *Figure 15*, parts a, b and f, and *Table 23*). Rates of faecal incontinence and loose stools were similar across the groups, but bloody stools were experienced more in the radical radiotherapy group from year 2 onwards (see *Figure 15*, part e) ($p < 0.001$). Bowel bother and quality-of-life impact scores were a little worse in the radical radiotherapy group.

Domain D: health-related quality of life

There were no differences between the groups in physical and mental health subscores in the generic health measure Short Form questionnaire-12 items, in anxiety or depression according to the Hospital Anxiety and Depression Scale or on any of the symptom or function scales of the EORTC-QLQ Q30 (European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30 module) at year 5.

Economic evaluation

The economic evaluation showed that from a NHS perspective active monitoring was less costly than the radical treatments. At the National Institute for Health and Care Excellence threshold of £20,000 per quality-adjusted life-year, the probabilities that each arm was the cost-effective option were 58% (radical radiotherapy), 32% (active monitoring) and 10% (radical prostatectomy).

Conclusions

To our knowledge, Prostate testing for cancer and Treatment (ProtecT) is to date the only randomised controlled trial comparing treatment effectiveness of radical prostatectomy, radical radiotherapy and active monitoring in clinically localised prostate cancer. At a median follow-up point of 10 years, there were no differences in disease-specific and all-cause mortality between the groups. Radical treatment reduced disease progression by approximately 50% compared with active monitoring; 55% of men receiving active monitoring moved to a radical treatment and 44% remained disease free and avoided the side effects of treatments. Patient-reported outcome measure analysis at the full 6-year follow-up demonstrated side-effect profiles of individual treatments, with surgery causing urinary incontinence and erectile symptoms, some of which persisted throughout the 6 years, and radiotherapy causing some erectile and bowel symptoms. Most symptoms did not return to baseline levels. Men receiving active monitoring had general decline in their urinary and sexual function with age and increased number of radical treatments. Quality of life, anxiety and depression were not different between the groups.

Longer follow-up is under way to investigate whether or not survival and disease progression will be affected in the longer term (15 years).

Implications for health care

- At an average follow-up point of 10 years, radical treatment of prostate-specific antigen-detected prostate cancer does not improve disease-specific or overall survival in men aged 50–69 years with clinically localised disease.
- Radical treatment reduces the risk of metastases and local progression by half compared with active monitoring.
- Radical treatments have a distinct side-effect profile.
- Men with clinically localised prostate cancer need to weigh the trade-off between possible oncological benefits and side effects of radical treatments compared with additional risk of metastases but fewer side effects with active monitoring.

Recommendations for further research

- Longer follow-up is essential to investigate the potential benefits of radical treatments for survival as well as the impact of the initial treatments and development of metastatic disease on men's quality of life.
- Translational research is essential to distinguish between lethal and non-lethal prostate cancer at diagnosis.
- The diagnostic pathway for prostate cancer needs to be developed further to avoid overdetection of low-risk disease as well as to optimise the diagnosis of lethal cancers.

Trial registration

This trial is registered as ISRCTN20141297.

Funding

This project was funded by the National Institute for Health Research Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 24, No. 37. See the National Institute for Health Research Journals Library website for further project information.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.370

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics Science Citation Index.

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 96/20/99. The contractual start date was in June 2001. The draft report began editorial review in March 2018 and was accepted for publication in November 2018. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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