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Patient-reported outcomes 12 years after treatment for localized prostate cancer

Jenny L Donovan PhD FMedSci[1#*], Freddie C Hamdy FRCS(Urol) FMedSci[2*], J Athene Lane PhD[1,3*], Grace J Young MSc[1,3*], Chris Metcalfe PhD[1,3*], Eleanor I Walsh MSc[1], Michael Davis BSc, MSc[1], Thomas Steuart-Feilding BA[1], Jane M Blazeby FRCS(Gen Surg) FMedSci[1], Kerry N.L. Avery PhD[1], Richard M Martin BMBS, PhD[1], Prasad Bollina MBBS, FRCS(Urol),[4] Andrew Doble MS FRCS(Urol),[5] Alan Doherty FRCS(Urol)[6], David Gillatt MS, FRCS(Urol)[7], Vincent Gnanapragasam (FRCS, PhD) [8], Owen Hughes [9], Roger Kockelbergh DM, FRCS(Urol) [10], Howard Kynaston MD, FRCS(Urol)[9], Alan Paul MD, FRCS(Urol)[11], Edgar Paez FRCS(Urol)[12], Phillip Powell MD FRCS[12], Derek J Rosario MD, FRCS(Urol) [13], Edward Rowe MD, FRCS(Urol)[14], Malcolm Mason MD, FRCR[15], James WF Catto PhD, FRCS(Urol)[13,16], Tim J Peters PhD FMedSci[1], Julia Wade PhD[1], Emma L Turner PhD[1], Naomi J Williams PhD,[1] Jon Oxley MD, FRCPath[17], John Staffurth MBBS, MD[18], Richard J Bryant, PhD FRCS(Urol)[2], David E Neal CBE, FMedSci[2,8*] and the ProtecT study group[§]

[*]Equal contributions.

[§] See appendix

[#] Corresponding Author:
Jenny L Donovan
Population Health Sciences
Bristol Medical School
Bristol
United Kingdom
Email: jenny.donovan@bristol.ac.uk

[1] Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK
[2] Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK
[3] Bristol Trials Centre, University of Bristol, UK
[4] Department of Urology and Surgery, Western General Hospital, University of Edinburgh, UK
[5] Department of Urology, Addenbrooke's Hospital, Cambridge, UK
[6] Department of Urology, Queen Elizabeth Hospital, Birmingham, UK
[7] Department of Urological Oncology and Robotic Surgery, Macquarie University, Sydney, Australia
[8] Division of Urology, Department of Surgery, and Cambridge Urology Translational Research and Clinical Trials Office, Cambridge, UK
[9] Department of Urology, Cardiff and Vale University Health Board, Cardiff, UK
[10] Department of Urology, University Hospitals of Leicester, Leicester, UK
[11] Department of Urology, Leeds Teaching Hospitals NHS Trust, Leeds, UK
[12] Department of Urology, Freeman Hospital, Newcastle upon Tyne, UK
[13] Academic Urology Unit, University of Sheffield, Sheffield, UK
[14] Department of Urology, Southmead Hospital and Bristol Urological Institute, Bristol, UK
[15] School of Medicine, University of Cardiff, Cardiff, UK
[16] Academic Urology Unit, Medical School, University of Sheffield, Sheffield, UK
[17] Department of Cellular Pathology, North Bristol NHS Trust, Bristol, UK
[18] Division of Cancer and Genetics, School of Medicine, Cardiff University, Cardiff, UK

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Abstract

BACKGROUND

Long-term patient-reported outcomes are needed to inform treatment decisions for localized prostate cancer. Follow-up of 1643 randomized participants in the Prostate-Testing-for-Cancer-and-Treatment (ProtecT) trial was continued to provide extended profiles of impact from prostatectomy, radiotherapy-with-neoadjuvant androgen-deprivation, and active-monitoring.

METHODS

Validated patient-reported outcome measures assessing impacts on urinary, bowel, and sexual function, generic and disease-specific quality-of-life were completed annually from 7 to 12 years. Data were analyzed according to randomized groups using random effects linear and logistic models.

RESULTS

Response rates exceeded 80% for most measures. There were sustained differences between the randomized groups over 7-12 years for urinary and sexual symptoms/bother ($p \leq 0.008$) and some bowel symptoms, but not in generic quality-of-life ($p \geq 0.32$). Urinary leakage continued to affect the prostatectomy group most, with 18-24% requiring pads over 7-12 years compared with 9-11% in the active monitoring group and 3-8% in the radiotherapy group ($p < 0.001$). The prostatectomy group also reported the worst sexual/erectile function: 18% had erections sufficient for intercourse at 7 years compared with 30% in the active monitoring group and 27% in the radiotherapy group. All groups converged to similarly low levels of potency by year 12. Urinary voiding and nocturia were better in the prostatectomy group than the other groups. Fecal leakage affected twice as many in the radiotherapy group (12%) compared with the other groups (6%) by year 12. The active monitoring group experienced gradual age-related declines in sexual and urinary function, avoiding radical treatment harms unless they changed management.

CONCLUSIONS

This long-term follow-up of ProtecT randomized participants provides robust evidence about the continued effects of treatments on aspects of urinary, sexual, and bowel function through 12 years, as reported directly by patients. These effects, comparable to those observed in short-term observational cohorts of contemporary treatments, provide extended and detailed long-term profiles of patient-reported treatment harms to be considered alongside the risks of prostate cancer progression/spread in the context of low prostate cancer-specific mortality over 15 years. Providing clarity about the short-, medium-, and longer-term trade-offs between treatment benefits and

harms will enable better-informed and prudent treatment decisions by men newly diagnosed with localized prostate cancer.

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[348 words, 350 max]

Introduction

Most men diagnosed with low- or intermediate-risk clinically localized prostate cancer can expect to live 15 years or longer after diagnosis.[1] Robust evidence is therefore needed about the harms of treatment modalities on sexual, urinary, and bowel function as well as quality-of-life over the short, medium, and long term to inform decision-making. Accurate information about treatment effects is critical to avoid later regret about treatment decisions.[2,3] Patients newly diagnosed with localized prostate cancer need to choose their initial treatment after weighing up the risks of adverse effects of treatments against the risks of cancer progression and low likelihood of dying of prostate cancer.[1] The U.K. National Institute for Health and Care Research–supported Prostate-Testing-for-Cancer-and-Treatment (ProtecT) trial compared prostatectomy (mostly open retropubic), radiotherapy (external-beam, 74 Gray in 37 fractions with neoadjuvant androgen-deprivation), and active monitoring (surveillance with six-monthly prostate-specific antigen - PSA - tests and annual clinical review). ProtecT participants completed PROMs (patient-reported outcome measures) annually. The primary analysis provided evidence that each treatment strategy produced a distinct profile of impact on sexual, urinary, and bowel function and related quality-of-life at six years, without differences between the groups in overall physical or mental health.[4]

Treatments have evolved since ProtecT participants were treated (2001-2009), but major studies initiated to evaluate treatments received in 2010-14 (including robot-assisted prostatectomy, active surveillance, intensity-modulated radiotherapy, brachytherapy) confirmed similar adverse-effect profiles up to three or five years following intervention[5-9] compared with the ProtecT six-year PROMs.[4] The ProtecT trial provides the only randomized comparison of the impacts of major treatment modalities, free of the selection biases that cannot be eradicated from cohort studies. Here we present the comprehensive range of PROMs completed annually by ProtecT trial participants over 7-12 years post-randomization, to show how the effects of prostatectomy, radiotherapy, and active monitoring continue over time and thus enable better informed treatment decisions.

Methods

ProtecT trial participants and PROMs

ProtecT trial recruitment methods, baseline, and pre-specified PROMs outcomes up to six years were published previously.[4,10,11] In brief, following population-based PSA testing and 10-core biopsy under ultrasound guidance, 1,643 participants with clinically localized prostate cancer were randomized between 2001-2009: 545 to active monitoring, 553 to prostatectomy, and 545 to radiotherapy (treatment details given above).[12] PROMs, completed annually, were scored and

analyzed according to a pre-specified analysis plan[13] in four key domains, as shown in Table 1 and described previously.[4] Measures used were: International Consultation on Incontinence Questionnaire (ICIQ),[14] International Continence Society male Short-Form (ICS*male*SF),[15] Expanded Prostate Index Composite (EPIC),[16] Medical Outcomes study Short-Form (SF-12),[17] Hospital Anxiety and Depression Scale (HADS),[18] and European Organization for Research and Treatment of Cancer Core questionnaire (EORTC-QLQ C30).[19] Some measures/items were added after study inception or removed from later versions to reduce respondent burden (Fig.S1).

Statistical analyses

Current analyses extend the previous 0-6-year findings[4] to 7-12 years. Participants were analyzed according to their original randomized allocation, with summary statistics presented by randomized group. Two-level random effects models were employed with each participant as the higher level and repeated measurements at the lower level to accommodate intra-individual correlations between the repeated measures. Two-level linear and logistic models with normal random effects distributions were used for continuous and binary responses. For each outcome, evidence against the null hypothesis of no difference across the three allocated groups in post-randomization means (or odds for binary outcomes) over 7-12 years' follow-up, was evaluated by Wald's/likelihood ratio tests. All models included covariates for the variables stratified by, or minimized in, the random allocation: age, and long-transformed PSA at baseline (continuous variables), Gleason score, and study center (dummy variables). Baseline measures were not included as covariates since some questionnaires were introduced after the study started. PROMs were comparable at baseline across allocated groups.[11] Missing data were not imputed. Participants with at least one post-randomization measure were included in the longitudinal analyses, and the random effects models provided unbiased estimates of treatment comparisons under the assumption that data were missing at random.

Secondary analyses included pre-specified subgroup analyses examining the relative treatment effects for key PROMs and whether these differed by age (<65 vs. ≥65 years) and risk-stratification groups (low vs. intermediate/high) at baseline. An exploratory analysis investigated the impact of receiving a radical treatment at any time on sexual function and urinary leakage compared with remaining on active monitoring in the active monitoring group. Stata version 17.0 was used for analyses.

Results

Completion of study questionnaires exceeded 80% for most measures and timepoints (Table 2). By 7 years, 249/545 (46%) in the active monitoring group had received a radical treatment compared

with 481/550 (88%) in the prostatectomy group and 484/544 (89%) in the radiotherapy group. By 12 years, the receipt of radical treatment had increased to 59%, 90%, and 92% respectively.

Patient-reported outcomes of key measures in the four functional and quality-of-life domains are portrayed graphically in Figs.1-4 with p-values relating to the period 7-12 years. Scores for all PROMs from baseline to 12 years are shown in Table S1.

Domain A - Urinary function and quality-of-life

There was strong evidence of sustained differences between the groups over 7-12 years for all pre-specified urinary function and related quality-of-life measures ($p<0.001$ Figs.1A-E,G, $p=0.008$ Fig.1F, Table S1A). The prostatectomy group had higher levels of urinary leakage than the other groups throughout (Fig.1A-B). Twice as many in the prostatectomy group reported needing to wear ≥1 pad per day (18% at 7 years rising to 24% by year 12), compared with 9-11% in the active monitoring group, and 3-8% in the radiotherapy group (Fig.1B). Urinary leakage was reported to interfere with life most often in the prostatectomy group and least often in the radiotherapy group (Fig.1C).

Urinary voiding difficulties continued in the active monitoring group over 7-12 years, with better function in the radiotherapy group, and better still in the prostatectomy group (Fig.1E). Nocturia (at least twice-per-night) continued to increase gradually in all groups, with more participants in the active monitoring and radiotherapy groups experiencing nocturia (40-47% years 7-12) than in the prostatectomy group (27-34%) (Fig.1G). The impact of all urinary symptoms including leakage on quality-of-life was sustained through years 7-12 with little impact in the radiotherapy group and slightly higher and similar impact in the other two groups (Fig.1F).

Domain B: Sexual function and quality-of-life

There was strong evidence of continued functional declines from 7-12 years and differences between the groups in all pre-specified sexual function measures ($p<0.001$ Figs.2A,2C, Table S1B). Sexual function outcomes were most affected in the prostatectomy group throughout. In year 7, 18% of participants in the prostatectomy group had erections firm enough for intercourse compared with 30% in the active monitoring group and 27% in the radiotherapy group (Fig.2A). While all groups converged to a similarly low level of potency by year 12, (13%-17%, Fig.2A), each group exhibited a different profile of decline, with sexual/erectile function retained most and for longest in the active monitoring group, with lower levels of function in the radiotherapy group, and least in the prostatectomy group.

Differences between the groups in related quality-of-life measures were similar but to a lesser degree than for the functional measures ($p\leq0.006$ Figs.2B,D,E), with moderate-to-severe impact

reported by 42% in the prostatectomy group, 37% in the active monitoring group, and 30% and radiotherapy group at year 7 (Fig.2E). Levels of impact remained relatively stable, even as sexual function declined.

Domain C: Bowel function and quality-of-life

There was statistical evidence of worse outcomes in the radiotherapy group for overall bowel function (Fig.3A) and bowel-related bother (Fig.3B), but absolute differences were negligible (Table S1C). However, fecal leakage (more than once-per-week) increased gradually to affect twice as many in the radiotherapy group (12%) compared with 6% in the prostatectomy and active monitoring groups by year 12 (Fig.3D $p<0.001$). In contrast, blood in stools, previously worse in the radiotherapy group, resolved, becoming similar to the other groups in years 7-12. There were no differences between the groups in loose stools or the impact of bowel habits on quality-of-life ($p\geq0.37$, Figs.3C,3F).

Domain D: Generic/health-related quality-of-life

There was no evidence of differences between the groups on any aspect of pre-specified generic measures over 7-12 years: physical or mental health, anxiety, depression, or cancer-related QoL at five years, and only weak evidence of less constipation in the radiotherapy group (one EORTC QLQ-C30 item) at 10 years (Table S1D). A gradual decline over time in physical health (Fig.4A) was not seen for mental health (Fig.4B). Although anxiety and depression fluctuated, they remained at similar levels throughout (Fig.4C,D).

Secondary analyses

There was evidence of differential effects on pad-use for urinary leakage across age-groups for prostatectomy versus active monitoring in years 7-12 ($p=0.002$ for pairwise comparison, Table S2A). Younger participants (<65 years) were more likely to use pads in the active monitoring group (odds ratio 0.95, 95% CI 0.90, 0.99) and older participants (≥65 years) were more likely to use pads in the prostatectomy group (odds ratio 1.04, 95% CI 1.00, 1.09). There was no evidence of differential effects on other PROMs or subgroups according to cancer risk-stratification (Table S2B). Participants in the active monitoring group who did not receive a radical treatment had much lower rates of urinary leakage and erectile difficulties than those who did receive a radical treatment (Table S3).

Discussion

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This 12-year follow-up of patient-reported outcomes in the ProtecT randomized trial provides the first robust, mature, and detailed evidence of sustained long-term differences in aspects of urinary, sexual, and bowel function and related quality-of-life between prostatectomy, radiotherapy, and active monitoring treatments. Urinary leakage continued to affect the prostatectomy group most over 7-12 years, with twice as many (18-24%) requiring pads compared with active monitoring (9-11%) and three times as many (3-8%) as in the radiotherapy group. Urinary leakage in the active monitoring group was related to the 59% who changed to a radical treatment by year 12 (Table S3), particularly among younger participants who were more likely to change to prostatectomy (Table S2A). While sexual function reached a similarly low level in all groups by year 12, each group exhibited a very distinct profile of impact over time. The impact of prostatectomy on sexual function continued during years 7-12 and it remained the most severely affected group. The radiotherapy group experienced an immediate and expected impact of treatment with androgen-deprivation, with some recovery. The active monitoring group retained the best sexual function throughout. Voiding symptoms including nocturia were better in the prostatectomy group compared with the other groups, with the removal of the prostate likely relieving bladder outflow obstruction. In the radiotherapy group, fecal leakage worsened in the longer-term, reported by 12% in the radiotherapy group compared with 6% in the other groups by year 12.

These findings need to be considered in the context of changes in treatments since ProtecT completed recruitment in 2009. Several trials and cohort studies investigating whether modern treatment techniques produced different PROMs profiles mostly found similarities, comparing their three or five-year follow-up with the ProtecT six-year analysis. Almost identical effects on urinary leakage, voiding, and sexual function were found for newer robot-assisted/laparoscopic procedures[5-9] compared with open procedures in ProtecT.[4] Similar PROMs profiles were also found for contemporary active surveillance compared with low-intensity active monitoring in ProtecT, even with different patient selection and surveillance methods.[6-8] Profiles for intensity-modulated radiotherapy techniques and brachytherapy did find some lesser impacts in the first year and after treatment without hormones, but similar impacts for those treated as in ProtecT with neo-adjuvant androgen-deprivation.[6-8] The increased fecal leakage found in ProtecT was beyond the shorter follow-up in the cohort studies, and there is further need to investigate this and whether image-guidance and hydrogel-spacers reduce bowel toxicity in the longer-term.[20]

The observational cohort studies concluded that little change was seen in PROMs after two years[8] and that treatment effects had attenuated by five years.[6] However, this ProtecT analysis at 7-12 years shows that harms did continue and change in the longer-term. Urinary leakage requiring pads persisted and increased to affect 24% of men in the prostatectomy group by year 12. Sexual function

profiles continued to be best in the active monitoring group and worst in the prostatectomy group - until the groups converged around year 12. There was an increase in fecal leakage in years 7-12 in the radiotherapy group. Previous long-term studies had found decrements in urinary and sexual function among prostate cancer survivors[21] including when compared with controls.[22] It is accepted that there is a need for lengthy follow-up of the clinical outcomes of localized prostate cancer because of the protracted natural history of prostate cancer. In parallel, lengthy follow up of patient-reported outcomes is also required (and now available) to enable full consideration of the trade-offs between the benefits and harms of treatments. Given high levels of consensus between the ProtecT results at six years and contemporary treatment cohorts with up to five years' follow-up, these ProtecT findings provide comprehensive long-term patient-reported outcome profiles to inform current treatment decisions.

Determining the clinical relevance of PROMs is challenging and debated, with suggestions of a target difference of 0.5 of a standard deviation[8] or a specific number of points on scores.[23] Applying the recommended numbers of points[23] at 7-years indicated that clinical relevance was reached only for the difference in urinary leakage between prostatectomy and radiotherapy. During 10-12 years, this benchmark was also reached for prostatectomy compared with active monitoring – but because of worsening in the prostatectomy group, not change in the active monitoring group (Table S1A). Our approach aims to preserve the meaning of the data for patients and clinicians by pre-specifying comparisons of key PROM items/scores, displaying them graphically over time (Figs 1-4), and publishing all outcomes with summary statistics (Table S1A-E).[4,13] This allows patients and clinicians to reach their own judgements about the relevance of PROMs based on all available data, and respects the rights of patients to use their own values and priorities when considering harms and benefits. This is important to avoid decisional regret associated with a lack of understanding of treatment side-effects,[24,25] and unmet needs among patients with post-prostatectomy urinary leakage.[26] Further research about the impact of adverse effects of treatments on individuals who experience them is warranted.

This 'as randomized' analysis provides robust policy-relevant evidence of average effects for comparable groups, but as the groups included some who did not receive their allocation, an 'as-treated' analysis can help patients to assess their own individual risks.[27] An 'as treated' analysis of ProtecT PROMs up to six years found greater immediate and more persistent effects following radical treatments and lesser, age-related effects in those remaining on active monitoring.[28] Minimal urinary leakage and longer preservation of sexual function were confirmed in those remaining on active monitoring without a radical treatment in an exploratory analysis here (Table S3).

Strengths and limitations

The strengths of ProtecT include its randomized design with balanced groups at baseline enabling unbiased comparisons, generalizable population-based recruitment following PSA testing and follow-up within a comprehensive cohort,[29] clinically localized patient group comprising up to one third with intermediate-risk prostate cancer,[1] implementation of standardized diagnostic and treatment protocols, sustained extremely high response rates (80%+) over 12 years, and comprehensive presentation of validated PROMs. Limitations include evolutions in treatments since ProtecT recruitment began, although contemporary treatment studies found similar short/medium-term results;[6-8] and the ProtecT cohort being mostly of white ethnicity, although no differences in PROMs were found between ethnic groups in a contemporary diverse cohort.[6]

Conclusions

This long-term follow-up of the ProtecT trial provides robust, mature, and detailed evidence about the effects of treatments on urinary, sexual, and bowel function on patients over 12 years, extending and enriching those reported by short-term studies of contemporary treatments. Prostatectomy continued to cause persistent urinary leakage in around one-fifth of participants and severely diminished sexual function. Radiotherapy with neo-adjuvant androgen-deprivation reduced sexual function and caused a late increase in fecal leakage. With active monitoring, natural age-related declines in sexual function and urinary voiding occurred, with the harms of radical treatments avoided unless or until management changed. Detailed profiles of patient-reported treatment effects are now available in the short-, medium-, and long-term. Patients newly diagnosed with localized prostate cancer can carefully consider the trade-offs between treatment harms and the risks of prostate cancer progression in the context of low cancer-specific mortality, and discuss these with clinicians, enabling well-informed and individualized treatment decisions.

[[Total 2701, limit 2700]]

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