Donovan , J. L., Lane, J. A., Metcalfe, C., Davis, M. J., Turner, E. L., Martin, R. M., Walsh, E. I., Peters, TJ., & Williams, N. J. (2023). Fifteen-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. *New England Journal of Medicine*, *388*(17), 1547-1558. https://doi.org/10.1056/NEJMoa2214122

15-year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer

Freddie C Hamdy FRCS(Urol), FMedSci[1], Jenny L Donovan PhD, FMedSci[2], J Athene Lane PhD[2,3], Chris Metcalfe PhD[2,3], Michael Davis BSc, MSc[2], Emma L Turner PhD[2], Richard M Martin BMBS PhD[2], Grace J Young MSc[2,3] Eleanor I Walsh MSc[2], Richard J Bryant PhD, FRCS(Urol)[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 PhD, FRCS(Urol)[8], Owen Hughes FRCS(Urol), DM[9], Roger Kockelbergh DM, FRCS(Urol)[10], Howard Kynaston MD, FRCS(Urol)[9], Alan Paul MD, FRCS(Urol)[11], Edgar Paez FRCS(Urol)[12], Philip 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[2], Jon Oxley MD, FRCPath[17], Naomi J. Williams PhD,[2] John Staffurth FRCR, FRCP,[18] David E Neal CBE, FMedSci[1,8] for the ProtecT study group

Dr. Hamdy, Dr. Donovan, Dr. Lane, Dr. Metcalfe, and Dr. Neal have contributed equally.

Members of the ProtecT study group can be found in the supplemental appendix.

Corresponding Author:
Freddie C Hamdy
Nuffield Department of Surgical Sciences
University of Oxford
Old Road Campus Research Building
Roosevelt Drive, Headington
Oxford OX3 7DQ
United Kingdom
Tel: +44 (0)1865 617 123
Email: Freddie.Hamdy@nds.ox.ac.uk

[1]Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK
[2]Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK
[3]Bristol Trials Centre, Bristol Medical School, 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 Biomedical Campus, Addenbrooke's Hospital, 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]Department of Urology, Royal Hallamshire Hospital, Sheffield
[14]Department of Urology, Southmead Hospital and Bristol Urological Institute, Bristol, UK
[15]School of Medicine, Cardiff University, 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, Cardiff University

ABSTRACT

Background

The Prostate-testing-for-cancer-and-Treatment (ProtecT) trial provides a~~the only~~ randomized comparison of active monitoring, prostatectomy, and radiotherapy for PSA-detected localized prostate cancer.

Methods

From 1999-2009, 82,429 50-69-year-old men received PSA-testing, 2,664 had localized disease, 1,643 were randomized to active monitoring (n=545), prostatectomy (n=553) or radiotherapy (n=545). We report prostate cancer-specific mortality, all-cause mortality, metastases, disease progression, and initiation of long-term androgen-deprivation at a median of 15-years' follow-up (range 11-21 years).

Results

Follow-up was complete for 1,610 (98%) men. Risk-stratification revealed intermediate/high-risk disease in over one-third. There were 45 (2.7%) prostate-cancer–specific deaths: 17 (3.1%) in the active monitoring, 12 (2.2%) in the prostatectomy, and 16 (2.9%) in the radiotherapy groups; p=0.53; and 356 (21.7%) evenly distributed all-cause deaths. Metastases developed in 51 men (9.4%) in the active monitoring, 26 (4.7%) in the prostatectomy, and 27 (5.0%) in the radiotherapy groups. Clinical progression occurred in 141 (25.9%) in the active monitoring, 58 (10.5%) in the prostatectomy, and 60 (11.0%) in the radiotherapy groups; 69 men (12.7%), 40 (7.2%), and 42 (7.7%) started long-term androgen-deprivation in the respective groups. In the active monitoring group, 133 (24.4%) remained alive without prostate cancer treatment. No differential effects on cancer-specific mortality were noted in relation to baseline PSA, clinical stage/grade, or risk-stratification. No treatment complications were reported post-10-year analysis.

Conclusions

At 15-years, prostate cancer-specific mortality was low irrespective of treatment assigned. Choice of therapy involves weighing ~~up~~ trade-offs between benefits and harms associated with localized prostate cancer treatments.

INTRODUCTION

Despite recent advances in early detection and treatment of localized prostate cancer, management of the disease remains controversial. While multiparametric Magnetic Resonance Imaging (mpMRI) and targeted biopsies may reduce the diagnosis of indolent disease, poor risk-stratification continues to drive over- and under-treatment. In the US in 2020, approximately 192,000 men were diagnosed with prostate cancer and 33,000 died of their disease.[1] Following updated recommendations by the US Preventive Services Task Force in 2012 and 2018,[2] the incidence of localized disease has declined, while rates for regional and advanced cases have increased.[3] Cancer-specific death rates, however, have remained unchanged.[4] Clinical outcomes reported herein help elucidate reasons for these findings.

The UK NIHR (National Institute for Health Research) ProtecT trial recruited 82,429 men aged 50-69 years from 1999 to 2009 for PSA-testing. Localized prostate cancer was diagnosed in 2,664 men fit for treatment with life-expectancy of at least 10-years, and 1,643 agreed to randomization to active monitoring (n=545), prostatectomy (n=553) or radiotherapy (n=545). Median age at diagnosis was 62 years (range 50-69 years), median PSA was 5.8µg/L (range 3-19.9µg/L). No clinico-pathological differences were seen among~~between~~ the randomized groups[5] or those who accepted/declined randomization.[6] This analysis evaluates the effectiveness of active monitoring, prostatectomy, and radiotherapy on prostate cancer-specific and all-cause mortality, metastases, initiation of long-term androgen-deprivation, and disease progression at 15-years median follow-up. As previous reports assumed from baseline data that around 77% of men in the ProtecT cohort had low-risk disease,[5,7-9] a comprehensive risk-stratification exercise was undertaken using CAPRA, D'Amico, and Cambridge Prognostic Groups to assist interpretation of the results.[10-12] Patient-reported outcomes, critical to assessing the full trade-offs between treatment benefits and harms are described in a separate~~companion~~ article.[13]

PATIENTS AND METHODS

Participants' flow through the trial is illustrated in **Figure 1.** Methods of recruitment, primary and secondary outcomes at 10-years median follow-up were published previously.[14] The ProtecT study was designed by the first, second, and last authors~~FCH, JLD, and DEN~~. ~~Data analysis was designed by CM and TJP and conducted by CM.~~ The authors vouch for the data analysis and fidelity to the protocol; the first author ~~are vouched for by JAL, FCH, JLD, DEN, and CM. FCH~~ wrote the first draft of the paper; all authors contributed to the final version. ~~FCH, JLD, and DEN decided to submit the paper for publication;~~ Iinstitutions, sponsor and funder had no role in the data analysis or writing the paper ~~publication~~. The study was approved by the UK East-Midlands Multicentre Research-Ethics Committee (01/4/025). Participants were diagnosed with localized prostate cancer between 1999 and 2009 following PSA-testing and transrectal-biopsy. Those consenting to randomization were allocated to active monitoring, prostatectomy, or radiotherapy.

Treatment procedures

Clinical management was standardized using study-specific pathways.[15] PSA concentrations were measured 3-monthly in the first year and 6-12 monthly thereafter. Participants were reviewed annually. With active monitoring, a rise in PSA of at least 50% over 12-months or patient/clinician concerns triggered a review, with management options including continued monitoring or further tests and radical/palliative treatments as required. Radiotherapy was delivered using neo-adjuvant androgen-deprivation for 3–6 months with 3D-conformal radiotherapy at 74 Gy in 37 fractions.[16,17] A management review was triggered if PSA concentrations rose by at least 2.0µg/L post-nadir, or concerns were raised about progression. In men receiving prostatectomy, adjuvant/salvage radiotherapy were discussed with patients who had positive surgical margins, extra-capsular disease, or a postoperative PSA of 0.2µg/L or higher. Bone-scintigraphy was recommended when PSA reached 10µg/L, and androgen-deprivation discussed when PSA reached 20µg/L.

Clinical outcome measures

The primary outcome was definite/probable prostate cancer mortality, adjudicated by an independent Cause-of-Death committee.[18] Secondary outcomes included all-cause mortality, metastases (defined by imaging or PSA levels of 100µg/L or higher), clinical progression (metastases, clinical T3/T4 disease, initiation of long-term androgen-deprivation, ureteric obstruction, rectal fistula, and/or urinary catheterization due to tumor-growth), and long-term androgen-deprivation. No new treatment complications were reported from 2015[14] until data collection was streamlined from 2018.

Subgroups

Eight diagnosis-related subgroups were pre-specified to investigate differential effects on prostate cancer-specific mortality: age (above *versus* below 65 years), Gleason-Grade-Group (1 *versus* 2 *versus* 3+), PSA (less than 10µg/L *versus* 10-19.9µg/L), stage (T1 *versus* T2), aggregate tumor-length in biopsies (less than 4mm *versus* 4mm+), maximum tumor-length in a single biopsy (less than 2mm *versus* 2mm+), and D'Amico, CAPRA, and, in an exploratory analysis, Cambridge Prognostic Group risk-stratification.

Statistical Analysis

A statistical-analysis-plan was developed before accessing data.[19] Prostate cancer-specific mortality at 15-years was presented with a 95% CI for each group, and compared between allocated groups using Cox's proportional hazards regression adjusted for study center, age, Gleason score, and baseline PSA (log-transformed). Pairwise significance tests were planned if the p-value for equal disease-specific mortality across allocated groups was less than 0.05 (keeping the overall false-positive rate at 5%).[20] Interaction terms were added to this model to investigate differential treatment effects across eight pre-defined subgroups. The regression model approach was adapted to secondary outcomes. As the statistical-analysis-plan did not include provision for correcting for multiplicity when conducting tests for secondary/other outcomes, results are reported as point estimates and 95% CI; widths of the CI have not been adjusted for multiplicity, so intervals should not be used in place of a hypothesis test. Exploratory analyses are presented in the supplement to assist with interpretation of findings.

The study was overseen by an independent Trial Steering Committee. All analyses were conducted in STATA version 17 (StataCorp, College Station, Texas, 2021).

RESULTS

Follow-up and risk-stratification

Clinical data were captured for 1,610/1,643 (98%) during the median 15-year follow-up (**Figure 1**). Although 77% were diagnosed with Gleason score 3+3=6 and 76% stage T1c at baseline, contemporary risk-stratification tools revealed that 369 (24%) had intermediate- and 147 (10%) high-risk disease according to D'Amico, 337 (21%) and 144 (9%) according to Cambridge Prognostic Group, and 428 (26%) and 40 (2%) according to CAPRA (**Table S1**). In addition, among the 488 men who underwent prostatectomy within 12 months of being allocated to any group, 138 (29%) were upstaged to pT3/T4 (**Table S2**), and 155 (32%) were upgraded, with 245 (51%) harboring Gleason-Grade-Group-2 or higher (**Table S3**). Of 13 men who received prostatectomy but died of prostate cancer, all were upstaged and 77% upgraded (**Table S4)**. Of the 104 men who developed metastases, 53 (51%) were diagnosed with Gleason-Grade-Group-1 at baseline and 49 (47%) had low-risk by CAPRA (**Table S5**).

Primary outcome

After median 15-years follow-up, there were 45 (2.7%) prostate-cancer deaths, 17 (3.1%) in the active monitoring group, 12 (2.2%) in the prostatectomy group, and 16 (2.9%) in the radiotherapy group (**Table 1, Figure 2A**). Prostate cancer-specific survival was around 97% irrespective of allocated group. No difference in prostate cancer mortality was noted between allocated groups after median 15-years follow up (likelihood ratio p=0.53). Including three men allocated to active monitoring whose death was 'possibly due to prostate cancer' in a repeat primary outcome analysis did not affect this conclusion (p=0.27) (**Table S6**).

The treatment effect comparing men allocated to radiotherapy and active monitoring varied over follow-up (test of proportional hazards assumption p=0.010), with 7/16 deaths in the radiotherapy group occurring after 15 years (**Figure S1**). We elaborated the primary analysis model to compare

radiotherapy and active monitoring separately in the first 12.76 years of follow-up when 23/45 prostate cancer deaths had occurred, and in the subsequent follow-up period. The resulting imprecise estimates (**Table S7**) suggest that this comparison favors radiotherapy early, but active monitoring later. This supports the conclusion of no evidence of a difference in prostate cancer mortality among the three allocated groups (p=0.51).

All-cause mortality

There were 356 (22%) all-cause deaths, evenly distributed across allocated groups (**Table 1, Figure S2**), with 101 (33%) from cardio-vascular/respiratory disease and 164 (53%) from other cancers (**Table S8**).

Metastases, androgen-deprivation, disease progression

Of the 104 men (6.3%) diagnosed with metastases, 51 (9.4%) were in the active monitoring group compared with 26 (4.7%) in the prostatectomy and 27 (5.0%) in the radiotherapy groups (**Table 1, Figure 2B**). The difference was most apparent among men with metastatic disease in regional nodes: 14 (3%) in the active monitoring group compared with 4 (less than 1%) in the radical treatment groups (**Table S9**). Of 151 men (9.2%) treated with long-term androgen-deprivation therapy, 69 (12.7%) were in the active monitoring group, 40 (7.2%) in the prostatectomy, and 42 (7.7%) in the radiotherapy groups (**Table 1, Figure S3**). Among 259 (15.8%) with local progression, 141 (25.9%) were in the active monitoring, 58 (10.5%) the prostatectomy, and 60 (11.0%) the radiotherapy groups (**Table 1, Figure S4**). When staging alone was analyzed as a measure of local progression, T3/T4 disease was found in 69 (13%) in the active monitoring group, 15 (3%) in the prostatectomy group, and 17 (3%) in the radiotherapy group (**Table S9**).

Change-of-management

By the end of follow-up, 504 men (92%) assigned to radiotherapy and 500 (90%) to prostatectomy had received radical interventions (**Figure 3**). This compares with 333 (61.1%) receiving radical treatment in the active monitoring group, a rise of 6.3% from 291 (54.8%) reported at 10-years.[14] By the end of follow-up, 133 (24%) allocated to active monitoring were alive and had not received radical treatment

nor started androgen-deprivation. Of these 133 men, 17 (13%) were D'Amico intermediate/high-risk and 14 (11%) had Gleason-Grade-Group-2 disease or higher at diagnosis (**Table S10**).

Pre-specified subgroup analyses

The relative risk of prostate cancer mortality in allocated groups differed according to men's age at diagnosis, with lower mortality observed among younger men receiving active monitoring or prostatectomy compared with radiotherapy; and among older men receiving prostatectomy or radiotherapy compared with active monitoring (**Table 2, Figure S5**). No evidence was seen of treatment effect modification according to PSA, clinical stage, grade-group, tumor-length, D'Amico, CAPRA, or Cambridge Prognostic Group risk-stratification (**Table 2**).

Exploratory analyses

The higher incidence of metastatic disease at 10-years in the active monitoring group was anticipated to impact prostate cancer-specific mortality at 15-years, but this was not the case. Among 40 men diagnosed with metastatic disease at 10-years, the risk of prostate cancer-specific mortality was lower in those allocated to active monitoring: 3/22 (14%), compared to prostatectomy 2/8 (25%) and radiotherapy 7/10 (70%) (**Figure S6).**

DISCUSSION

To date, ProtecT is a ~~the only~~ randomized trial to evaluate contemporary treatment effectiveness in PSA-detected clinically-localized prostate cancer. This 15-year analysis provides evidence of high long-term survival (97% prostate cancer-specific, 78% all-cause), irrespective of treatment allocation. Radical treatments reduced metastasis, local progression, and long-term androgen-deprivation by half compared with active monitoring. However, this did not translate into differences in deaths at 15-years, emphasizing the long natural history of this disease. Early radical treatments therefore can result in more harm than good. Clinicians need to avoid over-treatment by ensuring that men with newly diagnosed prostate cancer consider critical 'trade-offs' between short- and long-term effects of treatments on urinary, bowel and sexual function,[13] as well as the risks of progression.

Major guidelines recommend conventional clinico-pathological features such as baseline PSA, clinical stage, Gleason-Grade-Grouping, and biopsy characteristics to guide risk-stratification and treatment.[22,23] ProtecT has revealed the limitations of these methods. Contrary to previous perceptions that ProtecT comprised only low-risk disease,[5,7-9] contemporary methods of risk-stratification showed that up to 34% of the ProtecT cohort had intermediate-to-high-risk prostate cancer at diagnosis (**Table S1**). Further, pathological data from men who underwent prostatectomy within 12 months of diagnosis revealed that one-third were upstaged and upgraded, and one-half had Gleason-Grade-Group-2 or higher, suggesting that more intermediate-risk disease was present across the cohort than previously thought (**Tables S2, S3**).

Analysis of 13 men who received prostatectomy but died of prostate cancer further revealed the limitations of risk-stratification methods, as 46% were diagnosed with Gleason-Grade-Group-1 at baseline, all were upstaged, and 77% upgraded (**Table S4**). More than three-quarters of these men received surgery within two years of diagnosis and 84% received salvage radiotherapy, showing the aggressive nature of their disease. Despite the administration of multimodality treatments, these men who died from their cancer must have harbored features of lethality that were not identified at diagnosis or affected by treatment. Furthermore, of the 104 men who developed metastases, 51% were classified as low-risk Gleason-Grade-Group1 at baseline, and 47% were low-risk by CAPRA (**Table S5**). Novel prediction tools are needed, with better understanding and alignment of the tumor phenotype with its genotype, as well as the natural history of disease progression.[24,25]

While the rates of metastases increased, the number of prostate cancer deaths remained low (**Table 1**, **Figure 2B**) and the intervals between metastases and death continued to extend from 10 to 20 years, particularly in the active monitoring group (**Figure S6**). Of the 40 men diagnosed with metastases at 10-years, 3/22 had died of prostate cancer in the active monitoring group by 15 years, compared with 2/8 in the prostatectomy group and 7/10 in the radiotherapy group (**Figure S6**). New systemic therapies for progressive disease have become increasingly available and it is likely that these contributed to lengthening survival in participants with metastases observed in ProtecT. This finding is remarkable and

reassuring for such a common malignancy and seriously questions whether metastasis *per se* can be used as a surrogate of prostate cancer-lethality in localized disease.[28,29]

When the sites of metastatic disease were analyzed, 29% in the active monitoring group had regional lymph-node involvement, compared to 15% in each of the prostatectomy and radiotherapy groups (**Table S9**). The incidence of visceral and distant lymph-node involvement was low with no differences between the groups. Skeletal metastases accounted for a similar proportion of cases in the active monitoring (31%) and prostatectomy (35%) groups, with a lower proportion in the radiotherapy group (15%) (**Table S9**). This may be due to the presence of occult micrometastatic disease at diagnosis, suppressed by neo-adjuvant androgen-deprivation with radiotherapy. Caution is needed in interpreting rates of local progression because of the fourfold higher incidence of clinical restaging with active monitoring (13%) compared to radical treatments (3%). Many of these cases were based on subjective digital rectal examinations or CT-imaging, providing the weakest justification for initiating radical treatment (**Table S9**).

Following ProtecT's 10-year analysis,[14] reservations were expressed that the allocated radical treatment was not always received.[7-9] However, by 15-years, 90-92% of men allocated to a radical treatment had received either prostatectomy or radiotherapy, and in the active monitoring group, 61% received a radical treatment (**Figure 3**). Rates of change-of-management in ProtecT were similar to other active surveillance programs, with approximately 30% receiving radical treatment within three years, increasing to 55% at 10-years, and 61% at 15-years (**Figure 3**). Decisions to change in early years were often made without evidence of progression, likely related to patient and/or physician anxiety. At 15-years, 39% of men allocated to active monitoring had not undergone radical treatment, and 24% were alive without radical treatment or androgen-deprivation, 11% of whom had been Gleason-Grade-Group-2 or CAPRA-score-3 or higher, and stage T2 at diagnosis (**Table S10**).

The ProtecT findings accord with the US Prostate Intervention versus Observation trial (PIVOT), which showed no survival benefit for radical treatment in men with high levels of competing morbidities.[26] The

Scandinavian SPCG-4 trial found consistent benefits of radical treatment compared to watchful-waiting but this was a clinically presenting cohort, without surveillance in the watchful-waiting arm, and half had non-organ confined disease.[27] The US Preventive Services Task Force synthesized available data and recommended against screening in 2012 (modified to shared-decision in 2018).[2] Subsequent studies have shown stable survival statistics despite reduced PSA-testing and increased regional/advanced prostate cancer in the US.[3] ProtecT demonstrates that PSA-detected prostate cancer-survival is long, irrespective of patient-stratification, and lethal disease is not clearly impacted by radical treatment.

As with the PIVOT trial,[26] no evidence of differential treatment effects on prostate cancer-mortality was noted between subgroups defined by grading at diagnosis, aggregate/maximum tumor-length in biopsies, stage, PSA level, or D'Amico, Cambridge Prognostic Group, or CAPRA risk-stratification (**Table 2**). However, a suggestion of an age-effect not found in PIVOT or SPCG-4 was seen,[26,27] with men 65-years and older appearing to benefit from early radical treatment, and men aged less than 65-years benefiting from active monitoring or surgery compared to radiotherapy (**Table 2, Table S11**). This could reflect potential benefits of prompt radical treatment among older men but should be interpreted cautiously and needs further exploration.

The ProtecT study has some limitations. Since its inception, treatments and diagnostics have evolved. ProtecT did not use contemporary mpMRI or PSMA PET-CT scans, which were not available during the study, either at diagnosis or during follow-up, and biopsies were not image-targeted. Strengths of the study include the randomized comparison of men with PSA-detected clinically localized low/intermediate-risk prostate cancer, generalizable population-based recruitment with high levels of randomization, standardized treatment-pathways, and sustained high rates of follow-up.[6,30]

At median 15-year follow-up, ProtecT has demonstrated that PSA-detected prostate cancer mortality remains very low irrespective of treatment allocation. Radical treatment reduced disease progression compared with active monitoring but did not lower prostate cancer mortality. Although the ProtecT active monitoring protocol was perceived as less intensive than contemporary active surveillance, one-

quarter of men allocated to active monitoring were alive without having received any form of treatment. Longer-term follow-up to 20-years and beyond will be crucial to continue to evaluate 'trade-offs' between risks and benefits, and possible differential effects of treatments. In the meantime, greater awareness of the limitations of current risk-stratification methods and treatment recommendations in guidelines is needed. ProtecT shows that men with newly diagnosed localised prostate cancer and their treating clinicians should carefully consider the trade-offs between harms and benefits of treatments when making management decisions. ProtecT provides mature data to inform these individualized decisions.

ACKNOWLEDGEMENTS

The ProtecT trial is funded by the UK National Institute for Health and Care Research Health Technology Assessment Programme (projects 96/20/06, 96/20/99, with the University of Oxford as sponsor. UK Department of Health and Social Care disclaimer: The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health and Social Care. ProtecT Current Controlled Trials number, ISRCTN20141297; ClinicalTrials.gov number, NCT02044172.

FCH and RJB receive support from the Oxford NIHR Biomedical Research Centre, Surgical Innovation and Evaluation Theme. RMM receives support from the Bristol NIHR Biomedical Research Centre (BRC-1215-20011) and Cancer Research UK Integrative Cancer Epidemiology Programme (C18281/A29019). JAL and GJY receive support from NIHR for the Bristol Trials Centre. FCH, JLD, RMM and DEN are Emeritus or current NIHR Senior Investigators.

The authors acknowledge the tremendous contribution of all the ProtecT study participants; clinical, research, and administrative staff; DMC (Chairs: Adrian Grant and Ian Roberts, Members: Deborah Ashby, Richard Cowan, Peter Fayers, Killian Mellon, James N'Dow, Tim O'Brien, Michael Sokal); 1st TSC 2002-2016 (Chairs: Michael Baum and Peter Albertsen, Members: Anthony Zietman, David Dearnaley, Jan Adolfsson, Peter Albertsen, Fritz Schröder, Tracy Roberts); and 2nd TSC 2017-2022 (Chair: Deborah Ashby, Members: Chris Parker, Tom Walton, Timon Colegrove); and Cause of Death Evaluation Committee: (Chair: Peter Albertsen, Members: Anthony Zietman, Jon Oxley, Malcolm Mason, Tyler Seibert, Jan Adolfsson, Jon McFarlane, Richard Bryant, John Dormer).

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Figure 1. ProtecT study flowchart

Figure 2 Panel A. Prostate cancer mortality survival

Figure 2 Panel B. Kaplan–Meier Estimates of Freedom from Metastatic Disease, According to Treatment Group

Figure 3. Kaplan–Meier Estimates of the Cumulative Probability of Undergoing Radical Intervention during the Follow-up Period, According to Treatment Group. Radical intervention was defined as radical prostatectomy, radiotherapy (including brachytherapy), or high-intensity focused ultrasound therapy.

Table 1. Prostate cancer mortality, metastatic disease, initiation of long-term androgen deprivation therapy, clinical progression, and all-cause mortality, by randomized group

	Events / pyrs	Events / 1000 pyrs (95% CI)	Hazard ratio[1] (95% CI)	p-value[1]
Prostate cancer mortality[2]				
Active monitoring (n=545)	17 / 7633	2.2 (1.4, 3.6)	Comparison	0.53
Prostatectomy (n=553)	12 / 7766	1.5 (0.9, 2.7)	0.66 (0 31, 1.39)	
Radiotherapy (n=545)	16 / 7628	2.1 (1.3, 3.4)	0.88 (0.44,1.74)	
All-cause mortality				
Active monitoring	124 / 7633	16.2 (13.6, 19.3)	Comparison	
Prostatectomy	117 / 7766	15.0 (12.5, 18.0)	0.89 (0.69, 1.15)	
Radiotherapy	115 / 7628	15.0 (12.5, 18.0)	0.88 (0.68, 1.13)	
Metastatic disease				
Active monitoring	51 / 7324	7.1 (5.4, 9.3)	Comparison	
Prostatectomy	26 / 7594	3.5 (2.4, 5.1)	0.47 (0.29, 0.76)	
Radiotherapy	27 / 7467	3.7 (2.5, 5.4)	0.48 (0.30, 0.77)	
Androgen deprivation				
Active monitoring	69 / 7197	9.4 (7.4, 11.9)	Comparison	
Prostatectomy	40 / 7452	5.3 (3.9, 7.2)	0.54 (0.37, 0.80)	
Radiotherapy	42 / 7328	5.6 (4.2, 7.6)	0.54 (0.36, 0.79)	
Clinical progression[3]				
Active monitoring	141 / 6596	21.4 (18.1, 25.2)	Comparison	
Prostatectomy	58 / 7258	8.0 (6.2, 10.3)	0.36 (0.27, 0.49)	
Radiotherapy	60 / 7173	8.4 (6.5, 10.8)	0.35 (0.26, 0.48)	

Kaplan-Meier estimates of the probability of survival of prostate cancer mortality

	% Survival prostate cancer mortality	
	At 10 years (95% CI)	At 15 years (95% CI)
Active monitoring	98.7 (97.2, 99.4)	96.6 (94.4, 98.0)
Prostatectomy	99.0 (97.7, 99.6)	97.2 (94.8, 98.5)
Radiotherapy	99.4 (98.2, 99.8)	97.7 (95.5, 98.8)

[1]Hazard ratios are estimated and p-values calculated with adjustment for study center, age at baseline, Gleason score, and PSA at baseline (log-transformed). The p-value tests the null hypothesis "no difference in the population between the three treatment groups in prostate cancer mortality over a median 15-year follow-up." The widths of confidence intervals for secondary outcomes have not been adjusted for multiplicity and cannot be used in place of a hypothesis test. [2]Death probably or definitely due to prostate cancer or its treatment, judged by an independent committee. [3]Disease progression includes evidence of metastatic disease; the initiation of androgen deprivation therapy; diagnosis of clinical T3 or T4 disease; or ureteric obstruction, rectal fistula, or the need for a permanent catheter when these are not considered to be a complication of treatment.

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Table 2. Prostate cancer deaths by pre-specified subgroups (all subgroups established at diagnosis)

	AM	RP	RT	HR (95% CI)	HR (95% CI)
Age (n=1643)	**n/N (%)**	**n/N (%)**	**n/N (%)**	**RP versus AM**	**RT versus AM**
< 65 years	5/340 (1.5)	6/353 (1.7)	10/341 (2.9)	1.15 (0.35, 3.78)	2.06 (0.70, 6.03)
65 years+	12/205 (5.9)	6/200 (3.0)	6/204 (2.9)	0.47 (0.17, 1.24)	0.43 (0.16, 1.15)
Grade Group (n=1642)					
Group 1	11/419 (2.6)	5/425 (1.2)	9/424 (2.1)	0.43 (0.15, 1.24)	0.78 (0.32, 1.89)
Group 2	4/93 (4.3)	5/102 (4.9)	4/80 (5.0)	1.18 (0.32, 4.39)	1.15 (0.29, 4.62)
Group 3+	2/33 (6.1)	2/25 (8.0)	3/41 (7.3)	1.04 (0.15, 7.41)	1.18 (0.20, 7.08)
Aggregate tumour length in biopsy cores (n=1570)					
<4mm	6/209 (2.9)	3/233 (1.3)	5/233 (2.2)	0.43 (0.11, 1.73)	0.75 (0.23, 2.46)
4mm+	11/314 (3.5)	8/292 (2.7)	10/289 (3.5)	0.75 (0.30, 1.88)	0.94 (0.40, 2.21)
Maximum tumour length in any one biopsy core (n=1361)					
<2mm	2/111 (1.8)	4/124 (3.2)	4/119 (3.4)	1.76 (0.32, 9.63)	2.02 (0.37, 11.03)
2mm+	13/348 (3.7)	6/330 (1.8)	9/329 (2.7)	0.47 (0.18, 1.24)	0.69 (0.30, 1.62)
PSA level (n=1643)					
3.0-5.9 ng/ml	13/366 (3.6)	7/371 (1.9)	10/371 (2.7)	0.50 (0.20, 1.26)	0.71 (0.31, 1.61)
6.0-9.9 ng/ml	4/123 (3.3)	4/126 (3.2)	6/117 (5.2)	1.03 (0.26, 4.12)	1.71 (0.48, 6.07)
10+ ng/ml	0/56 (0)	1/56 (1.8)	0/57 (0)	-	-
Clinical stage (n=1643)					
T1c	10/410 (2.4)	6/410 (1.5)	10/429 (2.3)	0.58 (0.21, 0.61)	0.91 (0.38, 2.19)
T2	7/135 (5.2)	6/143 (4.2)	6/116 (5.2)	0.78 (0.26, 2.32)	1.03 (0.35, 3.07)
CAPRA risk score (n=1619)					
Score 0-2	11/381 (2.9)	6/382 (1.6)	13/388 (3.4)	0.52 (0.19, 1.41)	1.10 (0.49, 2.46)
Score 3-5	4/143 (2.8)	5/150 (3.3)	2/135 (1.5)	1.23 (0.33, 4.58)	0.57 (0.11, 3.14)
Score 6-10	2/13 (15)	0/8 (0)	1/19 (5.3)	-	0.16 (0.01, 1.76)
D'Amico risk group[1] (n=1530)					
Low	9/328 (2.7)	4/343 (1.2)	6/343 (1.7)	0.44 (0.13, 1.42)	0.63 (0.23, 1.78)
Intermediate	3/129 (2.3)	2/118 (1.7)	5/122 (4.1)	0.68 (0.11, 4.05)	1.64 (0.39, 6.86)
High	2/49 (4.1)	6/54 (11)	0/44 (0)	2.62 (0.53, 12.97)	-
Cambridge Prognostic Risk Score (n=1642)					
Group 1	11/382 (2.9)	5/395 (1.3)	9/384 (2.3)	0.43 (0.15, 1.23)	0.78 (0.32, 1.89)
Group 2	4/116 (3.4)	4/112 (3.6)	4/109 (3.7)	1.03 (0.26, 4.12)	1.04 (0.26, 4.17)
Groups 3-5	2/47 (4.3)	3/45 (6.7)	3/52 (5.8)	1.46 (0.24, 8.75)	1.42 (0.24, 8.49)

[1] 108 T2s excluded as could not be recoded as a/b/c
AM = Active Monitoring, RP = Radical Prostatectomy, RT = Radiotherapy, HR = Hazard Ratio, CI = Confidence Interval.

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