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Neal, D.E., Metcalfe, C., Donovan, J.L. et al. (26 more authors) (2020) Ten-year mortality, disease progression, and treatment-related side effects in men with localised prostate cancer from the ProtecT randomised controlled trial according to treatment received. European Urology, 77 (3). pp. 320-330. ISSN 0302-2838

https://doi.org/10.1016/j.eururo.2019.10.030

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

Ten-year Mortality, Disease Progression, and Treatment-related Side Effects in Men with Localised Prostate Cancer from the ProtecT Randomised Controlled Trial According to Treatment Received

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Article info

Article history:
Accepted October 30, 2019

Associate Editor:
Giacomo Novara

Abstract

Background: The ProtecT trial reported intention-to-treat analysis of men with localised prostate cancer randomly allocated to active monitoring (AM), radical prostatectomy, and external beam radiotherapy.
Objective: To report outcomes according to treatment received in men in randomised and treatment choice cohorts.
Design, setting, and participants: This study focuses on secondary care. Men with clinically localised prostate cancer at one of nine UK centres were invited to participate in the treatment trial comparing AM, radical prostatectomy, and radiotherapy.

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‡ Sadly, Professor Doug Altman passed away while this paper was being completed.
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https://doi.org/10.1016/j.eururo.2019.10.030

Keywords:
Prostate cancer
Disease progression
ProtecT trial
Active monitoring
Radical prostatectomy
Radiotherapy
Metastasis

Intervention: Two cohorts included 1643 men who agreed to be randomised and 997 who declined randomisation and chose treatment.
Outcome measurements and statistical analysis: Analysis was carried out to assess mortality, metastasis and progression and health-related quality of life impacts on urinary, bowel, and sexual function using patient-reported outcome measures. Analysis was based on comparisons between groups defined by treatment received for both randomised and treatment choice cohorts in turn, with pooled estimates of intervention effect obtained using meta-analysis. Differences were estimated with adjustment for known prognostic factors using propensity scores.
Results and limitations: According to treatment received, more men receiving AM died of PCa (AM 1.85%, surgery 0.67%, radiotherapy 0.73%), whilst this difference remained consistent with chance in the randomised cohort ($p = 0.08$); stronger evidence was found in the exploratory analyses (randomised plus choice cohort) when AM was compared with the combined radical treatment group ($p = 0.003$). There was also strong evidence that metastasis (AM 5.6%, surgery 2.4%, radiotherapy 2.7%) and disease progression (AM 20.35%, surgery 5.87%, radiotherapy 6.62%) were more common in the AM group. Compared with AM, there were higher risks of sexual dysfunction (95% at 6 mo) and urinary incontinence (55% at 6 mo) after surgery, and of sexual dysfunction (88% at 6 mo) and bowel dysfunction (5% at 6 mo) after radiotherapy. The key limitations are the potential for bias when comparing groups defined by treatment received and changes in the protocol for AM during the lengthy follow-up required in trials of screen-detected PCa.
Conclusions: Analyses according to treatment received showed increased rates of disease-related events and lower rates of patient-reported harms in men managed by AM compared with men managed by radical treatment, and stronger evidence of greater PCa mortality in the AM group.
Patient summary: More than 95 out of every 100 men with low or intermediate risk localised prostate cancer do not die of prostate cancer within 10 yr, irrespective of whether treatment is by means of monitoring, surgery, or radiotherapy. Side effects on sexual and bladder function are better after active monitoring, but the risks of spreading of prostate cancer are more common.

1. Introduction

Clinically localised prostate cancer detected by prostate-specific antigen (PSA) testing is a common problem with 164 690 men in the USA diagnosed in 2017 and 29 430 dying of the disease [1]. Management of men with low- or intermediate-risk disease [2] remains problematic for patients and clinicians [2,3]. It is recognised that many men with low- or intermediate-risk disease do not benefit from immediate radical intervention, although recent studies have shown improved future outcomes in high-risk men [4].

The UK National Institute for Health Research, Health Technology Assessment ProtecT study compared active monitoring (AM), surgery (radical prostatectomy [RP]), and radiotherapy (RT) for men aged 50–69 yr with localised prostate cancer detected through community-based PSA testing [5,6]. All 2664 men eligible to participate in the randomised controlled trial (RCT) were followed up identically [6]. A total of 1643 (62%) men agreed to be randomised ("randomised cohort"), and 997 men declined randomisation and chose treatment ("treatment choice cohort") [7]. Of the 1643 randomised, 22% did not receive their allocated treatment (16% AM, 28% RP, and 23% RT) [7].

Intention-to-treat (ITT) analysis gives unbiased estimates of differences in outcome between allocated treatments, but may underestimate differences between patient groups defined by treatment received [8–10]. This paper presents an analysis of groups defined according to treatment received in the randomised and treatment choice cohorts. Such analyses can be informative to individual patients considering which treatment to undergo, but groups defined by treatment received may not be comparable, as patients with less favourable prognoses may opt for more radical treatment, resulting in "confounding by indication". The analysis presented here attempted to control that confounding using a propensity score approach.

2. Patients and methods

2.1. Study design and participants

In brief, men with clinically localised prostate cancer at one of nine UK centres were invited to participate in the treatment trial comparing AM, RP, and RT [11]. Approval was obtained from the UK Trent Multicentre Ethics Committee (01/4/025; trial registration ISRCTN20141297, NCT02044172). The primary analysis was reported at 10-yr follow-up [2,3,11].

2.2. Interventions, definitions of "treatment received", and follow-up

Men managed by AM had PSA measured 3 monthly in the 1st year and 6–12 monthly thereafter. An increase of 50% or more in PSA over a 12-mo period triggered a clinical review. During RP, men with a PSA level of $\geq$10 μg/l or a Gleason score of $\geq$7 underwent lymphadenectomy. Adjuvant RT was considered for positive margins or extracapsular disease. The RT protocol included neoadjuvant androgen deprivation

therapy (ADT) for 3–6 mo before and concomitantly with three-dimensional conformal RT (74 Gy in 37 fractions). Men were considered to have received each of the treatments according to the following definitions; men who did not fulfil these were excluded:

1. AM if there were two or more PSA tests and no radical treatment in the 12 mo following diagnosis
2. Surgery (RP) if RP was carried out within 12 mo following diagnosis
3. RT if treatment protocol was started within 12 mo and completed within 15 mo; men who underwent brachytherapy within 12 mo of diagnosis were included in the RT arm

Follow-up was standardised according to treatment-specific pathways. In all groups, ADT was offered when serum PSA reached a concentration of 20 μg/l (or less if clinically indicated). Skeletal imaging was carried out if PSA was ≥10 μg/l.

2.3. Outcomes

Cause of death was determined as previously reported [2]. Metastatic disease was defined as bony, visceral, or lymph node metastases, or PSA levels above 100 μg/l. Progression included metastases, clinical T3 or T4 disease, long-term ADT, ureteric obstruction, rectal fistula, or need for urinary catheter due local tumour growth. Initiation of ADT is presented separately as a more objective marker of disease progression.

Cancer grades were classified into the following Gleason grade groups: (1) 3 + 3 = 6; (2) 3 + 4 = 7; (3) 4 + 3 = 7; (4) 4 + 4 = 8, 3 + 5 = 8, 5 + 3 = 8; and (5) ≥9. We combined the prognostic factors into a single "D'Amico" score: men in Gleason grade group 1, with PSA ≤10 μg/l, and having clinical stage ≤T2a were of low risk [12–14].

Health-related quality of life impacts on urinary, bowel, and sexual function were assessed using patient-reported outcome measures (PROMs) including the Expanded Prostate Index Composite (EPIC [15]) and the International Continence Society Male Short Form (ICSmaleSF [16]). We present these two PROMs completed at recruitment, 6 mo, and annually following randomisation; urinary incontinence was assessed by daily pad use over the preceding 4 wk (EPIC), nocturia two or more times per night (ICSmaleSF), potency (EPIC), and blood in stools at least half the time (EPIC). ICSmaleSF was included during the entire course of the trial and the EPIC instrument was used from 2005.

2.4. Statistical analysis

The analysis plan included a secondary analysis of the randomised cohort based on treatment received [17]. This prespecified secondary analysis accommodated multiple testing: if an overall test of event rates across the three groups gave evidence of a difference, this was followed by pairwise tests of RP versus AM and RT versus AM. The other analyses presented in this paper should be considered exploratory.

We compared outcome event rates using proportional hazard regression, with two propensity scores included as covariates. Methods based on the complier average causal effect approach offer better control of confounding by indication, as they control by known and unknown prognostic factors. We used a propensity score approach because it was straightforward generalisation for comparisons between three groups, we could use the same method for the randomised and treatment choice cohorts, and it was difficult to apply the prespecified instrumental variable methods in the current context of complex movements between treatments and the absence of a "usual care" control group.

The propensity score approach was applied to both the randomised and the choice cohort for treatment received. The propensity scores were generated using multinomial logistic regression, with treatment received as the three-category outcome variable, and the following covariates: cT stage (1 or 2), Gleason grade group (1, 2, 3, and >3 [4 and 5 combined]), log-transformed PSA, age in years, and study centre. The scores were generated for each man from the model-fitted values, to give probabilities of undergoing RP rather than AM and RT, and the probability of undergoing RT rather than AM and RP.

Hazard ratios for comparisons between RP and AM, and between RT and AM are presented for the randomised and treatment choice cohorts. The time scale started on the day of allocation. By definition, men in treatment-received groups cannot have an (outcome) event between diagnosis and meeting the group criteria; consequently, men became "at risk" at the second PSA test in the AM group, on the day of surgery in the RP group, and on the 1st day of the protocol in the RT group.

The weighted mean for each treatment comparison is presented ("pooled" estimate) with weighting by the inverse of the variance of the estimates ("fixed-effect" meta-analysis). Data from the two cohorts were combined, and survival curves for prostate cancer mortality and metastasis calculated from the nonparametric baseline hazard estimate of proportional hazard regression models, each model having an additional covariate to distinguish between the randomised and choice cohorts.

For the PROMs, data from the cohorts were combined, and all data after treatment were compared between treatment groups; a likelihood-ratio test quantified evidence against the null hypothesis of equal response over 6 yr of follow-up across the three treatment groups. Two-

Table 1 – Baseline characteristics of men in the randomised cohort and treatment choice cohort, in groups defined by the completion of curative surgery or radiotherapy, or remaining on protocol active monitoring for 12 mo after diagnosis

	Randomised cohort	Treatment choice cohort
Median age in years (Q1, Q3), *n*		
Active monitoring	63 (59, 67), 628	63 (59, 66), 507
Surgery	62 (58, 66), 488	62 (58, 65), 262
Radiotherapy	62 (58, 66), 491	63 (59, 66), 189
Managerial occupation (%)		
Active monitoring	260/621 (42)	256/496 (52)
Surgery	207/482 (43)	142/259 (55)
Radiotherapy	204/482 (42)	91/186 (49)
Median PSA in ng/ml (Q1, Q3), *n*		
Active monitoring	4.4 (3.6, 6.4), 628	4.6 (3.5, 6.5), 507
Surgery	4.7 (3.7, 6.9), 488	4.9 (3.7, 6.8), 262
Radiotherapy	4.7 (3.7, 6.9), 491	5.0 (3.8, 7.3), 189
PSA >10 ng/ml (%)		
Active monitoring	53/628 (8.4)	34/507 (6.7)
Surgery	41/488 (8.4)	26/262 (9.9)
Radiotherapy	51/491 (10)	28/189 (15)
Gleason grade group 1 (%)		
Active monitoring	503/628 (80)	417/507 (82)
Surgery	366/488 (75)	186/262 (71)
Radiotherapy	370/491 (75)	123/189 (65)
Gleason grade group 3 and higher (%)		
Active monitoring	30/628 (4.8)	17/507 (3.4)
Surgery	27/488 (5.5)	18/262 (6.9)
Radiotherapy	42/491 (8.6)	14/189 (7.4)
Clinical stage T2 (%)		
Active monitoring	137/628 (22)	108/507 (21)
Surgery	127/488 (26)	70/261 (27)
Radiotherapy	121/491 (25)	50/189 (26.5)
Low-risk disease (%)[a]		
Active monitoring	409/580 (71)	352/473 (74)
Surgery	293/447 (66)	146/239 (61)
Radiotherapy	298/451 (66)	88/171 (51)

PSA = prostate-specific antigen.
[a] For approximately 8% of men with T2 disease, no information was available on whether their tumour stage was T2a, T2b, or T2c, preventing risk categorisation according to the D'Amico scheme; these men are omitted for this measure.

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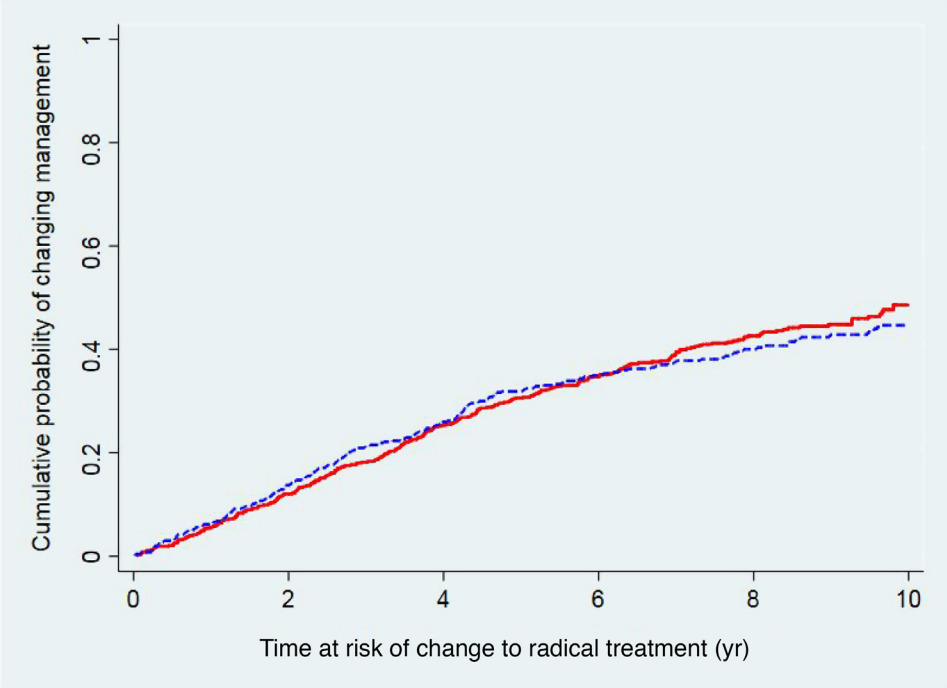

	0 yr	2 yr	4 yr	6 yr	8 yr	10 yr
Randomised cohort						
Men at risk at the start of the period	628	546	458	390	234	104
Switch to radical treatment by the start of the period		75	157	214	254	271
Treatment choice cohort						
Men at risk at the start of the period	507	433	368	308	175	84
Switch to radical treatment by the start of the period		69	130	174	193	203

Fig. 1 – Amongst men who were managed on active monitoring with at least two PSA measurements within 12 mo following diagnosis, the Kaplan-Meier estimates of cumulative probability of moving to a radical treatment subsequent to the second PSA test (time zero) in the randomised cohort (solid red line, *n* = 628) and the choice cohort (dashed blue line, *n* = 507). PSA = prostate-specific antigen.

level random-effect logistic models were used to accommodate repeated assessments, with Gaussian distributed random effects. All models included the same propensity measures employed in the analysis of the clinical event outcomes, and an additional covariate distinguishing men in the randomised and choice cohorts. Missing data were not imputed; all data from men with at least one measure available were included. The random-effect models provided unbiased estimates of treatment comparisons, on the assumption that any systematic determinant of missing data was predictable from the covariates in the model, such as treatment group or earlier measures of outcome (ie, data were "missing at random") [18]. All analyses were performed with Stata software, version 15.1 (StataCorp, College Station, TX, USA).

3. Results

Of the 1643 men who agreed to randomisation (randomised cohort), 1260 (78%) received the allocated treatment; the remaining men chose other treatments. The 997 men who declined randomisation and chose treatments (treatment choice cohort: AM 507 [51%], RP 262 [26%], RT per protocol 125 [13%], other RT including brachytherapy 64 [6%], and 39 other treatments or no treatments completed within the predefined time limits).

In the randomised cohort, 628 men were managed by AM, undergoing at least two PSA tests in their first 12 mo of monitoring. These men remained on monitoring for a median of 7.7 yr (90% range 1.8–13.1 yr) and underwent a median of 3.3 tests per year (90% range 2.1–4.7 tests per year). In the treatment choice cohort, 507 men underwent at least two PSA tests in their first 12 mo of monitoring, and were comparable with men in the randomised cohort in remaining on monitoring for a median of 7.5 yr (90% range 1.7–13.1 yr) and undergoing a median of 3.2 tests per year (90% range 2.0–4.6 tests per year). It is clear that in both cohorts, the vast majority of men managed by AM were undergoing more than the minimum of one PSA test every 12 mo.

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Table 2 – For men in the randomised cohort, clinical outcomes for groups defined by random allocation (ie, an intention-to-treat analysis), and for men in the randomised cohort and treatment choice cohort, clinical outcomes for groups defined by treatment received

	Treatment group as defined in the first column Events/*N* (rate/1000 person years)			*p* value[a]
	Active monitoring	Surgery	Radiotherapy	
Prostate cancer death—randomised cohort				
Randomised groups	8/545 (1.5)	5/553 (0.92)	4/545 (0.75)	0.50
Treatment received[b]	11/628 (1.8)	2/488 (0.43)	4/491 (0.85)	0.08
Prostate cancer death—treatment choice cohort				
Treatment received	10/507 (2.2)	3/262 (1.2)	1/189 (0.57)	0.05
Metastatic disease or prostate cancer death—randomised cohort				
Randomised groups	33/545 (6.1)	13/553 (2.4)	16/545 (3.0)	0.004
Treatment received	36/628 (6.0)	10/488 (2.2)	15/491 (3.2)	0.001
Metastatic disease or prostate cancer death—treatment choice cohort				
Treatment received	28/507 (6.1)	8/262 (3.3)	3/189 (1.7)	<0.001
Disease progression—randomised cohort				
Randomised groups	112/545 (20)	46/553 (8.5)	46/545 (8.6)	<0.001
Treatment received	142/628 (24)	26/488 (5.6)	30/491 (6.3)	<0.001
Disease progression—treatment choice cohort				
Treatment received	79/507 (17)	18/262 (7.5)	15/189 (8.5)	<0.001
Hormone treatment—randomised cohort				
Randomised groups	47/545 (8.7)	26/553 (4.8)	30/545 (5.6)	0.024
Treatment received	53/628 (8.8)	22/488 (4.8)	25/491 (5.3)	0.002
Hormone treatment—treatment choice cohort				
Treatment received	30/507 (6.5)	11/262 (4.6)	11/189 (6.2)	0.19
All death—randomised cohort				
Randomised groups	59/545 (11)	55/553 (10)	55/545 (10)	0.87
Treatment received	64/628 (11)	45/488 (9.7)	55/491 (12)	0.90
All death—treatment choice cohort				
Treatment received	54/507 (12)	23/262 (9.6)	17/189 (9.6)	0.41

[a] All *p* values are for a test of the null hypothesis "equal outcome across the three treatment groups", calculated using proportional hazard regression including the two propensity scores as covariates.
[b] This is a prespecified secondary analysis.

Table 3 – Estimated hazard ratios comparing each pair of treatments in turn: the groups are defined by "treatment received" with adjustment by propensity score to reduce confounding by indication

	Surgery versus active monitoring		Radiotherapy versus active monitoring		Radiotherapy versus surgery	
	Hazard ratio (95% confidence interval)	*p* value	Hazard ratio (95% confidence interval)	*p* value	Hazard ratio (95% confidence interval)	*p* value
Prostate cancer death						
Randomised cohort	0.24 (0.05, 1.07)		0.45 (0.14, 1.41)		1.89 (0.34,10.38)	
Treatment choice cohort	0.39 (0.10, 1.49)		0.14 (0.02, 1.15)		0.35 (0.03, 3.59)	
Pooled estimate	0.32 (0.12, 0.87)	0.026	0.34 (0.12, 0.92)	0.034	1.07 (0.27, 4.30)	0.9
Metastatic disease or prostate cancer death						
Randomised cohort	0.31 (0.16, 0.64)		0.48 (0.26, 0.89)		1.54 (0.69, 3.43)	
Treatment choice cohort	0.35 (0.15, 0.78)		0.18 (0.05, 0.62)		0.52 (0.13, 2.03)	
Pooled estimate	0.33 (0.19, 0.55)	<0.001	0.40 (0.23, 0.69)	0.001	1.17 (0.59, 2.34)	0.7
Disease progression						
Randomised cohort	0.19 (0.12, 0.29)		0.20 (0.13, 0.29)		1.05 (0.62, 1.78)	
Treatment choice cohort	0.31 (0.18, 0.53)		0.32 (0.18, 0.57)		1.04 (0.51, 2.09)	
Pooled estimate	0.23 (0.16, 0.33)	<0.001	0.23 (0.17, 0.32)	<0.001	1.05 (0.69, 1.60)	0.8
Hormone treatment						
Randomised cohort	0.47 (0.28, 0.77)		0.51 (0.32, 0.83)		1.09 (0.61, 1.95)	
Treatment choice cohort	0.54 (0.26, 1.09)		0.73 (0.35, 1.50)		1.36 (0.57, 3.26)	
Pooled estimate	0.49 (0.33, 0.74)	0.001	0.57 (0.38, 0.85)	0.005	1.17 (0.72, 1.89)	0.5
All death						
Randomised cohort	0.97 (0.66, 1.42)		1.06 (0.74, 1.52)		1.09 (0.74, 1.63)	
Treatment choice cohort	0.77 (0.46, 1.28)		0.73 (0.42, 1.29)		0.95 (0.49, 1.82)	
Pooled estimate	0.89 (0.66, 1.21)	0.5	0.95 (0.70, 1.29)	0.7	1.05 (0.75, 1.47)	0.8

Estimates for the randomised and treatment choice cohorts are combined as a "pooled estimate".

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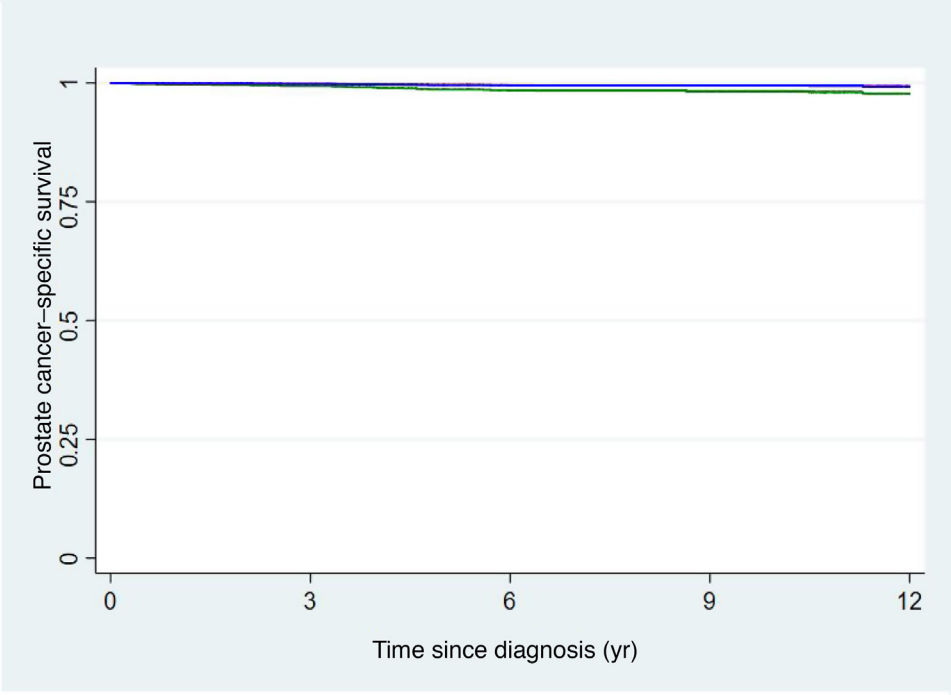

	0 yr	3 yr	6 yr	9 yr	12 yr
Randomised cohort					
Men at risk at the start of the period	1607	1580	1533	927	286
Prostate cancer deaths accumulated by the start of the period		2	6	10	15
Treatment choice cohort					
Men at risk at the start of the period	958	947	911	461	131
Prostate cancer deaths accumulated by the start of the period		3	9	13	13

Fig. 2 – Prostate cancer-specific survival curves (derived from the proportional hazard regression model) for groups defined by receiving active monitoring (green), surgery (red), and radiotherapy (blue), with corresponding groups combined across randomised and treatment choice cohorts.

Baseline characteristics of men in each of the groups are shown in Table 1 (with all Gleason grade groups presented in Supplementary Table 1). The vast majority underwent one of the study treatments as defined previously, with just 36/1643 (2.2%) and 39/997 (3.9%) of men in the randomised and choice cohorts, respectively, not included in the three defined treatment groups. The two cohorts differed in a greater proportion of men in managerial occupations in the choice cohort. Selection biases were evident, with men with higher-risk grade and stage disease being more likely to undergo radical treatments than AM [7].

Fig. 1 presents the Kaplan-Meier estimate of the probability of moving to radical treatment from AM over a median of 10 yr. Very similar rates were observed in the randomised and treatment choice cohorts, with around 45% of men in both having moved to radical treatment within 10 years.

Table 2 includes clinical outcomes for randomly allocated groups with the initial ITT comparison adjusted for the propensity scores. Outcomes are then presented for treatment-received groups in both the randomised and the choice cohort. While absolute differences are small, there is strong evidence of increased metastatic disease, disease progression, and initiation of ADT for AM compared with surgery and RT. The risks of disease-specific and all-cause death remain low and consistent with chance. Risks of these adverse clinical outcomes for treatment received in both the randomised and the choice cohort are similar, the exceptions being lower rates of disease progression and ADT in the treatment-choice group managed by AM. Supplementary Table 2 presents clinical outcomes by treatment-received group and Gleason grade group at diagnosis.

Most progression was development of a high stage (T3 or T4) or starting of ADT, and was higher in the AM group (60% [85/142] in the randomised cohort and 57% [45/79] in the choice cohort). The presence of stage T3 or T4 did not prevent subsequent radical treatment in some men, with 20% (22/112) undergoing RP and 35% (39/112) undergoing RT.

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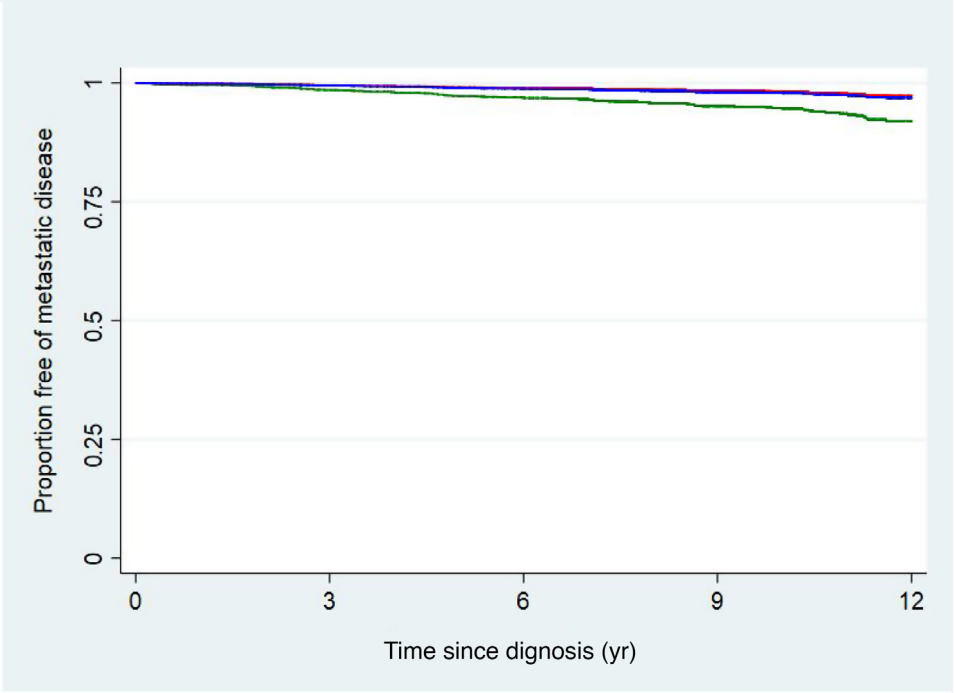

	0 yr	3 yr	6 yr	9 yr	12 yr
Randomised cohort					
Men at risk at the start of the period	1607	1568	1507	900	271
Metastatic disease accumulated by the start of the period		14	33	49	60
Treatment choice cohort					
Men at risk at the start of the period	958	937	897	452	129
Metastatic disease accumulated by the start of the period		13	24	32	37

Fig. 3 – Proportions free of metastatic disease (derived from the proportional hazard regression model) for groups defined by receiving active monitoring (green), surgery (red), and radiotherapy (blue), with corresponding groups combined across randomised and treatment choice cohorts.

Table 3 presents pairwise comparisons for treatment received in the randomised and choice cohorts separately, with the corresponding results from the two cohorts then being pooled. The pooled estimates indicate strong evidence that surgery and RT, each in comparison with AM, reduce the incidence of prostate cancer death (Fig. 2), metastatic disease (Fig. 3), disease progression, and the onset of hormone treatment. There was no evidence that either surgery or RT compared with AM reduced all-cause death, nor evidence of a difference on any of the five outcome measures when comparing surgery with RT.

In exploratory analyses, we combined the surgery group and the RT treatment-received group, and compared outcomes with AM. There was a reduction in prostate cancer-specific mortality with radical treatment compared with AM in the randomised cohort (hazard ratio = 0.34; 95% confidence interval [CI] 0.13, 0.94) and the treatment choice cohort (hazard ratio = 0.27; 95% CI 0.08, 0.91). Pooling of these two estimates suggested a marked decrease in prostate cancer mortality with radical treatment (hazard ratio = 0.31; 95% CI 0.14, 0.67; $p = 0.003$), although the small number of prostate cancer deaths means that the absolute reduction is modest.

Urinary incontinence, as measured by patient-reported pad use, was increased following surgery compared with AM and RT ($p < 0.001$; Fig. 4 and Supplementary Table 3). Six months after surgery, 55% reported daily use of pads, reducing to 20% after 3 yr and remaining stable thereafter. Pad use was negligible following RT but increased gradually to 7% in the AM group. An increased proportion of men reported nocturia in the 6 mo following RT (65%) before stabilising at 30–40% for all men irrespective of management ($p < 0.001$; Fig. 4 and Supplementary Table 4). RT and surgery both reduced the proportion of men reporting potency at 6 mo (18.5% and 5%, respectively). Although there was some recovery by 2 yr, only 28–30% of men in the RT group and 15% in the surgery group reported being potent at 6 yr ($p < 0.001$; Fig. 4 and Supplementary Table 5). More men in the AM group reported themselves as potent, but this reduced gradually over time, reflecting ageing and

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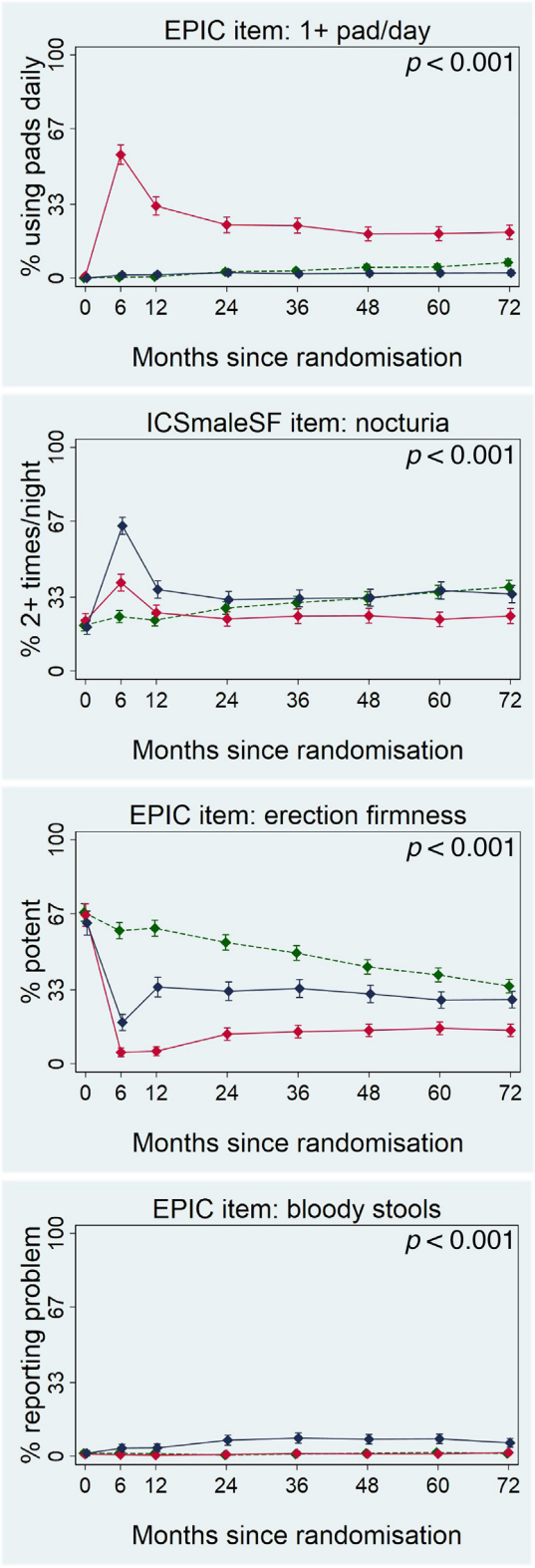

Fig. 4 – Patient-reported incontinence pad use, nocturia, potency, and bloody stools by active monitoring (green dash), radical prostatectomy (red), and radiotherapy (blue) groups, defined by treatment received. EPIC = Expanded Prostate Index Composite; ICSmaleSF = International Continence Society Male Short Form.

receipt of radical treatment during follow-up. Following RT, a small proportion of men (around 5%) experienced bloody stools at least half the time, with this proportion maintained over the 6-yr follow-up ($p < 0.001$; Fig. 4 and Supplementary Table 6).

4. Discussion

The analysis presented here compares groups according to treatment received in two cohorts within a trial with uniform initial recruitment: the randomised cohort that initially agreed to randomisation, and the treatment choice cohort that was eligible but declined randomisation and chose treatment. For the prespecified comparison of groups defined by treatment received within the randomised cohort, we found no evidence of a difference in prostate cancer death between the three treatments at a median follow-up of 10 yr, which is in accord with the primary ITT analysis [2].

The exploratory analyses comparing outcomes between groups defined by treatment received, in the combined and treatment choice cohorts, gave results that were in broad agreement with the ITT analysis [2]. However, when the outcomes for the two cohorts were pooled, there was evidence of a lower risk of prostate cancer death following surgery and RT compared with AM, although the absolute reduction in prostate cancer deaths with radical treatment was modest. However, recent studies suggest that the use of metastasis-free survival is a highly appropriate endpoint for prostate cancer trials [19–21]; studies with both the ITT and this comparison of groups defined by treatment received confirmed the increased rates of metastasis-free survival in the two radical treatment arms.

The four PROMs presented in this paper lead to the same conclusions as the ITT analysis [3], with the results being clearer. There was strong evidence of substantial and persistent elevations in the rates of urinary incontinence and erectile dysfunction following surgery, in the rates of nocturia in the 12 mo following RT, and in the rates of erectile dysfunction and bloody stools following RT. Men managed by AM avoided the impacts caused by radical treatments, although slow and gradual increases in urinary incontinence, nocturia, and erectile dysfunction were reported during follow-up, reflecting ageing and increased receipt of radical treatments over time. We have previously noted the "trade-off" that men with localised prostate cancer need to make between side effects on urinary, bowel, and sexual function, against reducing later risks of metastasis and progression, and resulting impacts on quality and length of life [2,3].

The key limitation to analyses based on treatment received rather than ITT is the potential for bias. Such groups will differ in terms of occupation, and prognostic factors that influence clinicians to advise patients to

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undergo specific treatments. In both the randomised and the treatment choice cohort, there was evidence that men with higher-risk disease were more likely to be managed by radical treatments and lower-risk men by AM [7]. However, despite such selection biases, clinical outcomes were worse in the AM group.

We employed propensity score methods to control for confounding due to imbalance in known prognostic factors. However, such approaches do not control for unknown factors, although confidence in the results reported here is increased by three factors. Firstly, the similarity with the primary ITT analysis from the RCT. Secondly, the direction of confounding by known prognostic factors (eg, patients with low-risk disease were more likely to be managed by AM) means that known confounding cannot explain increased prostate cancer-related events in the AM group. Thirdly, all-cause death rates are comparable across the three treatment-received groups, suggesting that a man's general health did not underlie the selection biases.

A second limitation results from the natural history of screen-detected and localised prostate cancer, requiring studies with many years of follow-up during which clinical practice evolves. Evaluation of men for AM has developed, largely driven by changes in the diagnostic pathway, which uses prebiopsy imaging using multiparametric magnetic resonance imaging (mpMRI) scanning, transperineal biopsy, and targeting of visible lesions. This will likely lead to a reduction in the diagnosis of low-risk, low-volume prostate cancer and an increase in the diagnosis of significant cancers requiring early intervention [22,23].

The CAP trial of a single screening round using PSA testing demonstrated that conventional diagnostic pathways miss cancers destined to be lethal. Many such men have PSA levels below the conventional threshold for referral, while diagnosing many low-risk tumours [24]. In addition, the results of AM reported here may reflect that some men choosing or being randomised to AM may not have been recommended for this option on the basis of current management that would include mpMRI [23]. Despite this limitation, and the low intensity of monitoring primarily by PSA kinetics, mortality from prostate cancer remained very low. Rates of change of management to radical treatments in both ProtecT cohorts were in keeping with previous active surveillance programmes reporting approximately 30% of men receiving radical treatment within 3 yr [25,26].

Treatments for progressing prostate cancer have also improved markedly in recent years, and it is likely that this has also contributed to the low prostate cancer mortality rates observed in the trial [27].

5. Conclusions

The ProtecT primary ITT analysis, and analyses of the randomised and treatment received cohorts according to treatment received have confirmed that surgery and RT reduce metastasis and progression compared with AM, but impact sexual, urinary, and bowel functioning. In addition, exploratory analyses suggest that radical treatments may be associated with lower prostate cancer mortality than AM, albeit the numbers of such deaths were low irrespective of treatment. The findings need to be considered in the context of potential biases and confounding variables in the treatment received analysis. Follow-up of these cohorts is continuing and will clarify further the various trade-offs that need to be weighed up when choosing treatment for localised prostate cancer.

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Obtaining funding: Hamdy, Donovan, Neal.
Administrative, technical, or material support: None.
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Malee Fernando, John Goepel, David Griffiths, Ken Grigor, Nick Mayer, Murali Varma, and Anne Warren. Radiologists and medical physics: Helen Appleby, Dominic Ash, Dean Aston, Steven Bolton, Graham Chalmers, John Conway, Nick Early, Tony Geater, Lynda Goddall, Claire Heymann, Deborah Hicks, Liza Jones, Susan Lamb, Geoff Lambert, Gill Lawrence, Geraint Lewis, John Lilley, Aileen MacLeod, Pauline Massey, Alison McQueen, Rollo Moore, Lynda Penketh, Janet Potterton, Neil Roberts, Helen Showler, Pam Shuttleworth, Stephen Slade, Alasdair Steele, James Swinscoe, Marie Tiffany, John Townley, Jo Treeby, Michael Weston, Joyce Wilkinson, Lorraine Williams, Lucy Wills, Owain Woodley, and Sue Yarrow. Other researchers and data managers: Lucy Brindle, Linda Davies, Michael Davis, Dan Dedman, Elizabeth Down, Hanan Khazragui, Richard M. Martin, Sian Noble, Hilary Taylor, Marta Tazewell, Emma L. Turner, Julia Wade, and Eleanor Walsh. Administrative support: Susan Baker, Elizabeth Bellis-Sheldon, Chantal Bougard, Joanne Bowtell, Catherine Brewer, Chris Burton, Jennie Charlton, Nicholas Christoforou, Rebecca Clark, Susan Coull, Christine Croker, Rosemary Currer, Claire Daisey, Gill Delaney, Rose Donohue, Jane Drew, Rebecca Farmer, Susan Fry, Jean Haddow, Alex Hale, Susan Halpin, Belle Harris, Barbara Hattrick, Sharon Holmes, Helen Hunt, Vicky Jackson, Donna Johnson, Mandy Le Butt, Jo Leworthy, Tanya Liddiatt, Alex Martin, Jainee Mauree, Susan Moore, Gill Moulam, Jackie Mutch, Kathleen Parker, Christopher Pawsey, Michelle Purdie, Teresa Robson, Lynne Smith, Carole Stenton, Tom Steuart-Feilding, Beth Stott, Chris Sully, Caroline Sutton, Carol Torrington, Zoe Wilkins, Sharon Williams, Andrea Wilson, and Ashleigh Weaver. Joint ProtecT and CAP cause of death committee: Richard M. Martin (research lead), Peter Albertsen (chair), Jan Adolfsson, Amit Bahl, Michael Baum, Anthony Koupparis, Jon McFarlane, Jon Oxley, Colette Reid, Mary Robinson, Emma Turner, and Anthony Zietman. Other researchers and data managers: Elizabeth Hill, Siaw Yein Ng, Naomi Williams, Jessica Toole, Charlotte Davies, Laura Hughes, Mari-Anne, Rowlands, Lindsey Bell, Sean Harrison, and Jainnee Mauree. Independent data monitoring committee: chairs: Adrian Grant and Ian Roberts; members: Deborah Ashby, Richard Cowan, Peter Fayers, Killian Mellon, James N'Dow, Tim O'Brien, and Michael Sokhal. Trial steering committee: Michael Baum (chair), Jan Adolfsson, Peter Albertsen, David Dearnaley, Fritz Schröder, Tracy Roberts, and Anthony Zietman.***Financial disclosures:*** David E. Neal certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

Acknowledgements: The views and opinions expressed in this article are those of the authors and do not necessarily reflect those of the U.K. Department of Health.

Supported by the U.K. National Institute for Health Research Health Technology Assessment Programme (NIHR HTA: projects 96/20/06, 96/20/99, with the University of Oxford as sponsor). Dr. Donovan is supported by the NIHR Collaboration for Leadership in Applied Health Research and Care West, hosted by University Hospitals Bristol NHS Foundation Trust, and Dr. Hamdy is supported by the Oxford NIHR Biomedical Research Centre Surgical Innovation and Evaluation Theme and the Cancer Research U.K. Oxford Centre. This study was conducted in collaboration with the Bristol Randomised Trials Collaboration (BRTC), a UKCRC Registered Clinical Trials Unit, which as part of the Bristol Trials Centre is in receipt of National Institute for Health Research CTU support funding.

We thank all the ProtecT trial participants and researchers for their contributions, and the members of the independent trial steering committee, data and safety monitoring committee, and cause-of-death evaluation committee.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2019.10.030.

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