

# The ProtecT trial: analysis of the patient cohort, baseline risk stratification and disease progression

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## Objective

To test the hypothesis that the baseline clinico-pathological features of the men with localized prostate cancer (PCa) included in the ProtecT (Prostate Testing for Cancer and Treatment) trial who progressed ( $n = 198$ ) at a 10-year median follow-up were different from those of men with stable disease ( $n = 1409$ ).

## Patients and Methods

We stratified the study participants at baseline according to risk of progression using clinical disease stage, pathological grade and PSA level, using Cox proportional hazard models.

## Results

The findings showed that 34% of participants ( $n = 505$ ) had intermediate- or high-risk PCa, and 66% ( $n = 973$ ) had low-risk PCa. Of 198 participants who progressed, 101 (51%) had baseline International Society of Urological Pathology Grade Group 1, 59 (30%) Grade Group 2, and 38 (19%) Grade Group 3 PCa, compared with 79%, 17% and 5%, respectively,

for 1409 participants without progression ( $P < 0.001$ ). In participants with progression, 38% and 62% had baseline low- and intermediate-/high-risk disease, compared with 69% and 31% of participants with stable disease ( $P < 0.001$ ). Treatment received, age (65–69 vs 50–64 years), PSA level, Grade Group, clinical stage, risk group, number of positive cores, tumour length and perineural invasion were associated with time to progression ( $P \leq 0.005$ ). Men progressing after surgery ( $n = 19$ ) were more likely to have a higher Grade Group and pathological stage at surgery, larger tumours, lymph node involvement and positive margins.

## Conclusions

We demonstrate that one-third of the ProtecT cohort consists of people with intermediate-/high-risk disease, and the outcomes data at an average of 10 years' follow-up are generalizable beyond men with low-risk PCa.

## Keywords

Prostate cancer, pathology, risk stratification

## Introduction

The Prostate Testing for Cancer and Treatment (ProtecT) randomized clinical trial (RCT) recruited men aged 50–69 years and compared the effectiveness of active monitoring

(AM), radical prostatectomy (RP) and radical radiotherapy (RT). A total of 1643 men with clinically localized prostate cancer (PCa) agreed to randomization. The primary intention-to-treat analysis at a median follow-up of 10 years showed that the rate of overall mortality was ~1%,

irrespective of treatment assigned. However, radical treatment was associated with ~50% reduced disease progression/metastasis compared with AM (AM 6.3, RT 3.0 and RP 2.4 events per 1000 person-years;  $P = 0.004$ ) [1].

Treatment decisions for localized PCa rely on patient stratification for disease progression risk using baseline clinico-pathological features, risk calculators, physician counselling and patient preference. Current risk stratifications are based on a combination of PSA value, clinical tumour (cT) stage, and biopsy Gleason score/International Society of Urological Pathology (ISUP) Grade Group [2,3], with considerable heterogeneity in outcomes within groupings.

We provide a comprehensive characterization of the ProtecT cohort composition according to risk stratification, as well as detailed pathological information on participants who received RP. We reviewed the baseline risk classification of all ProtecT participants using clinico-pathological features, including clinical stage, grade at diagnosis and serum PSA levels. The aim of the present study was to test the hypothesis that the clinico-pathological features of participants with disease progression differed from those of participants whose disease remained stable and that such an analysis may determine potential features associated with prediction of clinical outcomes.

## Methods

### Participants and Study Design

The ProtecT trial design, baseline socio-demographic and median 10-year outcomes have been published elsewhere [1,4–6]. A total of 2417 men were identified with localized PCa, 1643 of whom agreed to be randomized to AM, RP or RT (74 Gray in 37 fractions with neoadjuvant androgen deprivation therapy). AM is a form of active surveillance (AS), comprising regular PSA tests (>90% of participants received a minimum of two PSA tests per annum) and clinical review if PSA level rises  $\geq 50\%$  in a 12-month period. In some participants, further investigations and patient/physician preference triggered change of management to radical treatment.

Participants who started a protocol treatment within 12 months from randomization were the focus of the present analysis (1607/1643 men). The participants were categorized as receiving AM if they were monitored with at least two PSA tests within 1 year of eligibility (diagnosis), and as receiving RP if they underwent surgery within 1 year. The RT group comprised men who received this or similar (e.g. brachytherapy) within 12 months, and completed treatment within 15 months (or died before completion).

### Risk Status

Participants with localized PCa was defined as low risk if they had Gleason score 6 (Grade Group 1) and PSA level  $\leq 10$  ng/

mL and T1c/T2a disease; intermediate risk if they had Gleason score 7 (Grade Group 2–3), a PSA level  $> 10$  and  $\leq 20$  ng/mL, or T2b disease, and high risk if they had Gleason score  $\geq 8$  (Grade Group  $\geq 4$ ), or PSA  $> 20$  ng/mL, or T2c disease. Some participants had cT2 disease according to a previous TNM staging system and so could not be given a risk score ( $n = 129$ ).

### Pathology

Expert histopathologists reported prostate biopsy and RP pathology on standardized proformas [7]. Grade Group values for prostate biopsies were derived using the sum of the primary Gleason grade and the greater of the secondary or tertiary Gleason grades, reflecting current practice. Grade Group values for RP were derived using the sum of the primary and secondary Gleason grades. Aggregate and maximum tumour lengths in the core biopsies were measured in mm. The aggregate tumour length was calculated as the summation of lengths on the right, left and unknown sides and targeted biopsy. RP specimens were whole-embedded, and tumour volume calculated. Surgical margins were recorded as positive if tumour was seen at an inked margin, and classified as apical, basal, intraprostatic or extraprostatic [8]. The ProtecT pathology group performed regular internal audits of biopsy cores and RP specimens to minimize assessment variation.

### Progression and Metastasis

‘Progression’ was subdivided into two categories: PCa death and/or metastasis, and ‘other’ progression (change to  $\geq$ cT3 disease [extracapsular], indication for androgen deprivation therapy, ureteric obstruction, rectal fistula, or need for a urinary catheter due to local tumour growth). Cause of death was ascertained by an independent cause-of-death committee [9], and disease-specific deaths were classed as ‘definitely’ or ‘probably’ attributable to PCa. Metastatic disease was defined as bony, visceral, or lymph-node metastases on imaging, or PSA  $> 100$  ng/mL. Clinical progression was defined by the presence of any of the following: evidence of metastases, or ‘other’ progression (as defined above). Primary treatment failure after RP was defined as a PSA  $\geq 0.2$  ng/mL 3 months after surgery, and after RT was defined according to the Phoenix Consensus Conference recommendations [10].

### Statistical Analysis

All analyses were carried out using STATA 15.1 [11]. Cox proportional hazards models were used, all adjusting for treatment received and age at randomization, to estimate the hazard ratio, 95% CIs and  $P$  values. Competing risks regression was carried out as sensitivity analyses, where all-cause mortality (not including PCa deaths) was included in

the model as a competing risk, using the Fine and Gray method.

The Cox proportional hazards model and likelihood ratio test were used to test the interaction between treatment allocation and each of: baseline Grade Group (1,  $\geq 2$ ); clinical stage (cT1c, cT2); risk group (low, intermediate/high); age (<65,  $\geq 65$  years); and PSA level (<10 ng/mL,  $\geq 10$  ng/mL), on time to progression. The risk classification system, and its ability to predict progression, was also assessed using sensitivity and specificity calculations.

The above approach to the analysis was adapted to an investigation of participants randomized to, and receiving, RP within 12 months, the risk (hazard ratio) of progression was compared across surgical pathological features adjusted for participant age. Where the number of events was too low to successfully conduct a Cox proportional hazards model, the log rank test was used. Competing risks analyses were carried out as sensitivity analyses. Categorical variables were included in the model using dummy variables. Ordinal categories were included as continuous categories to assess linear trend. Upgrading was defined as an increase from Grade Group 1 at baseline to Grade Group  $\geq 2$  at RP, or moving from Grade Group 2 at baseline to Grade Group  $\geq 3$ . Upstaging was defined as moving from cT1/T2 disease at baseline ( ProtecT trial inclusion criterion) to pT3/T4 at RP.

## Study Ethics

Trial approval was obtained from the UK East Midlands (formerly Trent) Multicentre Research Ethics Committee (01/4/025). The University of Oxford is the trial sponsor (University of Sheffield prior to 2009). ProtecT is registered with Current Controlled Trials (ISRCTN20141297) and ClinicalTrials.gov (NCT00632983).

## Results

### ProtecT Cohort Composition

Randomized participants ( $n = 1643$ ) had a mean age of 62 years, were mainly of white ethnicity (98%), and had a median PSA level of 4.6 ng/mL. Their clinico-pathological characteristics have been reported previously [5]. Analysis of the randomized participants ( $n = 1643$ ) showed that 34% ( $n = 505$ ) had intermediate- or high-risk disease, and 66% ( $n = 973$ ) had low-risk PCa (Table 1). Of 1643 randomized participants, 1607 started a protocol treatment within 12 months. Of these, 1208 (75%) had Grade Group 1 disease, and 1222 (76%) had stage cT1c disease. Amongst participants with Grade Group 1 disease at diagnosis, 87% were in the low-risk category at baseline, and 13% had intermediate- or higher-risk disease.

### Baseline Clinico-Pathological Features of Participants with Disease Progression

Of 1607 participants analysed who received AM, RP or RT within 12 months, 198 (12%) developed PCa progression during a median follow-up of 10 years (Table 1). Of the participants with disease progression, 72% (142/198) received AM. The progression events included the following: 17 PCa-specific deaths; 44 participants who developed distant metastases, and 137 participants who had other clinical evidence of disease progression (Table 1).

Treatment received, age (65–69 vs 50–64 years), PSA, Grade Group, cT stage, risk group, number of PCa-involved biopsy cores, maximum length of tumour (median 5.0 vs 3.0 mm), aggregate length of tumour (median 8.0 vs 4.0 mm), and presence of perineural invasion were each associated with increased disease progression risk ( $P < 0.001$  for each; Table 1). There was no evidence of an interaction between Grade Group (Grade Group 1, Grade Group  $\geq 2$ ) and treatment allocation on time to progression ( $P = 0.709$ ; Table 2, Fig. 1). There was no evidence of an interaction between treatment allocation and PCa stage (Fig. 1), age group (Fig. 2) or PSA level (Fig. 2). At baseline and according to risk classification, 63 of 166 participants (38%) with disease progression had low-risk disease, and 103 (62%) had intermediate-/high-risk disease, compared with 69% (910/1312) and 31% (402/1312), respectively, of participants without progression ( $P < 0.001$ ). Additional adjustment for all characteristics in Table 1, excluding those used in the risk categorization, did not alter these associations ( $P < 0.001$ ). In assessing risk group as an indicator of progression, the prognostic sensitivity for intermediate-/ high- vs low-risk disease was 62% (103/166), while specificity was 69% (910/1312). Low-risk disease at baseline suggested that a participant was unlikely to progress (negative predictive value 94%), but the classification of intermediate and/or high risk was poor at predicting progression (positive predictive value 20%). Subdividing the groups into low-/ intermediate- vs high-risk disease led to sensitivity and specificity values of 18% and 91%, respectively.

### Radical Prostatectomy Pathology Characteristics

Of men randomized to RP, 397 received their allocated treatment within 12 months, with 19 developing progression after surgery. No participant who progressed after surgery had solely Grade Group 1 disease on RP histopathological examination, whereas eight participants had Grade Group 2, seven had Grade Group 3, and four had Grade Group  $\geq 4$ . This differed from participants without progression ( $P < 0.001$ ; Table 3). RP pathological features associated with progression included pathological Grade Group, stage, largest tumour volume, lymph node involvement, perineural

**Table 1** Hazard ratios for disease progression by baseline age and clinical characteristics of participants who commenced prostate cancer treatment within 1 year ( $N = 1607$ ).

| Characteristic                                             | N (%)     | No progression<br>(n = 1409) | Progression<br>(n = 198) | Progression HR<br>(95% CI); $P^*$ | Metastasis or<br>PCa-specific<br>death (n = 61) | Metastasis or<br>PCa-specific death<br>HR (95% CI); $P^*$ |
|------------------------------------------------------------|-----------|------------------------------|--------------------------|-----------------------------------|-------------------------------------------------|-----------------------------------------------------------|
| Treatment, n (%)                                           |           |                              |                          |                                   |                                                 |                                                           |
| Active monitoring                                          | 628 (39)  | 486 (77)                     | 142 (23)                 | —                                 | 36 (6)                                          | —                                                         |
| Radical prostatectomy                                      | 488 (30)  | 462 (95)                     | 26 (5)                   | 0.23 (0.15, 0.35); <0.001         | 10 (2)                                          | 0.37 (0.19, 0.76); 0.006                                  |
| Radical radiotherapy <sup>‡</sup>                          | 491 (31)  | 461 (94)                     | 30 (6)                   | 0.25 (0.17, 0.38); <0.001         | 15 (3)                                          | 0.54 (0.30, 0.99); 0.048                                  |
| Age <sup>§</sup>                                           |           |                              |                          |                                   |                                                 |                                                           |
| Median (IQR) age, years                                    |           | 62.0 (58.0, 66.0)            | 64.0 (59.0, 67.0)        | 1.04 (1.01, 1.07); 0.010          | 65.0 (59.0, 67.0)                               | 1.03 (0.98, 1.09); 0.206                                  |
| Age group 50–64 years, n (%)                               | 1005 (63) | 904 (90)                     | 101 (10)                 | —                                 | 29 (3)                                          | —                                                         |
| Age group 65–69 years, n (%)                               | 602 (37)  | 505 (84)                     | 97 (16)                  | 1.59 (1.20, 2.10); 0.001          | 32 (5)                                          | 1.85 (1.12, 3.06); 0.017                                  |
| PSA                                                        |           |                              |                          |                                   |                                                 |                                                           |
| Median (IQR) PSA, µg/L                                     |           | 4.5 (3.6, 6.4)               | 5.9 (4.3, 8.3)           | 1.13 (1.09, 1.18); <0.001         | 5.7 (4.3, 8.2)                                  | 1.11 (1.03, 1.18); 0.003                                  |
| PSA ≤10 µg/L, n (%)                                        | 1462 (91) | 1298 (89)                    | 164 (11)                 | —                                 | 50 (3)                                          | —                                                         |
| PSA >10 µg/L, n (%)                                        | 145 (9)   | 111 (77)                     | 34 (23)                  | 2.54 (1.75, 3.69); <0.001         | 11 (8)                                          | 2.27 (1.18, 4.38); 0.014                                  |
| ISUP Grade Group <sup>¶</sup> , n (%)                      |           |                              |                          |                                   |                                                 |                                                           |
| 1                                                          | 1208 (75) | 1107 (92)                    | 101 (8)                  | —                                 | 28 (2)                                          | —                                                         |
| 2                                                          | 296 (18)  | 237 (80)                     | 59 (21)                  | 3.32 (2.39, 4.61); <0.001         | 22 (7)                                          | 3.31 (2.39, 4.58); <0.001                                 |
| 3+                                                         | 103 (6)   | 65 (63)                      | 38 (37)                  | 8.33 (5.65, 12.26); <0.001        | 11 (11)                                         | 8.54 (5.81, 12.56); <0.001                                |
| Clinical stage, n (%)                                      |           |                              |                          |                                   |                                                 |                                                           |
| cT1c                                                       | 1222 (76) | 1100 (90)                    | 122 (10)                 | —                                 | 36 (3)                                          | —                                                         |
| cT2                                                        | 385 (24)  | 309 (80)                     | 76 (20)                  | 2.35 (1.76, 3.14); <0.001         | 25 (6)                                          | 2.30 (1.38, 3.84); 0.001                                  |
| Risk group **, n (%)                                       |           |                              |                          |                                   |                                                 |                                                           |
| Low                                                        | 973 (66)  | 910 (94)                     | 63 (6)                   | —                                 | 19 (2)                                          | —                                                         |
| Intermediate/High                                          | 505 (34)  | 402 (80)                     | 103 (20)                 | 4.12 (3.01, 5.63); <0.001         | 31 (6)                                          | 4.20 (3.06, 5.77); <0.001                                 |
| Biopsy cores with cancer, n (%)                            |           |                              |                          |                                   |                                                 |                                                           |
| 1                                                          | 502 (32)  | 467 (93)                     | 35 (7)                   | —                                 | 12 (2)                                          | —                                                         |
| 2                                                          | 328 (20)  | 288 (88)                     | 40 (12)                  | 1.82 (1.16, 2.87); 0.010          | 11 (3)                                          | 1.41 (0.62, 3.20); 0.411                                  |
| 3+                                                         | 759 (48)  | 637 (84)                     | 122 (16)                 | 2.80 (1.92, 4.08); <0.001         | 37 (5)                                          | 2.26 (1.18, 4.35); 0.014                                  |
| Perineural invasion, n (%)                                 |           |                              |                          |                                   |                                                 |                                                           |
| No                                                         | 1263 (80) | 1135 (90)                    | 128 (10)                 | —                                 | 37 (3)                                          | —                                                         |
| Yes                                                        | 320 (20)  | 252 (79)                     | 68 (21)                  | 2.49 (1.85, 3.34); <0.001         | 23 (7)                                          | 2.61 (1.55, 4.40); <0.001                                 |
| Median (IQR) maximum length<br>in any core, mm (n = 1454)  |           | 2.0 (1.0, 5.0)               | 5.0 (2.0, 7.0)           | 1.04 (1.02, 1.05); <0.001         | 5.0 (2.0, 7.0)                                  | 1.01 (0.99, 1.04); 0.265                                  |
| Median (IQR) aggregate length of<br>tumours, mm (n = 1571) |           | 4.0 (2.0, 10.0)              | 8.0 (4.0, 18.0)          | 1.02 (1.02, 1.03); <0.001         | 7.0 (3.0, 20.0)                                 | 1.02 (1.00, 1.03); 0.009                                  |

HR, hazard ratio; IQR, interquartile range; ISUP, International Society of Urological Pathology; PCa, prostate cancer. \*Cox models for time to progression, adjusting for age at randomization and treatment received unless covariates being tested. †Cox models for time to metastasis or prostate cancer death, adjusting for age at randomization and treatment received unless covariates being tested. ‡Includes trial protocol radiotherapy, non-protocol radiotherapy and brachytherapy. §Age at randomization. ¶ISUP Grade Group derived from sum of primary and highest Gleason grade of secondary and tertiary. \*\*Low if Grade Group = 1 and PSA ≤ 10 ng/mL and T1c/T2a, high if Grade Group ≥ 4 or PSA > 20 ng/mL or T2c and intermediate if Grade Group = 2/3 or 10 < PSA ≤ 20 ng/mL or T2b.

invasion, vascular invasion, any positive margin status, and disease upstaging ( $P < 0.05$  for each comparison). There was no evidence that the number of tumours in the prostate was related to progression. PCa upstaging after surgery was associated with disease progression ( $P < 0.001$ ) and there was weak evidence to suggest an association with histopathological upgrading ( $P = 0.059$ ).

## Discussion

The baseline characteristics of the 1643 randomized participants were described previously [1,5], and showed that 76% ( $n = 1249$ ) of participants had T1c disease, and 77% ( $n = 1266$ ) had ISUP Grade Group 1 PCa, suggesting that over three-quarters of our participants had low-risk disease. This has led to a perception that the favourable clinical outcomes at a median follow-up of 10 years were largely driven by the low-risk nature of the cohort. In the present study, following

a detailed analysis of baseline characteristics according to disease risk classification, we demonstrate that over one-third of the ProtecT participants receiving treatment within 12 months had intermediate- or high-risk disease. At baseline, 25% of participants indeed had ISUP Grade Group ≥2 PCa, but inclusion of PSA and clinical stage in the risk classification revealed a larger percentage with higher-risk disease. This therefore provides greater relevance of the clinical outcomes to participants with intermediate- or higher-risk PCa than hitherto described, and may improve management decision-making, along with the ‘trade-off’ that participants need to consider with their treating clinician.

Analysis of baseline clinical and demographic characteristics of ProtecT participants demonstrated features associated with disease progression, including treatment received, age, PSA, Grade Group, cT stage, risk group category, number of PCa-involved biopsy cores, maximum tumour length per core,



**Table 2** Disease progression and prostate cancer death and/or metastasis for clinical and age subgroups by randomized treatment allocation. [Correction added on 05 March 2020, after first online publication: Table 2 has been amended in this version.]

| Variable                      | Category            | n     | Clinical progression (n = 204) |                   |                        |                | PCa-specific death/metastasis (n = 62) |                   |                        |                    |
|-------------------------------|---------------------|-------|--------------------------------|-------------------|------------------------|----------------|----------------------------------------|-------------------|------------------------|--------------------|
|                               |                     |       | Active monitoring (n = 545)    | Surgery (n = 553) | Radiotherapy (n = 545) | P <sup>*</sup> | Active monitoring (n = 545)            | Surgery (n = 553) | Radiotherapy (n = 545) | P                  |
|                               |                     | n (%) | n (%)                          | n (%)             | n (%)                  |                | n (%)                                  | n (%)             | n (%)                  |                    |
| Age (at randomization)        | Younger (<65 years) | 1034  | 59 (17)                        | 23 (7)            | 23 (7)                 | 0.924          | 12 (4)                                 | 7 (2)             | 11 (3)                 | 0.068              |
|                               | Older (≥65 years)   | 609   | 53 (26)                        | 23 (12)           | 23 (11)                |                | 21 (10)                                | 6 (3)             | 5 (2)                  |                    |
| PSA                           | ≤10 ng/mL           | 1495  | 94 (19)                        | 34 (7)            | 41 (8)                 | 0.135          | 26 (5)                                 | 9 (2)             | 16 (3)                 | 0.187 <sup>†</sup> |
|                               | >10 ng/mL           | 148   | 18 (35)                        | 12 (25)           | 5 (10)                 |                | 7 (14)                                 | 4 (8)             | 0 (0)                  |                    |
| ISUP Grade Group <sup>‡</sup> | 1                   | 1237  | 60 (15)                        | 20 (5)            | 25 (6)                 | 0.709          | 14 (3)                                 | 6 (1)             | 9 (2)                  | 0.626              |
|                               | 2+                  | 405   | 52 (39)                        | 26 (18)           | 21 (17)                |                | 19 (14)                                | 7 (5)             | 7 (6)                  |                    |
| Clinical stage                | cT1c                | 1249  | 71 (17)                        | 28 (7)            | 28 (7)                 | 0.694          | 19 (5)                                 | 7 (2)             | 11 (3)                 | 0.867              |
|                               | cT2                 | 393   | 41 (30)                        | 18 (13)           | 18 (16)                |                | 14 (10)                                | 6 (4)             | 5 (4)                  |                    |
| Risk group <sup>§</sup>       | Low                 | 1021  | 38 (12)                        | 15 (4)            | 15 (4)                 | 0.912          | 9 (3)                                  | 5 (1)             | 7 (2)                  | 0.480              |
|                               | Intermediate/High   | 489   | 55 (33)                        | 26 (16)           | 22 (14)                |                | 18 (11)                                | 6 (4)             | 6 (4)                  |                    |

ISUP, International Society of Urological Pathology; PCa, prostate cancer. \*P values calculated with likelihood ratio interaction test of the null hypothesis of no difference in the relative effectiveness of the three treatments across the binary subgroup levels (unadjusted due to low number of events). <sup>†</sup>To achieve this P value one participant, with a PSA > 10 ng/mL and receiving radical radiotherapy, was recoded as dying from PCa to avoid a zero numerator. <sup>‡</sup>ISUP Grade Group-derived sum of primary and highest Gleason grade of secondary and tertiary. <sup>§</sup>Defined as 'low' if Grade Group = 1 and PSA ≤ 10 ng/mL and T1c/T2a, 'high' if Grade Group ≥ 4 or PSA > 20 ng/mL or T2c, 'intermediate' if Grade Group = 2/3 or 10 < PSA ≤ 20 ng/mL or T2b.

aggregate tumour length, and perineural invasion. These factors were not able to reliably predict progression in individuals.

The observation that diagnostic biopsy Grade Group was associated with post-treatment recurrence/progression concurs with previous evidence [12–15]. However, 53% (105/198) of ProtecT participants with progression had baseline Grade Group 1 disease, demonstrating inadequate sampling by PSA testing followed by 10-core TRUS-guided biopsies. This was substantiated by the observation that none of the participants who received RP and progressed had pure Grade Group 1 tumours. It is recognized that true low-risk low-volume Grade Group 1 PCa does not behave aggressively [16], and that participants with true Grade Group 1 disease are 'unnecessarily' cured by radical intervention. It has been suggested that Grade Group 1 PCa is not cancerous [17], but there is evidence that low-grade malignant foci can progress to lethality [18]. Grade Group 1 lesions may, therefore, comprise a spectrum of disease, indicating the need to delineate molecular features associated with disease progression.

The protocol for PCa detection in ProtecT was designed in the 1990s, before use of multiparametric MRI (mpMRI) imaging. The PROMIS and PRECISION studies suggest that mpMRI aids diagnosis of clinically significant PCa, whilst reducing over-detection of indolent disease [19,20], albeit with a small associated false-negative rate [19]. Introducing pre-biopsy imaging and targeted biopsies, alongside genomic and other assays, will probably improve diagnosis of clinically significant disease requiring intervention, improving

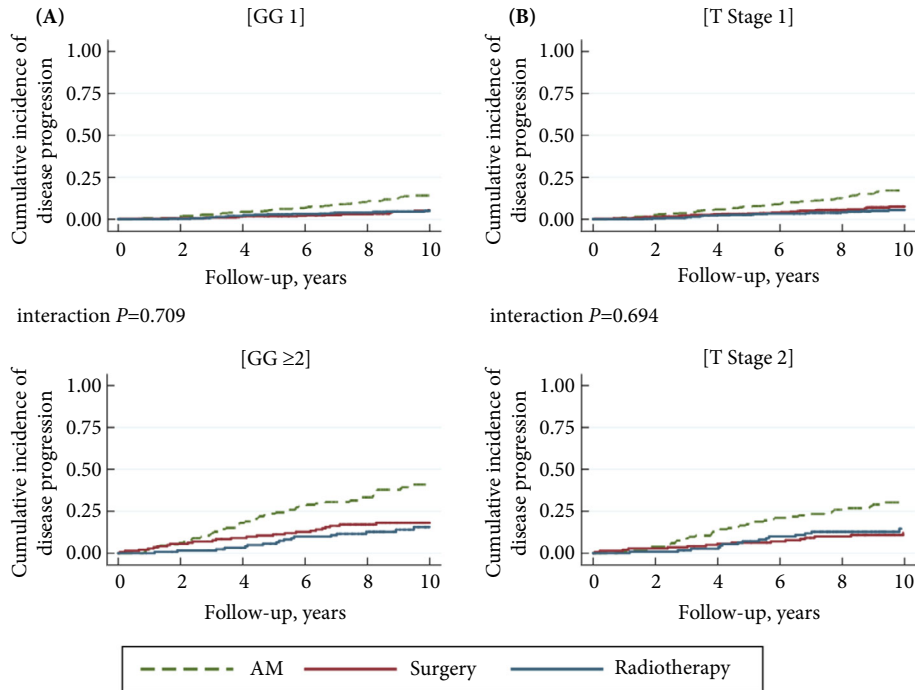
outcomes. Molecular-based risk stratification using diagnostic samples aims to improve performance of risk stratification tools. Incorporating baseline molecular tumour profiling may lead to more accurate personalized risk stratification than conventional clinico-pathological features, but these require prospective evaluation.

Participants in ProtecT with cT2 disease were more likely to progress compared with those with cT1 disease, and 29% of participants with cT2b tumours had extraprostatic extension at RP. The observation that an increased number of positive cores in the diagnostic biopsies, and an increased maximum tumour length, were associated with progression is consistent with AS cohort evidence [21]. Baseline PSA was higher in ProtecT participants who progressed compared with those with stable disease, consistent with PSA being a prognostic factor for recurrent/lethal PCa after radical treatment [22–24].

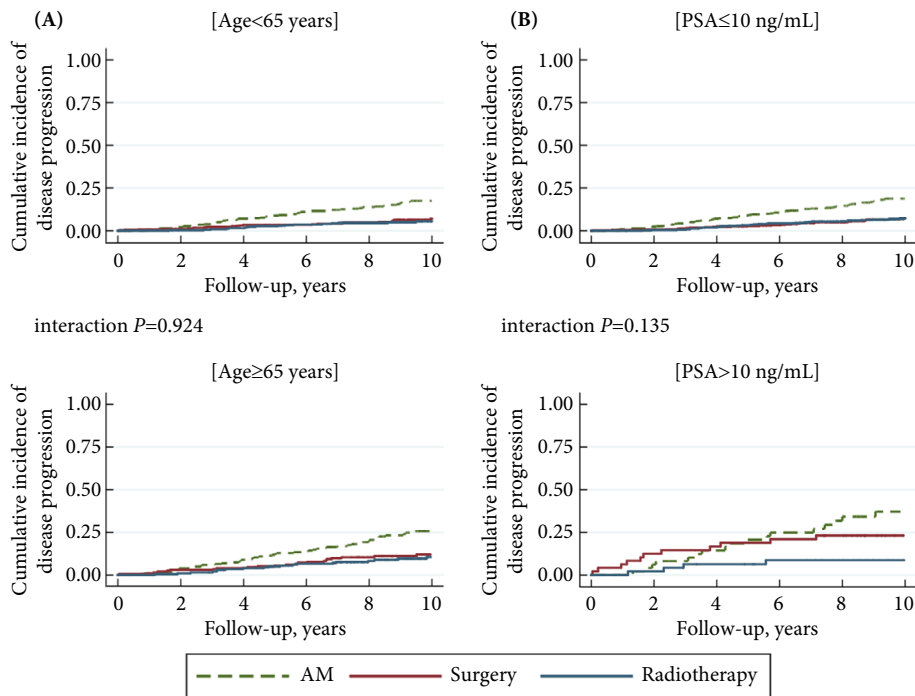
Of participants who progressed, 101 had Grade Group 1 disease at baseline, and 28 of these developed metastases and/or died from PCa, suggesting that transrectal 10-core biopsy without prior mpMRI (as employed in the ProtecT trial protocol) probably under-sampled and/or under-detected high-grade tumours in at least some participants.

The present study has a number of limitations. First, the ProtecT trial's standardized diagnostic pathway of combined DRE, PSA, and TRUS-guided biopsy over-detects indolent disease, and under-detects significant disease compared with mpMRI and targeted biopsies [19,20]. The CAP trial (Cluster Randomized Trial of PSA Testing for Prostate Cancer) demonstrated that PSA testing with a single round of

**Fig. 1** Cumulative incidence of disease progression by International Society of Urological Pathology Grade Group (GG) and clinical stage, based on intention to treat groups. AM, active monitoring.



**Fig. 2** Cumulative incidence of disease progression by age and PSA level, based on intention-to-treat groups. AM, active monitoring.



screening, followed by TRUS-guided biopsies, detected many low-risk cancers, but also missed lethal cases [25]. Second, the ProtecT AM protocol was less intensive than contemporary

AS regimes, although no current method has been validated to improve long-term clinical outcomes. Third, there were very few participants with high-risk disease at baseline (3%).

**Table 3** Hazard ratios for disease progression by surgical pathological characteristics in participants who were randomized to and received radical prostatectomy within 1 year. [Correction added on 05 March 2020, after first online publication: Table 3 has been amended in this version.]

| Surgical characteristic            | Category     | N (%)    | No progression (n = 378) n (%) | Progression outcome (n = 19) n (%) | HR (95% CI); P value        | Metastasis and/ or PCa-specific death (n = 7) n (%) | HR (95% CI); P value <sup>†</sup> |
|------------------------------------|--------------|----------|--------------------------------|------------------------------------|-----------------------------|-----------------------------------------------------|-----------------------------------|
| ISUP Grade Group <sup>†</sup>      | 1            | 196 (50) | 196 (100)                      | 0 (0)                              |                             | 0 (0)                                               |                                   |
|                                    | 2            | 162 (41) | 154 (95)                       | 8 (5)                              | <0.001 <sup>‡</sup>         | 2 (1)                                               | <0.001 <sup>‡</sup>               |
|                                    | 3+           | 36 (9)   | 25 (69)                        | 11 (31)                            |                             | 5 (14)                                              |                                   |
| Pathological stage                 | pT2          | 275 (70) | 273 (99)                       | 2 (1)                              | —                           | 0 (0)                                               | —                                 |
|                                    | pT3/T4       | 117 (30) | 100 (85)                       | 17 (15)                            | 22.01 (5.02, 96.50); <0.001 | 7 (6)                                               | <0.001 <sup>‡</sup>               |
| Largest tumour volume, n = 305     | Median (IQR) |          | 0.8 (0.3, 1.9)                 | 4.0 (2.1, 5.6)                     | 1.23 (1.11, 1.36); <0.001   | 4.1 (2.3, 5.6)                                      | 1.22 (1.04, 1.43); <0.001         |
| Number of tumours                  | One          | 76 (19)  | 71 (93)                        | 5 (7)                              |                             | 2 (3)                                               | —                                 |
|                                    | Multiple     | 315 (81) | 301 (96)                       | 14 (4)                             | 0.72 (0.26, 1.99); 0.524    | 5 (2)                                               | 0.66 (0.13, 3.42); 0.623          |
| Involvement of lymph nodes         | Negative     | 290 (99) | 276 (95)                       | 14 (5)                             | —                           | 4 (1)                                               | —                                 |
|                                    | Positive     | 4 (1)    | 1 (25)                         | 3 (75)                             | 22.77 (6.36, 81.49); <0.001 | 2 (50)                                              | 85.12 (11.46, 632.10); <0.001     |
| Extraprostatic perineural invasion | No           | 278 (71) | 275 (99)                       | 3 (1)                              | —                           | 0 (0)                                               | —                                 |
|                                    | Yes          | 112 (29) | 96 (86)                        | 16 (14)                            | 14.38 (4.15, 49.87); <0.001 | 7 (6)                                               | <0.001 <sup>‡</sup>               |
| Vascular invasion                  | No           | 383 (98) | 369 (96)                       | 14 (4)                             | —                           | 5 (1)                                               | —                                 |
|                                    | Yes          | 8 (2)    | 3 (38)                         | 5 (63)                             | 26.39 (9.11, 76.50); <0.001 | 2 (25)                                              | 17.05 (3.22, 90.36); 0.001        |
| Positive margins                   | No           | 270 (68) | 262 (97)                       | 8 (3)                              | —                           | 4 (1)                                               | —                                 |
|                                    | Yes          | 127 (32) | 116 (91)                       | 11 (9)                             | 2.89 (1.16, 7.19); 0.023    | 3 (2)                                               | 1.41 (0.31, 6.35); 0.657          |
| Upgraded <sup>‡</sup>              | No           | 257 (69) | 253 (98)                       | 4 (2)                              | —                           | 1 (<1)                                              | —                                 |
|                                    | Yes          | 116 (31) | 110 (95)                       | 6 (5)                              | 3.40 (0.96, 12.112); 0.059  | 2 (2)                                               | 4.32 (0.39, 47.75); 0.233         |
| Upstaged <sup>§</sup>              | No           | 275 (70) | 273 (99)                       | 2 (1)                              | —                           | 0 (0)                                               | —                                 |
|                                    | Yes          | 117 (30) | 100 (85)                       | 17 (15)                            | 22.01 (5.02, 96.50); <0.001 | 7 (6)                                               | <0.001 <sup>‡</sup>               |

ISUP, International Society of Urological Pathology; PCa, prostate cancer. <sup>†</sup>Cox models for time to progression, adjusting for age at randomization. <sup>‡</sup>ISUP Grade Group-derived sum of radical prostatectomy Gleason primary and secondary grades. <sup>§</sup>Low number of events so log rank test. <sup>‡</sup>Defined as Grade Group 1 to >Grade Group 1 or Grade Group 2 to ≥Grade Group 3, with the denominator equal to those with Grade Group 1 or Grade Group 2 at baseline. <sup>§</sup>Defined as T1/T2 to T3/T4 disease, with the denominator equal to those with T staging of T1 or T2 at baseline.

Fourth, we recognize that the ProtecT cohort under-represents the racial diversity seen in other more global practices, particularly for African-Caribbean men who comprised only 2% of ProtecT participants. The lack of racial diversity of the ProtecT trial, which reflects the ethnic composition of the UK recruiting centres, has been raised in previous publications [26].

The main strengths of ProtecT are threefold. First, its size, with over 82 000 tested individuals, second the standardized diagnostic approach that was employed widely in Europe prior to recent pre-biopsy mpMRI introduction (and which is still used in many parts of the USA), and third, the high randomization rate of men enrolled to ProtecT [27].

The findings of this study differ from those of registry-based data, such as those in the Surveillance, Epidemiology, and End Results (SEER) programme in the USA, as the ProtecT trial is an RCT of treatment effectiveness for localized PCa, embedded within a trial of PSA-based screening. Moreover, participants in ProtecT have ongoing clinical follow-up, with the median 15-year follow-up data to be reported in the next 2 years. SEER, and similar Scandinavian registries, are observational series rather than RCTs, therefore ProtecT provides us with a unique insight into the baseline clinic-pathological features of patients who progress, vs those who

do not progress, after long-term follow-up following treatment intervention in the context of an RCT.

None of the 174 ProtecT participants with pathological Grade Group 1 after undergoing RP progressed, suggesting surgery cures definite low-risk Grade Group 1 disease. This probably represents over-treatment of disease that would not have progressed if simply observed. If accurately identified, such patients may benefit from AM and avoid treatment side effects without deleterious oncological outcomes, as advocated in AS protocols [28,29].

The absence of any association between the number of tumour foci in the RP specimen and disease progression contrasts with data suggesting multifocal disease is associated with increased recurrence risk [30]. Evidence from ProtecT suggests solitary tumours were found in only one-fifth of RP specimens with PSA-detected localized disease [31].

In conclusion, baseline clinico-pathological features of men with localized PCa within ProtecT were associated with disease progression, but these associations were not strong enough to reliably predict individual progression. As the genomic diversity of PCa is elucidated, it is becoming clear that stratification methods need refinement with pre-biopsy imaging and targeted sampling, alongside utilisation of

validated genomic and other emerging biomarkers. This will need to be assessed in large-scale prospective early detection programmes. Only then will clinicians and patients be able to refine the complex decision-making processes needed to manage this ubiquitous malignancy.

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## Conflict of Interest

F.C.H. and J.W.F.C. have attended an Advisory board for Steba Biotech. R.J.B. has undertaken consultancy for Owen Mumford Ltd. M.M. has received a speaker's fee from Janssen. J.D. has undertaken pathology reporting at Spire and Nuffield Health Hospitals, Leicester. M.V. has received consultancy fees from Roche Products Ltd and AstraZeneca. J.S. has received honoraria from, and advised, Bayer. D.J.R. has received honoraria from Ferring and Research Funding from Bayer. R.J.B. reports grants from Cancer Research UK, The Urology Foundation, and UCARE. D.F.G. reports grants from UK National Institute for Health Research Health Technology Assessment Program. R.M.M. reports grants from Cancer Research UK during the conduct of the study.

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## Appendix 1

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**Abbreviations:** PCa, prostate cancer; RCT, randomized clinical trial; AM, active monitoring; RP, radical prostatectomy; RT, radical radiotherapy; ISUP, International Society of Urological Pathology; AS, active surveillance; mpMRI, multiparametric MRI; SEER, Surveillance, Epidemiology, and End Results; NIHR, National Institute for Health Research.