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Fifteen-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer

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ABSTRACT

BACKGROUND

Between 1999 and 2009 in the United Kingdom, 82,429 men between 50 and 69 years of age received a prostate-specific antigen (PSA) test. Localized prostate cancer was diagnosed in 2664 men. Of these men, 1643 were enrolled in a trial to evaluate the effectiveness of treatments, with 545 randomly assigned to receive active monitoring, 553 to undergo prostatectomy, and 545 to undergo radiotherapy.

METHODS

At a median follow-up of 15 years (range, 11 to 21), we compared the results in this population with respect to death from prostate cancer (the primary outcome) and death from any cause, metastases, disease progression, and initiation of long-term androgen-deprivation therapy (secondary outcomes).

RESULTS

Follow-up was complete for 1610 patients (98%). A risk-stratification analysis showed that more than one third of the men had intermediate or high-risk disease at diagnosis. Death from prostate cancer occurred in 45 men (2.7%): 17 (3.1%) in the active-monitoring group, 12 (2.2%) in the prostatectomy group, and 16 (2.9%) in the radiotherapy group (P=0.53 for the overall comparison). Death from any cause occurred in 356 men (21.7%), with similar numbers in all three groups. Metastases developed in 51 men (9.4%) in the active-monitoring group, in 26 (4.7%) in the prostatectomy group, and in 27 (5.0%) in the radiotherapy group. Long-term androgen-deprivation therapy was initiated in 69 men (12.7%), 40 (7.2%), and 42 (7.7%), respectively; clinical progression occurred in 141 men (25.9%), 58 (10.5%), and 60 (11.0%), respectively. In the active-monitoring group, 133 men (24.4%) were alive without any prostate cancer treatment at the end of follow-up. No differential effects on cancer-specific mortality were noted in relation to the baseline PSA level, tumor stage or grade, or risk-stratification score. No treatment complications were reported after the 10-year analysis.

CONCLUSIONS

After 15 years of follow-up, prostate cancer–specific mortality was low regardless of the treatment assigned. Thus, the choice of therapy involves weighing trade-offs between benefits and harms associated with treatments for localized prostate cancer. (Funded by the National Institute for Health and Care Research; ProtecT Current Controlled Trials number, ISRCTN20141297; ClinicalTrials.gov number, NCT02044172.)

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*A list of members of the ProtecT Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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Despite recent advances in early detection and treatment of localized prostate cancer, management of the disease remains controversial. Although multiparametric magnetic resonance imaging (MRI) and targeted biopsies may reduce the diagnosis of indolent disease, the challenging aspects of risk stratification continue to drive both overtreatment and undertreatment. In the United States in 2020, approximately 192,000 men received a diagnosis of prostate cancer and 33,000 died of the disease.[1] Since the U.S. Preventive Services Task Force updated its recommendations in 2012 and 2018,[2] the incidence of localized disease has declined, whereas the incidences of regional and advanced cases have increased.[3] During this period, cancer-specific mortality has remained unchanged.[4] Clinical outcomes that are reported here may help to elucidate reasons for these findings.

In the United Kingdom between 1999 and 2009, a total of 82,429 men between the ages of 50 and 69 years at nine centers were enrolled in the Prostate Testing for Cancer and Treatment (ProtecT) trial to evaluate the effectiveness of conventional treatments in clinically localized prostate cancer that was detected on prostate-specific antigen (PSA) testing. Localized prostate cancer was diagnosed in 2664 men who had a life expectancy of at least 10 years and who were eligible for treatment. Of these men, 1643 underwent randomization to receive active monitoring (545 men), prostatectomy (553 men), or radiotherapy (545 men). The median age at diagnosis was 62 years (range, 50 to 69), and the median PSA level was 4.6 ng per milliliter (range, 3.0 to 18.9). No material clinicopathological differences were seen among the randomized groups[5] or among the men who accepted or declined to undergo randomization.[6]

In the current phase of the trial at a median follow-up of 15 years, we evaluated the relative effectiveness of active monitoring, prostatectomy, and radiotherapy on prostate cancer–specific and all-cause mortality, metastases, disease progression, and the initiation of long-term androgen-deprivation therapy. At the time of diagnosis, approximately 77% of the men were deemed to have low-risk disease.[5,7-9] Thus, we performed a comprehensive analysis using several risk-stratification systems — including the Cancer of the Prostate Risk Assessment (CAPRA) and scoring systems of D'Amico and the Cambridge Prognostic Group — to assist in the interpretation of the results.[10-12] Patient-reported outcomes, which are critical to an assessment of the full trade-offs between treatment benefits and harms, are described in a separate article.[13]

METHODS

TRIAL DESIGN AND OVERSIGHT

Methods of trial recruitment and the results of the primary and secondary outcomes at a median of 10 years of follow-up were published previously[14]; trial-group assignments are shown in Figure 1. The ProtecT trial was funded by the National Institute for Health and Care Research in the United Kingdom; the University of Oxford sponsored the trial management. The trial was approved by the East-Midlands Multicenter Research Ethics Committee. The trial was overseen by an independent trial steering committee throughout and by a separate data and safety monitoring committee until 2015. All the patients provided written informed consent. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org.

TREATMENTS

Clinical management was standardized with the use of trial-specific pathways.[15] We measured PSA levels every 3 months during the first year of the trial and every 6 to 12 months thereafter. Patients were evaluated annually, according to trial-group assignment. In the active-monitoring group, an increase of at least 50% in the PSA level during a 12-month period or any concern on the part of the patient or clinician triggered a review, with management options that included continued monitoring or further testing and radical or palliative treatments. Radical intervention was defined as prostatectomy or radiotherapy. In the prostatectomy group, the use of adjuvant or salvage radiotherapy was discussed with patients who had positive surgical margins, extracapsular disease, or a postoperative PSA level of 0.2 ng per milliliter or higher. Radiotherapy was delivered along with neoadjuvant androgen-deprivation therapy for 3 to 6 months with three-dimensional conformal radiotherapy at 74 Gy in 37 fractions.[16,17] A management re-

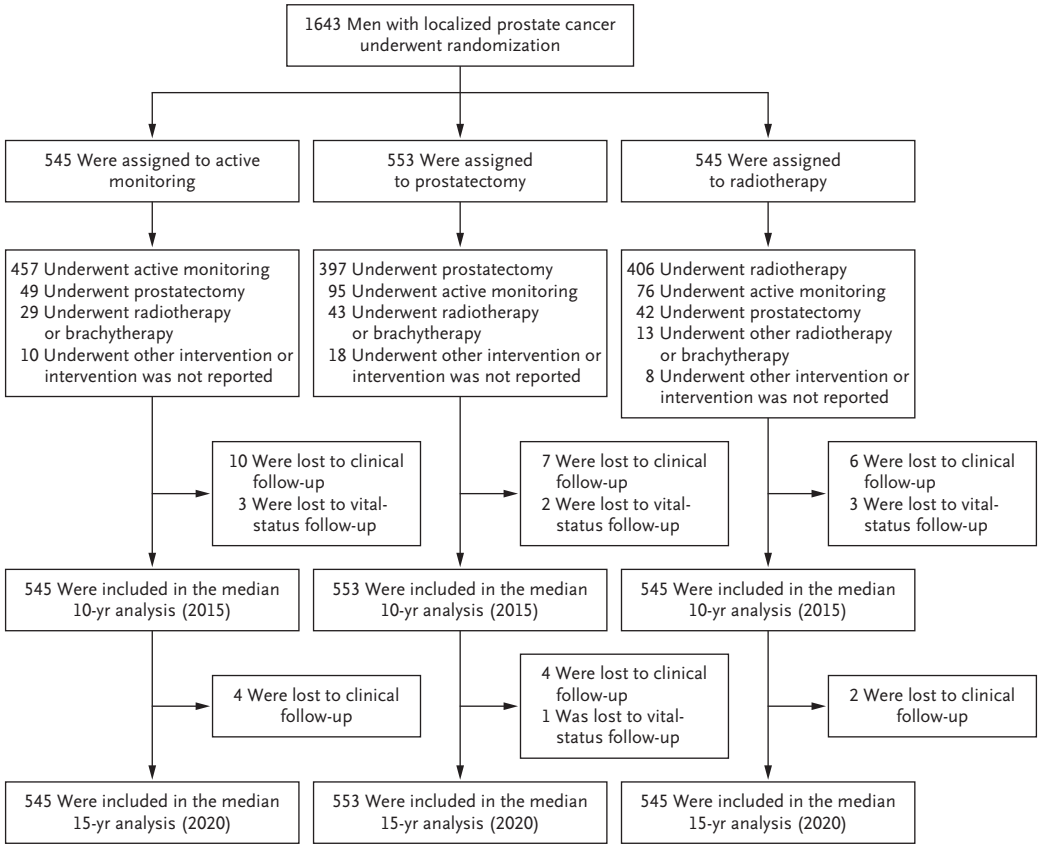

Figure 1. Enrollment and Outcomes in the 15-Year Follow-up Intention-to-Treat Analysis.

All the patients were included in the analysis for as long as they were under clinical follow-up. Data were censored at the point that the patients were lost to follow-up.

view was triggered if the PSA level increased by at least 2.0 ng per milliliter over the nadir level or concern was raised about disease progression. In all groups, bone scintigraphy was recommended if the PSA level increased to 10 ng per milliliter, and androgen-deprivation therapy was discussed if the PSA level increased to 20 ng per milliliter.

CLINICAL OUTCOME MEASURES

The primary outcome was death from prostate cancer, as adjudicated by an independent cause-of-death committee.[18] Secondary outcomes were death from any cause, metastases (as confirmed on imaging or a PSA level of ≥100 ng per milliliter), clinical progression (a composite of metastases, clinical T3 or T4 disease, initiation of long-term androgen-deprivation therapy, ureteric obstruction, rectal fistula, or urinary catheterization because of tumor growth), and long-term androgen-deprivation therapy alone. No new treatment complications were reported during the period from 2015[14] through 2018, when data collection was streamlined.

SUBGROUP ANALYSES

Eight diagnosis-related subgroups were prespecified for the assessment of differential effects on prostate cancer–specific mortality: age (<65 years or ≥65 years), Gleason grade group (1 vs. 2 vs. ≥3), PSA level (<10 ng per milliliter or 10 to 19.9 ng per milliliter), stage (T1 or T2), aggregate tumor length in biopsies (<4 mm or ≥4 mm), maximum tumor length in a single biopsy (<2 mm or ≥2 mm), and risk-stratification score (D'Amico or CAPRA). In an exploratory analysis, we also evaluated risk stratification according to the Cambridge Prognostic Group criteria.

STATISTICAL ANALYSIS

A statistical analysis plan was developed before the data in the current report had been accessed.[19] We used Cox proportional-hazards regression after adjustment for trial center, patient's age, Gleason score, and baseline PSA (log-transformed) to compare prostate cancer–specific mortality at 15 years in the three groups on an intention-to-treat basis. Pairwise significance tests were planned if the P value for equal disease-specific mortality across the trial groups was less than 0.05 (on the basis of an overall false positive risk of 5%).[20] Interaction terms were added to this model to investigate differential treatment effects across the eight prespecified subgroups.

The regression-model approach was adapted to secondary outcomes. Because the statistical analysis plan did not provide for correction for multiplicity regarding secondary or exploratory outcomes, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so intervals should not be used in place of hypothesis testing. All the men were included in the analysis for as long as they were undergoing clinical follow-up; data were censored at the time that the men were lost to follow-up. Exploratory analyses are presented in the Supplementary Appendix (available at NEJM .org) to assist with the interpretation of findings. All analyses were conducted with the use of Stata software, version 17 (StataCorp).

RESULTS

PATIENTS AND RISK STRATIFICATION

During a median follow-up of 15 years, clinical data were fully captured for 1610 of 1643 men (98.0%) (Fig. 1). At baseline, 77.2% of the men were in Gleason grade group 1 (Gleason score, 3+3=6); 76.0% had stage T1c cancer. Contemporary risk-stratification tools revealed that 369 men (24.1%) had intermediate disease and 147 (9.6%) had high-risk disease, according to the D'Amico criteria; the corresponding values were 428 (26.4%) and 40 (2.5%), respectively, according to the CAPRA criteria, and 337 (20.5%) and 144 (8.8%), respectively, according to the Cambridge Prognostic Group criteria (Table S1 in the Supplementary Appendix). In addition, among the 488 men who had undergone prostatectomy within 12 months after assignment to any group, 138 (28.5%) had an increase in the pathological cancer stage to pT3 or pT4 (Table S2); 155 (32.0%) had an increase in tumor grade, and 245 (50.5%) had a Gleason score of 7 (3+4, grade group 2) or higher (Table S3). Of the 13 men who had undergone prostatectomy but died of prostate cancer, all had an increase in the tumor stage and 76.9% had an increase in the tumor grade (Table S4). Of the 104 men in whom metastases developed, 53 (51.0%) had Gleason grade group 1 disease at baseline, and 49 (47.6%) were identified has having low-risk disease according to the CAPRA criteria (Table S5).

PRIMARY OUTCOME

After median follow-up of 15 years, 45 patients (2.7%) had died of prostate cancer: 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 and Fig. 2A). No significant difference in prostate cancer mortality was found among the trial groups (P=0.53). In the active-monitoring group, the inclusion of data from 3 men whose death was considered to be "possibly" from prostate cancer in a repeat primary-outcome analysis did not affect this finding (P=0.27) (Table S6). Thus, prostate cancer–specific survival was approximately 97% regardless of the trial-group assignment (Table 2).

The treatment effect in the comparison of men in the active-monitoring group with those in the radiotherapy group varied during the follow-up period (test of proportional-hazards assumption, P=0.01), with 7 of 16 deaths in the radiotherapy group occurring after 15 years (Fig. S1). We elaborated the primary analysis model to compare active monitoring with radiotherapy separately during the first 12.8 years of follow-up, when 23 of 45 prostate cancer deaths had occurred, and during the subsequent follow-up period. The resulting imprecise estimates suggest that this comparison favored radiotherapy early but active monitoring later (Table S7). This finding supports the conclusion of no evidence of a difference in prostate cancer mortality among the three assigned groups (P=0.51).

DEATH FROM ANY CAUSE

Death from any cause occurred in 356 patients (21.7%), with a similar distribution across the three groups (Table 1 and Fig. S2). Among the

Table 1. Primary and Secondary Outcomes.

Outcome and Trial Group	No. of Events	No. of Person-Yr	Rate per 1000 Person-Yr (95% CI)	Hazard Ratio (95% CI)*
Primary outcome				
Death from prostate cancer†				
Active monitoring	17	7633	2.2 (1.4–3.6)	Reference
Prostatectomy	12	7766	1.5 (0.9–2.7)	0.66 (0.31–1.39)
Radiotherapy	16	7628	2.1 (1.3–3.4)	0.88 (0.44–1.74)
Secondary outcomes				
Death from any cause				
Active monitoring	124	7633	16.2 (13.6–19.3)	Reference
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)	Reference
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 therapy				
Active monitoring	69	7197	9.4 (7.4–11.9)	Reference
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‡				
Active monitoring	141	6596	21.4 (18.1–25.2)	Reference
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)

* Hazard ratios were estimated after adjustment for trial center, patient's age at baseline, Gleason score, and prostate-specific antigen level at baseline (log-transformed). The widths of confidence intervals for secondary outcomes have not been adjusted for multiplicity and cannot be used in place of hypothesis testing.
† The primary outcome was definite or probable prostate cancer mortality, as adjudicated by an independent cause-of-death committee. P=0.53 for the primary-outcome comparison.
‡ Disease progression included evidence of metastatic disease, the initiation of long-term androgen-deprivation therapy, diagnosis of clinical T3 or T4 disease, ureteric obstruction, rectal fistula, or urinary catheterization because of tumor growth.

318 patients for whom data regarding the cause of death were available, 101 deaths (31.8%) were from cardiovascular or respiratory disease and 164 (51.6%) from other cancers (Table S8).

METASTASES, ANDROGEN-DEPRIVATION THERAPY, AND DISEASE PROGRESSION

Of the 104 men (6.3%) in whom metastases were diagnosed, 51 (9.4%) were in the active-monitoring group, 26 (4.7%) in the prostatectomy group, and 27 (5.0%) in the radiotherapy group (Fig. 2B). The difference was most apparent among men with metastatic disease in regional nodes: 14 (2.6%) in the active-monitoring group and 4 (<1%) in each of the radical treatment groups (Table S9). Of 151 men (9.2%) who received long-term androgen-deprivation therapy, 69 (12.7%) were in the active-monitoring group, 40 (7.2%) in the prostatectomy group, and 42 (7.7%) in the radiotherapy group (Fig. S3). Of the 259 men (15.8%) with local progression, 141 (25.9%) were in the active-monitoring group, 58 (10.5%) the prostatectomy group, and 60 (11.0%) the radiotherapy group (Fig. S4). When staging alone was analyzed as a measure of local progression, T3 or T4 disease was found in 69 men (12.7%) in

Table 2. Prostate Cancer Survival.*

Trial Group	Survival (95% CI)	
	At 10 Yr	At 15 Yr
	percentage of patients	
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)

* Prostate cancer survival was estimated with the use of the Kaplan–Meier method at 10 years and 15 years for each assigned group.

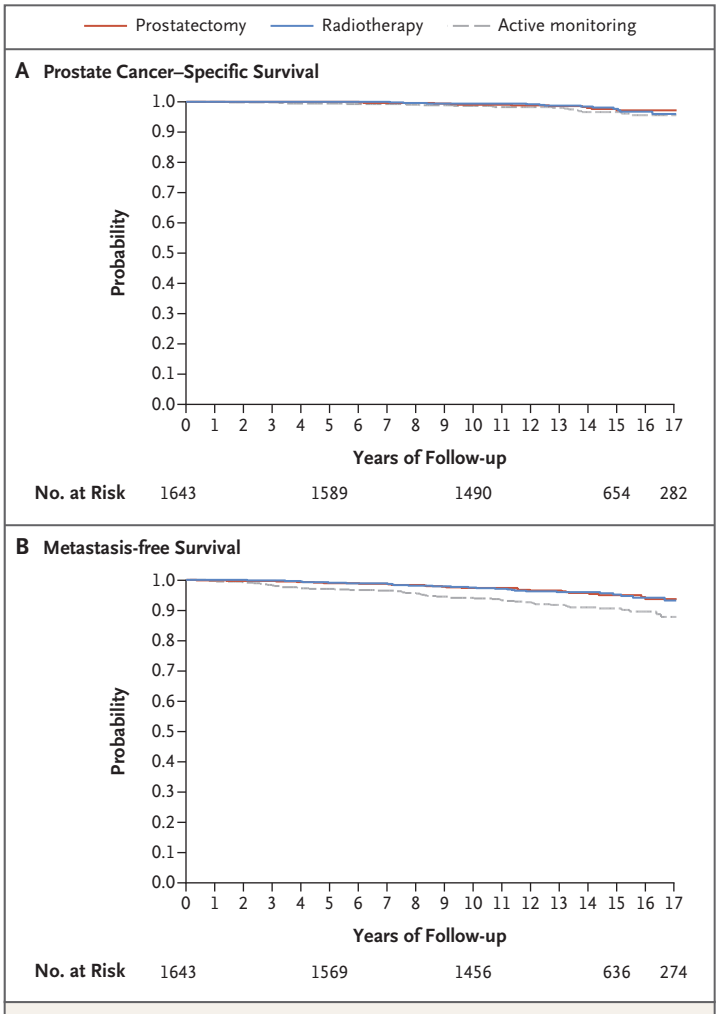

Figure 2. Survival from Prostate Cancer and Metastasis-free Survival.
Panel A shows the probability of survival from prostate cancer among the trial patients in the active-monitoring group, the prostatectomy group, and the radiotherapy group over the years. Panel B shows Kaplan–Meier estimates of freedom from metastatic disease, according to treatment group.

the active-monitoring group, 15 (2.7%) in the prostatectomy group, and 17 (3.1%) in the radiotherapy group (Table S9).

CHANGE OF MANAGEMENT

By the end of the median 15-year follow-up, radical treatment had been performed in 504 men (92.5%) in the radiotherapy group and in 500 (90.4%) in the prostatectomy group (Fig. 3). This finding compares with 333 men (61.1%) who received radical treatment in the active-monitoring group, an absolute increase of 6.3 percentage points from the 291 men (54.8%) who had received radical treatment at 10 years.[14] By the end of follow-up, 133 men (24.4%) in the active-monitoring group were alive and had neither received radical treatment nor started androgen-deprivation therapy. Of these men at the time of diagnosis, 17 (12.8%) were considered to have intermediate or high-risk disease according to the D'Amico criteria and 14 (10.5%) had Gleason grade group 2 disease or higher (Table S10).

PRESPECIFIED SUBGROUP ANALYSES

The relative risk of death from prostate cancer in the three groups differed according to the men's age at diagnosis. Among the men who were under the age of 65 years, those who had undergone either active monitoring or prostatectomy had a lower risk of death from prostate cancer than those who had undergone radiotherapy; among those who were 65 years of age or older, those who had undergone prostatectomy or radiotherapy had a lower risk of death from prostate cancer than those who had undergone active monitoring (Table 3 and Fig. S5). No evidence was seen of a change in treatment effect according to the PSA level, clinical stage, Gleason grade group, tumor length, or risk stratification according to the three criteria.

EXPLORATORY ANALYSES

The higher incidence of metastatic disease in the active-monitoring group at 10 years was anticipated to have an effect on prostate cancer–specific mortality at 15 years, but this was not the case. Among the 40 men in whom metastatic disease had been diagnosed at 10 years, the risk of death from prostate cancer was lower among those in the active-monitoring group (3 of 22

[13.6%]) than in either the prostatectomy group (2 of 8 [25.0%]) or the radiotherapy group (7 of 10 [70.0%]) (Fig. S6).

DISCUSSION

For more than two decades, our trial has been evaluating the effectiveness of contemporary treatments among men with PSA-detected, clinically localized prostate cancer. The current 15-year analysis provides evidence of a high percentage of long-term survival in the trial population (97% from prostate cancer–specific death and 78% from death from any cause), regardless of treatment group. Radical treatments (prostatectomy or radiotherapy) reduced the incidence of metastasis, local progression, and long-term androgen-deprivation therapy by half as compared with active monitoring. However, these reductions did not translate into differences in mortality at 15 years, a finding that emphasizes the long natural history of this disease.

Thus, our findings indicate that depending on the extent of side effects associated with early radical treatments, more aggressive therapy can result in more harm than good. Clinicians may avoid overtreatment by ensuring that men with newly diagnosed, localized prostate cancer consider critical trade-offs between short-term and long-term effects of treatments on urinary, bowel, and sexual function,[13] as well as the risks of progression.

Major guidelines recommend conventional clinicopathological features such as the baseline PSA level, clinical stage, Gleason grade group, and biopsy characteristics to guide risk stratification and treatment.[21,22] However, our trial has revealed the limitations of such methods. The trial was initiated in 1999, and when the baseline data were published, it appeared that more than three quarters of the men had features suggesting low-risk disease on the basis of the risk-stratification methods that were being used at the time.[5,7-9] However, contemporary methods of risk stratification have shown that up to 34% of the ProtecT cohort actually had intermediate or high-risk prostate cancer at the time of diagnosis (Table S1).[23] Furthermore, pathological data from men who had undergone prostatectomy within 12 months after diagnosis revealed that one third went on to have an increase in both the grade and stage of prostate cancer and one half had Gleason grade group 2 disease or higher, which suggests that more intermediate-risk disease was present across the cohort than was previously thought (Tables S2 and S3).

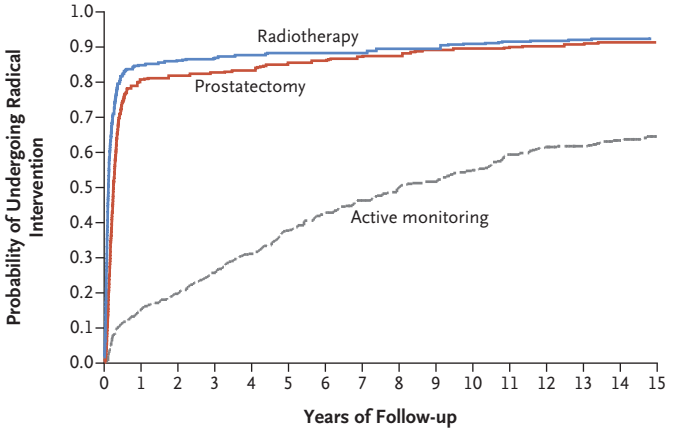

Figure 3. Probability of Undergoing Radical Intervention during the Follow-up Period.

Shown are Kaplan–Meier estimates of the cumulative probability that trial patients would undergo a radical intervention — prostatectomy, radiotherapy, or other intervention — during the follow-up period, according to trial-group assignment at the time of diagnosis.

An analysis of data from the 13 men who had undergone prostatectomy but later died of prostate cancer further revealed the limitations of risk-stratification methods, because 46% were diagnosed with Gleason grade group 1 disease at baseline; all the men had an increase in stage and 77% had an increase in grade (Table S4). More than three quarters of these men underwent surgery within 2 years after diagnosis and 84% received salvage radiotherapy, treatments that indicated the aggressive nature of their disease. Despite the administration of multimodality treatments, these men who died from prostate cancer must have harbored features of lethality that were not identified at diagnosis or affected by treatment. Furthermore, of the 104 men in whom metastases developed, 51% were classified as being at low risk (Gleason grade group 1) at baseline and 47% were considered to be at low risk according to the CAPRA criteria (Table S5). Thus, additional prediction tools are needed, with better understanding and alignment of the tumor phenotype with its genotype,

Table 3. Prostate Cancer Deaths, According to Prespecified Subgroup at Diagnosis.*

Variable	Active Monitoring (N = 545)	Prostatectomy (N = 553)	Radiotherapy (N = 545)	Hazard Ratio (95% CI)	
				Prostatectomy vs. Active Monitoring	Radiotherapy vs. Active Monitoring
	no. of patients/total no. (%)				
Age					
<65 yr	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 yr	12/205 (5.9)	6/200 (3.0)	6/204 (2.9)	0.47 (0.17–1.24)	0.43 (0.16–1.15)
Gleason grade 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)
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)
≥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 tumor length in biopsy cores					
<4 mm	6/209 (2.9)	3/233 (1.3)	5/233 (2.1)	0.43 (0.11–1.73)	0.75 (0.23–2.46)
≥4 mm	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 tumor length in any one biopsy core					
<2 mm	2/111 (1.8)	4/124 (3.2)	4/119 (3.4)	1.76 (0.32–9.63)	2.02 (0.37–11.03)
≥2 mm	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					
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 (5.1)	1.03 (0.26–4.12)	1.71 (0.48–6.07)
≥10 ng/ml	0/56	1/56 (1.8)	0/57	NA	NA
Clinical stage					
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‡					
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)
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)
6–10	2/13 (15.4)	0/8	1/19 (5.3)	NA	0.16 (0.01–1.76)
D'Amico risk score§					
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 (11.1)	0/44	2.62 (0.53–12.97)	NA
Cambridge Prognostic Group risk score¶					
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)
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)
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)

* Data are shown for all patients who could be evaluated in each category. Details regarding the scoring systems that are described in this study are provided in Table S1. NA denotes not applicable, and PSA prostate-specific antigen.

† Patients in grade group 1 have a Gleason score of 6 (3+3), indicating low risk of progression; those in grade group 2 have a Gleason score of 7 (3+4), indicating favorable intermediate risk of progression; and those in grade group 3 have a Gleason score of 7 (4+3), indicating intermediate risk of progression. Grade groups 4 and 5 indicate high risk of progression.

‡ The Cancer of the Prostate Risk Assessment (CAPRA) score is graded on a scale of 1 to 10 on the basis of points assigned to the age at diagnosis, PSA level at diagnosis, Gleason score, clinical stage, and the percentage of biopsy cores involved with cancer. A CAPRA score of 0 to 2 indicates low risk, 3 to 5 intermediate risk, and 6 to 10 high risk.

§ The D'Amico risk score is calculated according to the PSA level, Gleason score, and clinical T stage to score prostate cancer as low, intermediate, or high risk. Low risk is a PSA level of less than 10, a Gleason score of 6 or less, and a clinical stage of T1 or T2a. Intermediate risk is a PSA level of 10 to 20, a Gleason score of 7, or a clinical stage of T2b. High risk is a PSA level of more than 20, a Gleason score of 8 or more, or a clinical stage of T2c or T3a.

¶ The Cambridge Prognostic Group (CPG) risk score for prostate cancer is calculated as CPG 1 (similar to low risk), CPG 2 and CPG 3 (similar to medium or intermediate risk), and CPG 4 and CPG 5 (similar to high risk).

as well as the natural history of disease progression.[24,25]

Even though the incidence of metastases increased, the number of prostate cancer deaths remained low and the intervals between metastases and death continued to extend from 10 to 20 years in some cases, particularly in the active-monitoring group (Fig. S6). Of the 40 men in whom metastases had been diagnosed at 10 years, 14% had died of prostate cancer in the active-monitoring group by 15 years as compared with 25% in the prostatectomy group and 70% in the radiotherapy group. New systemic therapies for progressive disease have become increasingly available, and it is likely that these treatments contributed to lengthening survival in the men with metastases in our trial. This finding is remarkable and reassuring for such a common cancer and calls into question whether metastasis per se can be used as a surrogate for the lethality of prostate cancer in men who present with localized disease.[26,27]

When the sites of metastatic disease were analyzed, 29% of the men in the active-monitoring group had regional lymph-node involvement, as compared with 15% in each of the prostatectomy and radiotherapy groups (Table S9). The incidence of visceral and distant lymph-node involvement was low and similar in the three groups. Skeletal metastases accounted for a similar percentage of cases in the active-monitoring group (31%) and the prostatectomy group (35%), with a lower percentage in the radiotherapy group (15%). This finding may be due to the presence of occult micrometastatic disease at diagnosis that was subsequently suppressed by neoadjuvant androgen-deprivation therapy given before the administration of radiotherapy. Caution is needed in interpreting rates of local progression because the incidence of clinical restaging with active monitoring (13%) was higher by a factor of 4 than that with radical treatments (3%). Many of these cases were based on subjective digital rectal examinations or computed tomographic (CT) imaging, methods that provide the weakest justification for the initiation of radical treatment.

After the 10-year follow-up of our trial,[14] reservations were expressed that the assigned radical treatments were not always received.[7-9] However, by the 15-year follow-up, 90 to 92% of the men had undergone either prostatectomy or radiotherapy according to the randomized assignment. In the active-monitoring group, 61% had undergone either prostatectomy or radiotherapy. Change-of-management rates in our trial were similar to those in other active surveillance programs, with approximately 30% of the patients undergoing either prostatectomy or radiotherapy within 3 years, a percentage that increased to 55% at 10 years and 61% at 15 years. Decisions to change the management approach in the early years were often made without evidence of progression, which probably reflected anxiety on the part of either the patients or their physicians. At 15 years, 39% of the men in the active-monitoring group had not undergone radical treatment, and 24% were alive without either radical treatment or androgen-deprivation therapy. Of these men at the time of diagnosis, 11% had a Gleason grade group of 2 to 5 or a CAPRA score of 3 to 5 and stage T2 disease (Table S10).

Our findings are consistent with those of the Prostate Cancer Intervention versus Observation Trial (PIVOT), which showed no survival benefit of radical treatment in men with a high number of coexisting illnesses.[28] In the Scandinavian Prostate Cancer Group Study 4 (SPCG-4),[29] investigators found consistent benefits of radical treatment as compared with watchful waiting among patients with clinical symptoms, half of whom had evidence of disease outside the prostate. In addition, those in the watchful-waiting group were not receiving active surveillance. In 2012, the U.S. Preventive Services Task Force synthesized available data and advised against routine PSA screening, a recommendation that was modified in 2018 to include shared decision making by patients and their physicians.[2] Subsequent studies have shown stable survival statistics despite reduced PSA testing and an increased incidence of regional or advanced prostate cancer in the United States.[3] Our trial provides evidence that survival after PSA-detected prostate cancer is long, regardless of the patient-stratification method that was used, and that lethal disease is not easily affected by radical treatment.

Like the PIVOT investigators,[28] we found no evidence of differential treatment effects on prostate cancer mortality among subgroups that were defined according to tumor grade at diagnosis, aggregate or maximum tumor length, tumor stage, PSA level, or risk-stratification method. However, we found a suggestion of an age effect

that was not seen in either PIVOT or SPCG-4,[28,29] in which men who were at least 65 years of age at the time of diagnosis appeared to have benefited from early radical treatment, whereas those who were younger than 65 years of age benefited more from active monitoring or surgery than from radiotherapy (Table S11). This finding could reflect potential benefits of prompt radical treatment among older men but should be interpreted cautiously and warrants further exploration.

Our trial has several limitations. Since its inception, treatments and diagnostic methods have evolved. During trial recruitment, investigators were not using contemporary multiparametric MRI or positron-emission tomography with prostate-specific membrane antigen, and biopsies were not image-targeted. The strengths of the trial include the randomized comparison of findings in men with PSA-detected, clinically localized, low- or intermediate-risk prostate cancer, along with generalizable population-based recruitment with high levels of randomization, standardized treatment pathways, and sustained high rates of follow-up.[6,30]

At a median follow-up of 15 years, we found that mortality from PSA-detected prostate cancer remained very low regardless of whether men had been assigned to receive active monitoring, prostatectomy, or radiotherapy. Radical treatment resulted in a lower risk of disease progression than active monitoring but did not lower prostate cancer mortality. Even though the active-monitoring protocol was perceived as less intensive than contemporary active surveillance, one quarter of the men in the active-monitoring group 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 possible differential effects of various treatments. Our findings provide evidence that greater awareness of the limitations of current risk-stratification methods and treatment recommendations in guidelines is needed. Men with newly diagnosed, localized prostate cancer and their clinicians can take the time to carefully consider the trade-offs between harms and benefits of treatments when making management decisions.

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

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APPENDIX

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