2017

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ORIGINAL ARTICLE

Follow-up of Prostatectomy versus Observation for Early Prostate Cancer

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ABSTRACT

BACKGROUND

We previously found no significant differences in mortality between men who underwent surgery for localized prostate cancer and those who were treated with observation only. Uncertainty persists regarding nonfatal health outcomes and long-term mortality.

METHODS

From November 1994 through January 2002, we randomly assigned 731 men with localized prostate cancer to radical prostatectomy or observation. We extended follow-up through August 2014 for our primary outcome, all-cause mortality, and the main secondary outcome, prostate-cancer mortality. We describe disease progression, treatments received, and patient-reported outcomes through January 2010 (original follow-up).

RESULTS

During 19.5 years of follow-up (median, 12.7 years), death occurred in 223 of 364 men (61.3%) assigned to surgery and in 245 of 367 (66.8%) assigned to observation (absolute difference in risk, 5.5 percentage points; 95% confidence interval [CI], –1.5 to 12.4; hazard ratio, 0.84; 95% CI, 0.70 to 1.01; P=0.06). Death attributed to prostate cancer or treatment occurred in 27 men (7.4%) assigned to surgery and in 42 men (11.4%) assigned to observation (absolute difference in risk, 4.0 percentage points; 95% CI, –0.2 to 8.3; hazard ratio, 0.63; 95% CI, 0.39 to 1.02; P=0.06). Surgery may have been associated with lower all-cause mortality than observation among men with intermediate-risk disease (absolute difference, 14.5 percentage points; 95% CI, 2.8 to 25.6) but not among those with low-risk disease (absolute difference, 0.7 percentage points; 95% CI, –10.5 to 11.8) or high-risk disease (absolute difference, 2.3 percentage points; 95% CI, –11.5 to 16.1) (P=0.08 for interaction). Treatment for disease progression was less frequent with surgery than with observation (absolute difference, 26.2 percentage points; 95% CI, 19.0 to 32.9); treatment was primarily for asymptomatic, local, or biochemical (prostate-specific antigen) progression. Urinary incontinence and erectile and sexual dysfunction were each greater with surgery than with observation through 10 years. Disease-related or treatment-related limitations in activities of daily living were greater with surgery than with observation through 2 years.

CONCLUSIONS

After nearly 20 years of follow-up among men with localized prostate cancer, surgery was not associated with significantly lower all-cause or prostate-cancer mortality than observation. Surgery was associated with a higher frequency of adverse events than observation but a lower frequency of treatment for disease progression, mostly for asymptomatic, local, or biochemical progression. (Funded by the Department of Veterans Affairs and others; PIVOT ClinicalTrials.gov number, NCT00007644.)

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N Engl J Med 2017;377:132-42.
DOI: 10.1056/NEJMoa1615869

We previously reported that radical prostatectomy was not associated with significantly lower all-cause or prostate-cancer mortality than observation with noncurative palliative interventions through 12 years among men with localized prostate cancer detected during the early era of prostate-specific antigen (PSA) testing.[1] In light of the protracted disease course and extended survival of many patients, treatment decisions often require information about additional treatments received, patient-reported outcomes, and very-long-term mortality. Three other randomized trials compared radical prostatectomy with observation or PSA-based active monitoring. One older trial showed no significant difference in overall mortality.[2] Another trial, also conducted before the widespread use of PSA screening, showed differences favoring surgery in all-cause and prostate-cancer mortality of 12.7 and 11.0 percentage points, respectively, with similar differences in the risk of distant metastases at a median follow-up of 13.4 years.[3] The most recent trial, involving men with disease detected by PSA screening, showed no significant difference in all-cause or prostate-cancer mortality after a median of 10 years of follow-up among radiation therapy, surgery, and PSA-based active monitoring and delayed radical intervention.[4] We report all-cause and prostate-cancer mortality through nearly 20 years of follow-up and describe disease progression, treatments received, and patient-reported outcomes during the original follow-up.

METHODS

TRIAL DESIGN

We previously described the design, methods, and baseline results of the Prostate Cancer Intervention versus Observation Trial (PIVOT).[1,5] The trial was approved by the institutional review board at each site. Patients provided written informed consent. After completion of follow-up through January 2010, we amended the protocol to assess extended all-cause and prostate-cancer mortality. The original and revised protocols, including the statistical analysis plan, are available with the full text of this article at NEJM.org.

PATIENTS

From November 1994 through January 2002, we randomly assigned 731 men with localized prostate cancer (mean age, 67 years; median PSA value, 7.8 ng per milliliter) to radical prostatectomy or observation at Department of Veterans Affairs and National Cancer Institute medical centers.[1,5] Patients had to be medically fit for radical prostatectomy and have histologically confirmed, clinically localized prostate cancer (stage T1-T2NxM0 in the tumor–node–metastasis classification system according to the American Joint Committee on Cancer[6]) of any grade diagnosed within the previous 12 months. Patients had to have a PSA value of less than 50 ng per milliliter, an age of 75 years or younger, negative results on a bone scan for metastatic disease, and a life expectancy of at least 10 years. Trial sites assessed eligibility on the basis of local PSA values and biopsy readings. One of the authors, who is a pathologist, reviewed and reclassified biopsy specimens at a central location. The pathologist was unaware of the long-term fate of the patient and of the original Gleason score assessment at the local center.

FOLLOW-UP AND CLINICAL OUTCOMES

We assessed all-cause and prostate-cancer mortality through August 2014, for a minimum of 12 years and a maximum of 19.5 years or until the patient died. Logistic and analytic difficulties, including difficulty in obtaining information about and adjudicating the cause of death, delayed the reporting of findings. An end-points committee whose members were unaware of the trial-group assignments determined the cause of death on the basis of information extracted from the patients' medical records.[1,7] Data on disease progression, treatment received, and patient-reported health outcomes were based on follow-up through January 2010. After January 2010, data on treatment and follow-up were not systematically collected. We classified progression as local, regional, systemic, or biochemical (PSA) and as symptomatic or asymptomatic (Table S1 in the Supplementary Appendix, available at NEJM.org). We defined treatments as "definitive intervention" (Fig. S1 in the Supplementary Appendix), any surgery (including radical prostatectomy), radiation therapy, hormone therapy, chemotherapy, or immunotherapy, and we report treatments according to type of disease progression.

STATISTICAL ANALYSIS

Our primary outcome was all-cause mortality. Our secondary outcome was prostate-cancer mortality, which was defined as death that was definitely

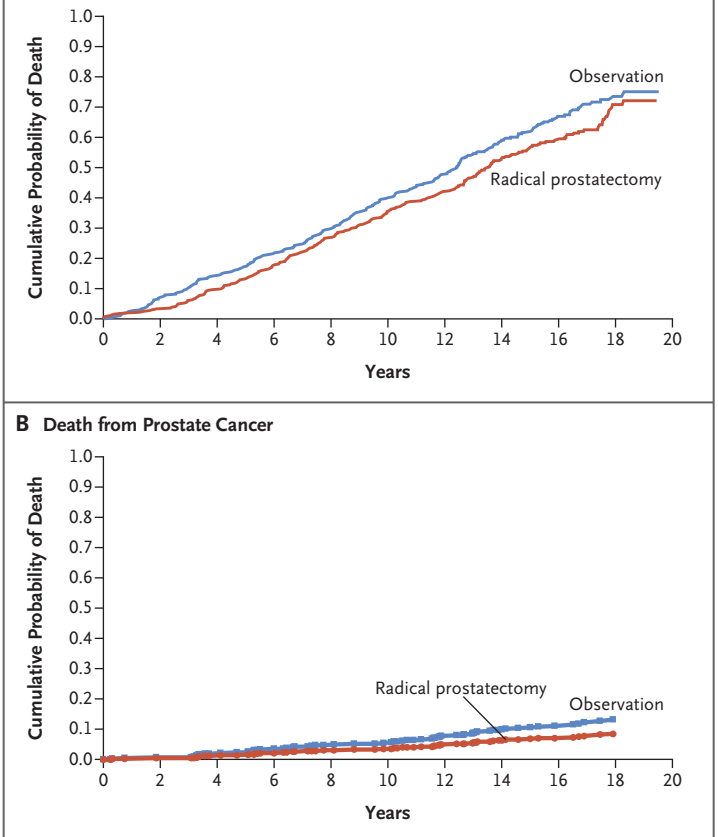


Figure 1. Kaplan–Meier Plots of Mortality.

By the end of the trial, 468 of 731 men (64.0%) had died from any cause (Panel A). Death attributed to prostate cancer or treatment occurred in 69 men (9.4%) (Panel B).

or probably due to prostate cancer or definitely or probably due to treatment for prostate cancer. End points through January 2010 included the following: local, regional, systemic, and biochemical (PSA) progression; additional treatments; adverse events requiring treatment; and patient-reported outcomes of urinary incontinence, erectile and sexual dysfunction, worry about health, "bother" due to prostate cancer or treatment, physical discomfort, satisfaction with sexual functioning, and functional limitations due to prostate cancer or treatment.

Analyses were performed according to the intention-to-treat principle with the use of Kaplan–Meier methods and corresponding 95% confidence intervals. We used the Fine and Gray method to compare groups with respect to prostate-cancer mortality in the presence of competing risks, because the Kaplan–Meier method for unadjusted survival analysis yields unreliable results for survival estimates in the presence of competing risks.[8-10] We assessed the cumulative incidence of death, between-group differences, and relative risks at 4, 8, 12, and 16 years and at the end of follow-up. P values of less than 0.05 were considered to indicate statistical significance, with no adjustment for multiple comparisons. We prespecified seven subgroups according to baseline characteristics, as described previously[1]: age, race, coexisting conditions,[11] self-reported performance status, PSA level, Gleason score,[12] and D'Amico tumor risk score.[13] We also assessed mortality outcomes on the basis of central histopathological reclassification. Patient-reported outcomes were analyzed at baseline, 6 months, 1 year, 2 years, 5 years, and 10 years with the use of Fisher's exact test for categorical outcomes or a t-test for continuous measures. We used SAS software, versions 9.3 and 9.4 (SAS Institute), for the analyses.[14]

RESULTS

ALL-CAUSE AND PROSTATE-CANCER MORTALITY

As of August 2014, a total of 468 of 731 men (64.0%) had died. The vital status of all the participants was available, although we were unable to ascertain the cause of death in 7 men (2 assigned to surgery and 5 to observation). The median follow-up from randomization to death or the end of follow-up was 12.7 years (interquartile range, 7.3 to 15.5). All-cause mortality was not significantly lower with surgery than with observation (hazard ratio, 0.84; 95% confidence interval [CI], 0.70 to 1.01; P=0.06) (Fig. 1A). The 19.5-year cumulative incidence of death was 61.3% among men assigned to radical prostatectomy and 66.8% among those assigned to observation (relative risk, 0.92; 95% CI, 0.82 to 1.02) (Table 1). Absolute differences in risk, although not significant, increased from 3.1 percentage points at 8 years to 5.5 percentage points at the end of follow-up (Table S3 in the Supplementary Appendix). The median survival was 13.0 years (95% CI, 12.5 to 13.5) with surgery and 12.4 years (95% CI, 11.4 to 12.8) with observation.

Death attributed to prostate cancer or treatment occurred in 69 men (9.4%); 65 deaths were attributed to prostate cancer and 4 to treatment. Prostate-cancer mortality was not significantly

Table 1. Cumulative Incidence of Death from Any Cause through 19.5 Years.*

Variable	Radical Prostatectomy		Observation		Absolute Difference in Risk (95% CI)	Relative Risk (95% CI)
	No. of Events/ Total No.	% (95% CI)	No. of Events/ Total No.	% (95% CI)		
					percentage points	
Overall	223/364	61.3 (56.2 to 66.1)	245/367	66.8 (61.8 to 71.4)	5.5 (–1.5 to 12.4)	0.92 (0.82 to 1.02)
Age at diagnosis						
<65 yr	58/122	47.5 (38.9 to 56.3)	78/131	59.5 (51.0 to 67.6)	12.0 (–0.3 to 23.8)	0.80 (0.63 to 1.01)
≥65 yr	165/242	68.2 (62.1 to 73.7)	167/236	70.8 (64.7 to 76.2)	2.6 (–5.7 to 10.8)	0.96 (0.86 to 1.09)
Race†						
White	150/232	64.7 (58.3 to 70.5)	155/220	70.5 (64.1 to 76.1)	5.8 (–2.8 to 14.3)	0.92 (0.81 to 1.04)
Black	64/111	57.7 (48.4 to 66.4)	75/121	62.0 (53.1 to 70.1)	4.3 (–8.2 to 16.7)	0.93 (0.75 to 1.15)
PSA						
≤10 ng/ml	140/238	58.8 (52.5 to 64.9)	151/241	62.7 (56.4 to 68.5)	3.8 (–4.9 to 12.5)	0.94 (0.81 to 1.08)
>10 ng/ml	83/126	65.9 (57.2 to 73.6)	93/125	74.4 (66.1 to 81.2)	8.5 (–2.8 to 19.6)	0.89 (0.75 to 1.04)
Risk category‡						
Locally assessed						
Low	82/148	55.4 (47.4 to 63.2)	83/148	56.1 (48.0 to 63.8)	0.7 (–10.5 to 11.8)	0.99 (0.81 to 1.21)
Intermediate	77/129	59.7 (51.1 to 67.8)	89/120	74.2 (65.7 to 81.2)	14.5 (2.8 to 25.6)	0.80 (0.67 to 0.96)
High	55/77	71.4 (60.5 to 80.3)	59/80	73.8 (63.2 to 82.1)	2.3 (–11.5 to 16.1)	0.97 (0.80 to 1.17)
Centrally assessed						
Low	58/111	52.3 (43.0 to 61.3)	67/122	54.9 (46.1 to 63.5)	2.7 (–10.0 to 15.2)	0.95 (0.75 to 1.21)
Intermediate	97/155	62.6 (54.7 to 69.8)	99/139	71.2 (63.2 to 78.1)	8.6 (–2.2 to 19.1)	0.88 (0.75 to 1.03)
High	55/78	70.5 (59.6 to 79.5)	63/85	74.1 (63.9 to 82.2)	3.6 (–10.0 to 17.2)	0.95 (0.79 to 1.15)

* PSA denotes prostate-specific antigen.
† Race was reported by the participants.
‡ The risk category was determined according to the D'Amico risk score, which is based on tumor stage, histologic score, and PSA level.

lower with radical prostatectomy than with observation (hazard ratio, 0.63; 95% CI, 0.39 to 1.02; P=0.06) (Fig. 1B). The cumulative incidence of death due to prostate cancer or treatment was 7.4% with surgery and 11.4% with observation (absolute difference, 4.0 percentage points; 95% CI, −0.2 to 8.3) (Table 2). Relative and absolute differences in risk remained stable after 12 years (Table S4 in the Supplementary Appendix). Death that was considered to be definitely due to prostate cancer or treatment occurred in 18 men (4.9%) assigned to surgery and 22 men (6.0%) assigned to observation.

SUBGROUP ANALYSES

The effect of surgery on mortality did not differ significantly according to baseline patient characteristics (Fig. 2A and 2B and Tables 1 and 2, and Tables S3 and S4 in the Supplementary Appendix). Among men younger than 65 years of age, the absolute difference in all-cause mortality between the surgery group and the observation group increased from –1.5 percentage points (95% CI, –11.7 to 8.5) at 8 years to 12.0 percentage points (95% CI, −0.3 to 23.8) at the end of follow-up. Among men 65 years of age or older, the absolute difference at the end of follow-up was 2.6 percentage points (95% CI, –5.7 to 10.8).

The effect of surgery on all-cause mortality may have differed according to baseline PSA value (P=0.06 for interaction) and tumor risk category (P=0.08 for interaction) (Fig. 2A and Table 1, and Table S3 in the Supplementary Appendix). Surgery was not associated with lower

Table 2. Cumulative Incidence of Death from Prostate Cancer through 19.5 Years.

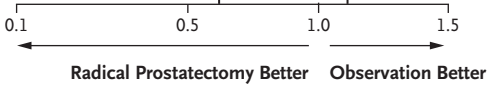
Variable	Radical Prostatectomy		Observation		Absolute Difference in Risk (95% CI)	Relative Risk (95% CI)
	No. of Events/ Total No.	% (95% CI)	No. of Events/ Total No.	% (95% CI)		
					percentage points	
Overall	27/364	7.4 (5.2 to 10.6)	42/367	11.4 (8.6 to 15.1)	4.0 (–0.2 to 8.3)	0.65 (0.41 to 1.03)
Age at diagnosis						
<65 yr	9/122	7.4 (3.9 to 13.4)	15/131	11.5 (7.1 to 18.0)	4.1 (–3.4 to 11.5)	0.64 (0.29 to 1.42)
≥65 yr	18/242	7.4 (4.8 to 11.5)	27/236	11.4 (8.0 to 16.1)	4.0 (–1.3 to 9.4)	0.65 (0.37 to 1.15)
Race						
White	17/232	7.3 (4.6 to 11.4)	28/220	12.7 (9.0 to 17.8)	5.4 (–0.2 to 11.1)	0.58 (0.32 to 1.02)
Black	8/111	7.2 (3.7 to 13.6)	11/121	9.1 (5.2 to 15.6)	1.9 (–5.6 to 9.2)	0.79 (0.33 to 1.90)
PSA						
≤10 ng/ml	16/238	6.7 (4.2 to 10.6)	23/241	9.5 (6.4 to 13.9)	2.8 (–2.2 to 7.9)	0.70 (0.38 to 1.30)
>10 ng/ml	11/126	8.7 (4.9 to 15.0)	19/125	15.2 (10.0 to 22.5)	6.5 (–1.7 to 14.7)	0.57 (0.29 to 1.16)
Risk category						
Locally assessed						
Low	6/148	4.1 (1.9 to 8.6)	8/148	5.4 (2.8 to 10.3)	1.4 (–3.9 to 6.7)	0.75 (0.27 to 2.11)
Intermediate	11/129	8.5 (4.8 to 14.6)	19/120	15.8 (10.4 to 23.4)	7.3 (–0.9 to 15.7)	0.54 (0.27 to 1.08)
High	10/77	13.0 (7.2 to 22.3)	15/80	18.8 (11.7 to 28.7)	5.8 (–5.9 to 17.2)	0.69 (0.33 to 1.45)
Centrally assessed						
Low	1/111	0.9 (0.2 to 4.9)	8/122	6.6 (3.4 to 12.4)	5.7 (0.5 to 11.6)	0.14 (0.02 to 1.08)
Intermediate	14/155	9.0 (5.5 to 14.6)	12/139	8.6 (5.0 to 14.5)	–0.4 (–7.0 to 6.5)	1.05 (0.50 to 2.18)
High	10/78	12.8 (7.1 to 22.0)	20/85	23.5 (15.8 to 33.6)	10.7 (–1.3 to 22.3)	0.54 (0.27 to 1.09)

all-cause mortality than observation among men with a PSA value of 10 ng per milliliter or less or among those with low-risk or high-risk cancers but may have been associated with lower mortality among men with a PSA value of more than 10 ng per milliliter or among those with intermediate-risk disease. Among men with low-risk disease, the absolute difference in risk between the trial groups was 0.7 percentage points (95% CI, –10.5 to 11.8). Among men with intermediate-risk tumors, the absolute difference in risk was 14.5 percentage points (95% CI, 2.8 to 25.6). The absolute difference in risk was smaller and not significant among men with disease that was determined to be intermediate-risk on the basis of central (rather than local) Gleason grading.

Figure 2 (facing page). Forest Plots for All-Cause and Prostate-Cancer Mortality, According to Patient Subgroups.
There were no significant between-group differences in all-cause mortality (Panel A) or prostate-cancer mortality (Panel B) according to prespecified subgroups. However, the effect of surgery on all-cause mortality may have differed according to baseline prostate-specific antigen (PSA) value (P=0.06 for interaction) and tumor risk (D'Amico tumor risk score [low, intermediate, or high], which was based on tumor stage, histologic score, and PSA level; P=0.08 for interaction). Scores on the Charlson comorbidity index range from 0 to 33, with higher scores indicating greater disease burden. Scores for self-reported performance status range from 0 to 4, with 0 indicating fully active and higher scores indicating poorer functional status. Scores on the Gleason histologic scale range from 2 to 10, with 10 indicating the most poorly differentiated tumors. The bars indicate 95% confidence intervals.

A Death from Any Cause

Subgroup	Observation	Radical Prostatectomy	Hazard Ratio (95% CI)	P Value for Interaction
	no. of events/total no.			
Overall	245/367	223/364	0.84 (0.70–1.01)	
Age				0.56
<65 yr	78/131	58/122	0.73 (0.52–1.02)	
≥65 yr	167/236	165/242	0.88 (0.71–1.09)	
Race				0.87
White	155/220	150/232	0.82 (0.66–1.03)	
Black	75/121	64/111	0.87 (0.62–1.22)	
Other	15/26	9/21	0.64 (0.28–1.46)	
PSA				0.06
≤10 ng/ml	151/241	140/238	0.91 (0.72–1.14)	
>10 ng/ml	93/125	83/126	0.73 (0.54–0.98)	
Risk				0.08
Low	83/148	82/148	0.98 (0.72–1.33)	
Intermediate	89/120	77/129	0.68 (0.50–0.92)	
High	59/80	55/77	0.78 (0.54–1.13)	
Charlson score				0.79
0	128/220	117/224	0.84 (0.65–1.07)	
≥1	117/147	106/140	0.85 (0.65–1.10)	
Performance status				0.55
0	200/310	184/312	0.84 (0.69–1.03)	
1–4	45/57	39/52	0.83 (0.54–1.28)	
Gleason score				0.84
<7	167/261	145/254	0.82 (0.65–1.02)	
≥7	63/86	68/98	0.83 (0.59–1.17)	



B Death from Prostate Cancer

Subgroup	Observation	Radical Prostatectomy	Hazard Ratio (95% CI)	P Value for Interaction
	no. of events/total no.			
Overall	42/367	27/364	0.63 (0.39–1.02)	
Age				0.99
<65 yr	15/131	9/122	0.63 (0.28–1.43)	
≥65 yr	27/236	18/242	0.63 (0.35–1.15)	
Race				0.49
White	28/220	17/232	0.55 (0.30–1.01)	
Black	11/121	8/111	0.78 (0.32–1.91)	
Other	3/26	2/21	0.82 (0.14–4.65)	
PSA				0.62
≤10 ng/ml	23/241	16/238	0.70 (0.37–1.32)	
>10 ng/ml	19/125	11/126	0.54 (0.26–1.13)	
Risk				0.89
Low	8/148	6/148	0.74 (0.26–2.13)	
Intermediate	19/120	11/129	0.53 (0.25–1.11)	
High	15/80	10/77	0.64 (0.29–1.41)	
Charlson score				0.44
0	25/220	19/224	0.72 (0.40–1.31)	
≥1	17/147	8/140	0.49 (0.21–1.13)	
Performance status				0.61
0	35/310	24/312	0.66 (0.40–1.11)	
1–4	7/57	3/52	0.47 (0.12–1.80)	
Gleason score				0.97
<7	20/261	12/254	0.60 (0.30–1.24)	
≥7	21/86	15/98	0.59 (0.30–1.13)	

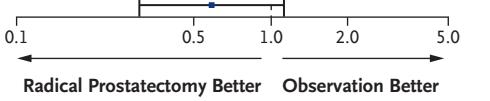


Table 3. Disease Progression and Treatment for Disease Progression or Adverse Events (Original Follow-up).

Variable	Radical Prostatectomy (N=364)	Observation (N=367)	Absolute Difference (95% CI)	Hazard Ratio (95% CI)
	number (percent)		*percentage points*	
Disease progression*				
Local, regional, or systemic progression				
Any	149 (40.9)	251 (68.4)	27.5 (20.4 to 34.2)	0.39 (0.32 to 0.48)
Asymptomatic	89 (24.4)	161 (43.9)	19.4 (12.6 to 26.0)	0.46 (0.35 to 0.59)
Local progression				
Any	124 (34.1)	227 (61.9)	27.8 (20.7 to 34.5)	0.37 (0.29 to 0.46)
Asymptomatic	61 (16.8)	119 (32.4)	15.7 (9.5 to 21.7)	0.43 (0.32 to 0.59)
Regional progression				
Any	33 (9.1)	52 (14.2)	5.1 (0.4 to 9.8)	0.60 (0.39 to 0.92)
Asymptomatic	22 (6.0)	30 (8.2)	2.1 (–1.7 to 6.0)	0.69 (0.40 to 1.20)
Systemic progression				
Any	37 (10.2)	54 (14.7)	4.5 (–0.3 to 9.4)	0.64 (0.42 to 0.97)
Asymptomatic	25 (6.9)	38 (10.4)	3.5 (–0.6 to 7.6)	0.62 (0.37 to 1.03)
Treatment for disease progression†				
For any reason	122 (33.5)	219 (59.7)	26.2 (19.0 to 32.9)	0.45 (0.36 to 0.56)
For increasing or persistently elevated PSA value	74 (20.3)	139 (37.9)	17.5 (11.0 to 23.9)	0.46 (0.34 to 0.61)
For local progression	45 (12.4)	93 (25.3)	13.0 (7.3 to 18.5)	0.44 (0.31 to 0.63)
For regional progression	2 (0.5)	3 (0.8)	0.3 (–1.3 to 1.9)	0.64 (0.11 to 3.82)
For systemic progression	17 (4.7)	32 (8.7)	4.0 (0.4 to 7.8)	0.49 (0.27 to 0.88)
Adverse events requiring treatment‡				
Erectile dysfunction	53 (14.6)	20 (5.4)	–9.1 (–13.5 to –4.8)	2.77 (1.65 to 4.63)
Incontinence	63 (17.3)	16 (4.4)	–12.9 (–17.5 to –8.6)	4.22 (2.44 to 7.30)
Other	45 (12.4)	41 (11.2)	–1.2 (–5.9 to 3.5)	1.08 (0.71 to 1.65)

* Disease progression was defined according to the trial protocol as the time to evidence of disease progression or persistence. Progression was classified according to clinical stage (local, regional, or systemic) and whether asymptomatic or causing clinical signs or symptoms.
† Data reflect recorded treatments and indications for treatment on the basis of clinical stage, including an increasing or persistently elevated PSA level. A patient could be counted as having received treatment for more than a single type of disease progression.
‡ Data are based on treatments with a known start date.

Exploratory analyses in men with T1c (nonpalpable, PSA-detected) tumors, including those with a PSA value of more than 10 ng per milliliter or a Gleason score of 7 or more (on a scale from 2 to 10, with 10 indicating the most poorly differentiated tumors), showed nonsignificant differences in all-cause and prostate-cancer mortality between the surgery group and the observation group (Tables S3 and S4 in the Supplementary Appendix). Few deaths from prostate cancer or treatment occurred among men with T1c tumors, and confidence intervals were wide (Tables S3 and S4 in the Supplementary Appendix).

DISEASE PROGRESSION AND ADDITIONAL TREATMENTS

Fewer men assigned to surgery had disease progression or received additional treatment than men assigned to observation (Table 3, and Figs. S2 through S4 in the Supplementary Appendix). Any progression occurred in 40.9% of the men assigned to surgery versus 68.4% of the men assigned to observation. Most disease progression was local, and approximately half the cases of local progression were asymptomatic. Definitive treatment occurred in 20.4% of the men assigned to observation, rarely after 5 years of follow-up,

and in 85.5% of the men assigned to surgery, almost all occurring within 1 year (Fig. S1 in the Supplementary Appendix). Treatment for cancer progression, mostly for asymptomatic, local, or PSA progression, occurred in 33.5% of the men assigned to surgery and in 59.7% of the men assigned to observation (Table 3, and Fig. S3 in the Supplementary Appendix). Androgen-deprivation therapy was less frequent among men assigned to surgery than among those assigned to observation (21.7% vs. 44.4%). The absolute difference in the risk of systemic progression or treatment for systemic progression was approximately 4 percentage points, in favor of surgery.

The frequency of treatment for local progression was lower with surgery than with observation in all tumor risk groups. Among men with low-risk disease, treatment for regional or systemic disease was infrequent and did not differ significantly between the surgery group and the observation group. Among men with intermediate-risk disease, the frequency of treatment for systemic progression was lower with surgery than with observation (5.4% vs. 11.7%). Among men with high-risk disease, the frequency of treatment for an increasing or persistently elevated PSA value was lower with surgery than with observation (33.8% vs. 52.5%), but there was no significant difference with respect to treatment for regional or systemic progression. (Details regarding treatment according to progression type and tumor risk category are provided in Fig. S4 in the Supplementary Appendix.) Physician-prescribed treatment for erectile dysfunction and urinary incontinence due to prostate-cancer progression or treatment was more common with surgery than with observation (Table 3).

PATIENT-REPORTED OUTCOMES

Patient-reported overall health, physical or mental health assessed with the use of the Medical Outcomes Study 12-Item Short-Form General Health Survey (SF-12), and worry about health did not differ significantly between the groups. As compared with men assigned to observation, men assigned to surgery were more likely to report bother due to prostate cancer or treatment, physical discomfort, and limitations in activities of daily living through 2 years but not at later time points. The use of absorbent pads because of incontinence was greater through 10 years in men treated with surgery than in those assigned to observation; absolute differences exceeded 30 percentage points at all time points. Erectile dysfunction as well as decreases in sexual function, activity, interest, and satisfaction were much greater through 5 years in men assigned to surgery than in those assigned to observation. Details on patient-related outcomes are provided in Figures S5 through S9 and Tables S5 through S7 in the Supplementary Appendix.

DISCUSSION

After nearly 20 years, the absolute difference in all-cause mortality between men assigned to surgery and those assigned to observation was less than 6 percentage points, and the absolute difference in prostate-cancer mortality was 4 percentage points. The extended follow-up yielded slightly greater differences in mortality favoring surgery than those described earlier, although the differences remained nonsignificant.[1,14-16] The frequencies of disease progression and treatment for disease progression were lower with surgery than with observation, although most events of progression were asymptomatic, local, or biochemical. There were large, long-term differences in urinary incontinence and erectile and sexual dysfunction in favor of observation and smaller, shorter-term differences in adverse effects with respect to physical function and activities of daily living.

Although relative differences in prostate-cancer mortality between the trial groups appeared to be larger, absolute differences were small, both relative and absolute differences were nonsignificant, and statistical measures were not adjusted for multiple comparisons; such an adjustment would have further reduced the levels of significance of the differences.[17] We encourage readers to focus on absolute differences in risk and corresponding confidence intervals.[14-16] The difference was 1 percentage point when the end point was death that was considered to be definitely due to prostate cancer or treatment. Using all-cause mortality as our primary end point avoided pitfalls in cause-of-death ascertainment.[7,18]

We urge caution in interpreting subgroup effects.[19] Our trial was not powered to detect small differences between subgroups, but significant results may be due to multiple analyses.[17] If differences in all-cause mortality exist, they were confined to men with intermediate-risk disease

and depend on histopathological classification methods. For men with low-risk or high-risk disease, differences in all-cause mortality were 3 percentage points or less and were not significant. Surgical effects on mortality did not vary according to patient factors.

Most treatment for disease progression was for local, asymptomatic reasons, especially increasing or persistently elevated PSA values. Among men assigned to surgery, 41% had disease progression and 34% received treatment for disease progression. There were few differences in quality of life and worry about health between the surgery group and the observation group. Long-term erectile and sexual dysfunction and urinary incontinence and physician-directed treatment were substantially greater with surgery than with observation. Functional limitations and bother due to prostate cancer or treatment were greater with surgery than with observation through at least 2 years, whereas worry about health was less at 10 years.

Our findings are generally consistent with those of the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4)[3,20] and the Prostate Testing for Cancer and Treatment (ProtecT) trial.[4,21] SPCG-4, like PIVOT, compared surgery with observation, whereas the ProtecT trial compared surgery or radiation with active monitoring and delayed radical intervention based primarily on PSA results without surveillance biopsies. Data from randomized trials are lacking to assess biopsy-based active surveillance, the predominant active-monitoring practice in the United States. PIVOT involved men who received a diagnosis of prostate cancer, and who used treatments available, in the United States during the early era of PSA testing,[1,5] a midpoint between the era before PSA testing (SPCG-4) and the later era of PSA testing (the ProtecT trial). Mortality differences across these studies may reflect differences in patient age and coexisting conditions but more likely reflect differences in the natural history of prostate cancer that are related to detection methods and possibly treatment approaches, including improvements in medical treatment for progressive disease. Only 9.4% of PIVOT participants died from prostate cancer. The absolute difference in all-cause mortality between the trial groups was 5.5 percentage points in favor of surgery, and the absolute difference in prostate-cancer mortality was 4.0 percentage points. In the ProtecT trial, mortality and the incidence of metastatic disease (which included asymptomatic disease detected by surveillance imaging and biochemical [PSA] testing) as well as absolute differences between the trial groups in favor of radical intervention (1 percentage point for mortality and 4 percentage points for metastatic-disease incidence) were much lower through 10 years than in SPCG-4 or PIVOT.

Our results, together with those of SPCG-4, the ProtecT trial, and two earlier trials that showed no mortality benefits of surgery[2] or radiation[22] as compared with observation, have clinical implications. First, they show that long-term prostate-cancer mortality remains low among most men with localized prostate cancer who are treated with observation and that death from prostate cancer is very uncommon among men with low-risk and low-PSA disease. Reducing overtreatment is needed. Men with low-risk and PSA-based screening–detected disease can safely avoid harms and costs of early radical intervention or of biopsy-guided active surveillance with delayed radical treatment.[4,21,23] Observation, PSA-based monitoring, and active surveillance with delayed radical intervention remain infrequently used, even among older men,[24-26] despite a frequency of metastatic progression of less than 3%,[27] prostate-cancer mortality of 1% or less,[28-31] and cost-effectiveness that is superior to that with early radical intervention.[23,32] PSA-based monitoring and biopsy-based active-surveillance programs should reduce the frequency of surveillance biopsy and increase biopsy and PSA thresholds that trigger radical interventions.

Second, surgery may have mortality benefits in some men, particularly those with intermediate-risk prostate cancer who have long life expectancies. However, the comparative effects of active surveillance and PSA-based monitoring in many men with intermediate-risk disease should be examined. In addition, the risk of progression or death as well as the absolute treatment benefit diminish while overtreatment harms increase in men with smaller-volume, screening-detected lower-risk cancers. Beneficial effects depend on proper histopathological grading, which is fraught with interobserver and intraobserver variation. Revisions in Gleason grading and risk-score classification systems have resulted in an upgrading of prostate cancers that are classified today, as compared with those in men enrolled in PIVOT.

This has led to more men being classified with intermediate-risk or high-risk disease, resulting in fewer men being considered eligible for observation or active monitoring.[33-36]

Third, although men with high-risk disease have a poor prognosis, surgery may not provide large benefits with respect to mortality. Safer and more effective options are needed. Fourth, surgery is associated with a decreased risk of disease progression and treatment for disease progression. However, most progression is asymptomatic, local, or biochemical, for which the treatment benefit is uncertain. Among men with low-risk disease in our trial, the frequency of treatment for regional or systemic progression was not significantly lower with surgery than with observation. Reducing treatment for asymptomatic progression would decrease harms and costs, with little, if any, effect on mortality. Fifth, surgery causes perioperative and longer-term adverse effects, some requiring treatment. Nonetheless, regardless of the initial treatment, we found few differences between the trial groups in long-term bother, physical discomfort, worry about health, overall health, or limitations in activities due to prostate cancer or treatment. Differences in satisfaction with sexual functioning remained significant through 5 years.

In conclusion, radical prostatectomy was not associated with significantly lower all-cause or prostate-cancer mortality than observation through 20 years of follow-up among men with localized prostate cancer that was diagnosed during the early era of PSA testing. Absolute differences remained below 6 percentage points. Death from prostate cancer was very uncommon among men with low-risk disease who were assigned to observation. Surgery may be associated with decreased mortality among men with intermediate-risk prostate cancer, depending on the pathological classification. Surgery resulted in substantially greater long-term urinary incontinence and erectile and sexual dysfunction than observation and was associated with a significantly lower risk of disease progression and additional treatments, most for local or asymptomatic biochemical progression.

Supported by the Department of Veterans Affairs, the Agency for Healthcare Quality and Research, and the National Cancer Institute.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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