ORIGINAL ARTICLE

Radical Prostatectomy or Watchful Waiting in Prostate Cancer — 29-Year Follow-up

Anna Bill-Axelson, M.D., Ph.D., Lars Holmberg, M.D., Ph.D., Hans Garmo, Ph.D., Kimmo Taari, M.D., Ph.D., Christer Busch, M.D., Ph.D., Stig Nordling, M.D., Ph.D., Michael Häggman, M.D., Ph.D., Swen-Olof Andersson, M.D., Ph.D., Ove Andrén, M.D., Ph.D., Gunnar Steineck, M.D., Ph.D., Hans-Olov Adami, M.D., Ph.D., and Jan-Erik Johansson, M.D., Ph.D.

ABSTRACT

BACKGROUND

Radical prostatectomy reduces mortality among men with clinically detected localized prostate cancer, but evidence from randomized trials with long-term follow-up is sparse.

METHODS

We randomly assigned 695 men with localized prostate cancer to watchful waiting or radical prostatectomy from October 1989 through February 1999 and collected follow-up data through 2017. Cumulative incidence and relative risks with 95% confidence intervals for death from any cause, death from prostate cancer, and metastasis were estimated in intention-to-treat and per-protocol analyses, and numbers of years of life gained were estimated. We evaluated the prognostic value of histopathological measures with a Cox proportional-hazards model.

RESULTS

By December 31, 2017, a total of 261 of the 347 men in the radical-prostatectomy group and 292 of the 348 men in the watchful-waiting group had died; 71 deaths in the radical-prostatectomy group and 110 in the watchful-waiting group were due to prostate cancer (relative risk, 0.55; 95% confidence interval [CI], 0.41 to 0.74; P<0.001; absolute difference in risk, 11.7 percentage points; 95% CI, 5.2 to 18.2). The number needed to treat to avert one death from any cause was 8.4. At 23 years, a mean of 2.9 extra years of life were gained with radical prostatectomy. Among the men who underwent radical prostatectomy, extracapsular extension was associated with a risk of death from prostate cancer that was 5 times as high as that among men without extracapsular extension, and a Gleason score higher than 7 was associated with a risk that was 10 times as high as that with a score of 6 or lower (scores range from 2 to 10, with higher scores indicating more aggressive cancer).

CONCLUSIONS

Men with clinically detected, localized prostate cancer and a long life expectancy benefited from radical prostatectomy, with a mean of 2.9 years of life gained. A high Gleason score and the presence of extracapsular extension in the radical prostatectomy specimens were highly predictive of death from prostate cancer. (Funded by the Swedish Cancer Society and others.)

From the Department of Surgical Sciences (A.B.-A., L.H., M.H.), Regional Cancer Center Uppsala Örebro (H.G.), and the Department of Pathology (C.B.), Uppsala University Hospital, Uppsala, the School of Health and Medical Sciences, Örebro University, and the Department of Urology, Örebro University Hospital, Örebro (S.-O.A., O.A., J.-E.J.), the Department of Medical Epidemiology and Biostatistics (H.-O.A.), Karolinska Institutet, Stockholm, and the Division of Clinical Cancer Epidemiology, Sahlgrenska Academy, Gothenburg (G.S.) — all in Sweden; the School of Medicine, Division of Cancer Studies (L.H., H.G.), and the School of Cancer and Pharmaceutical Sciences (L.H.), King's College London, London; the Department of Urology, Helsinki University Hospital (K.T.), and the Department of Pathology, University of Helsinki (S.N.), Helsinki; the Department of Epidemiology, Harvard T.C. Chan School of Public Health, Boston (H.-O.A.); and the Clinical Effectiveness Research Group, Institute of Health and Society, University of Oslo, Oslo (H.-O.A.). Address reprint requests to Dr. Bill-Axelson at anna.bill.axelson@surgsci.uu.se.

Drs. Bill-Axelson and Holmberg contributed equally to this article.

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In Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4), we compared radical prostatectomy with watchful waiting among men with localized prostate cancer. Enrollment, which began in 1989, predominantly included men with clinically detected tumors. In this follow-up study conducted 29 years after the start of the trial, at a point at which 80% of the men enrolled had died, we analyzed whether the survival benefit after radical prostatectomy continued, whether the benefit differed according to age at diagnosis, whether protocol violations had biased the results, and how many years of life, on average, had been saved for each man after radical prostatectomy. We also investigated whether histopathological variables predicted a long-term prognosis in the radical-prostatectomy group.

Methods

Trial Design

Overall, 695 men with localized prostate cancer were randomly assigned to either radical prostatectomy or watchful waiting in 14 centers in Sweden, Finland, and Iceland between October 1989 and February 1999. The trial has been described in detail in previous publications,[1-5] and the protocol is available with the full text of this article at NEJM.org. The regional ethics committees at all the centers approved the trial. Men were included in the trial if they were younger than 75 years of age, had a life expectancy of more than 10 years and no other known cancer that was considered likely to shorten survival, had a prostate-specific antigen (PSA) level of less than 50 ng per milliliter, and had a localized tumor.[6] Tumors were required to be highly to moderately highly differentiated according to the World Health Organization classification, based on core biopsy or fine-needle aspiration. A negative bone scan was also required for eligibility.

Surgery started with removal of lymph nodes in the obturator fossa and continued if there were no nodal metastases detected in a frozen section.[7] If signs of local recurrence (a palpable nodule or histologically confirmed recurrence) developed in a patient in the radical-prostatectomy group, androgen-deprivation therapy was initiated. Confirmed metastases were treated hormonally in both groups. In 2003, androgen-deprivation treatment was allowed if tumor progression occurred, if the PSA level increased, or if the therapy was judged to be of potential clinical benefit. In 1999, all core-biopsy specimens were reviewed by four uropathologists and graded according to the Gleason system (scores range from 2 to 10 and are calculated as the sum of two scores [each ranging from 1 to 5] indicating the aggressiveness of the two most common histologic patterns in a prostate tumor, with higher scores indicating more aggressive cancer).[8] In 2006, the specimens from radical prostatectomy were reviewed and graded according to the Gleason system and evaluated for positive surgical margins and for extracapsular extension.[3]

Follow-up

Patients underwent a follow-up examination every 6 months for the first 2 years and then annually. Metastases were diagnosed at bone scan or were histologically confirmed at sites outside the pelvic area. In the radical-prostatectomy group, local recurrence was defined as a palpable mass on digital rectal examination or a histologically confirmed tumor on transrectal biopsy. In the watchful-waiting group, tumor progression was defined as palpable extracapsular extension or voiding obstruction that required intervention.

Causes of death were determined by an independent end-point committee whose members were unaware of the treatment assignments and who received extracted information according to a protocol. The members of the end-point committee individually determined the cause of death and reached consensus for cases initially classified differently. All participants were followed until December 31, 2017, and no patient was lost to follow-up.

Statistical Analysis

The end points we investigated were death from any cause, death from prostate cancer, and metastasis, with death from other causes treated as competing risk. Gray's test was used to assess treatment effects.[9] Effect sizes were quantified by analyzing relative risks (with 95% confidence intervals) and differences in cumulative incidence (with 95% confidence intervals). Relative risks were estimated from Cox proportional-hazards models in which proportionality was verified by visual inspection of Schoenfeld residuals. Cumulative-incidence proportions were used to account for competing risks among various causes of death.[10] Analyses were also stratified according to age at diagnosis (<65 years vs. ≥65 years). All

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the men were followed until death or December 31, 2017, whichever came first. The median follow-up time was calculated with the use of the reverse Kaplan–Meier method.[11] Differences in residual mean survival time at 23 years were used to calculate the years of life gained.[12]

A per-protocol analysis involving all the men who survived at least 1 year was performed and was based on treatments given during the first year. Men who were randomly assigned to radical prostatectomy and did not undergo the procedure and men who were randomly assigned to watchful waiting who underwent radical prostatectomy or lymph-node dissection during the first year were excluded from the per-protocol analysis. Data from men in the watchful-waiting group who later underwent surgery were censored. For the per-protocol analysis, we used a Cox regression with adjustment for baseline characteristics: age, tumor stage, PSA level, and Gleason score of the core-biopsy specimen. Missing data were imputed with the use of chained equations with five imputation data sets per value.[13]

We assessed the prognostic value of margins (positive or negative), extracapsular tumor growth (not present or any extension), and Gleason score (2 to 6, 7 [separated into Gleason grade 3+4 and 4+3, with the latter designation indicating that grade 4 was the more common histologic pattern in the tumor], or 8 to 10) in the radical-prostatectomy specimens and expressed the results as relative risks obtained from multivariable Cox proportional-hazards models. One model included the histopathological measures one at a time and was adjusted for age group (<65 vs. ≥65 years). The other model included the histopathological measure of interest but was adjusted for the two other histopathological measures, for PSA level, and for age group.

RESULTS

PATIENTS

In all, 347 men were randomly assigned to the radical-prostatectomy group and 348 to the watchful-waiting group. The baseline characteristics of the two groups were similar, with a mean age of 65 years. Only 12% of the patients had nonpalpable stage T1c tumors at inclusion. The mean PSA level was approximately 13 ng per milliliter (Table 1). By December 31, 2017, a total of 294 of the 347 men (85%) in the radical-prostatectomy group had undergone a radical prostatectomy, and 52 of the 348 men (15%) in the watchful-waiting group had undergone curative treatment (Fig. S1 in the Supplementary Appendix, available at NEJM.org). The median follow-up time was 23.6 years, the minimum follow-up time was 20 days, the maximum observed follow-up time was 28.0 years, and the maximum potential follow-up time was 29.3 years.

MORTALITY

Of the 695 men who were included in the analysis, 553 (80%) had died by the end of 2017. In 181 patients (32%), the deaths were due to prostate cancer (71 in the radical-prostatectomy group and 110 in the watchful-waiting group). One man in the radical-prostatectomy group died shortly after surgery. The cumulative incidence of death at 23 years was 71.9% in the radical-prostatectomy group and 83.8% in the watchful-waiting group (difference, 12.0 percentage points; 95% confidence interval [CI], 5.5 to 18.4). The corresponding relative risk based on data for the complete follow-up period was 0.74 (95% CI, 0.62 to 0.87; P<0.001) (Fig. 1 and Table 2, and Table S1 in the Supplementary Appendix). The cumulative incidence of death from prostate cancer at 23 years was 19.6% in the radical-prostatectomy group and 31.3% in the watchful-waiting group (difference, 11.7 percentage points; 95% CI, 5.2 to 18.2), and the relative risk for the complete follow-up period was 0.55 (95% CI, 0.41 to 0.74; P<0.001) (Fig. 1 and Table 2, and Table S1 in the Supplementary Appendix). The mean years of life gained in the radical-prostatectomy group at 23 years of follow-up was 2.9 years.

DISTANT METASTASES

Distant metastases were diagnosed in 92 men in the radical-prostatectomy group and in 150 men in the watchful-waiting group. The cumulative incidence of distant metastases at 23 years was 26.6% in the radical-prostatectomy group and 43.3% in the watchful-waiting group (difference, 16.7 percentage points; 95% CI, 9.6 to 23.7). The relative risk based on data from the complete follow-up period was 0.54 (95% CI, 0.42 to 0.70; P<0.001) (Fig. 2 and Table 2).

ANALYSES ACCORDING TO AGE

The effect of radical prostatectomy among men who were younger than 65 years of age at diagnosis was greater than the effect on those who were older than 65 years with regard to all three

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Table 1. Clinical Characteristics of the Patients.*

Characteristic	All Patients		Patients <65 Yr of Age		Patients ≥65 Yr of Age	
	Radical Prostatectomy (N=347)	Watchful Waiting (N=348)	Radical Prostatectomy (N=157)	Watchful Waiting (N=166)	Radical Prostatectomy (N=190)	Watchful Waiting (N=182)
Age — yr	64.6±64.6	64.5±64.5	60.0±60.0	60.2±60.2	68.4±68.4	68.4±68.4
Mean PSA level — ng/ml	13.5	12.3	12.7	12.4	14.2	12.2
Tumor stage — no. (%)†						
T1b	33 (9.5)	50 (14.4)	14 (8.9)	22 (13.3)	19 (10.0)	28 (15.4)
T1c	43 (12.4)	38 (10.9)	24 (15.3)	21 (12.7)	19 (10.0)	17 (9.3)
T2	270 (77.8)	259 (74.4)	119 (75.8)	123 (74.1)	151 (79.5)	136 (74.7)
Missing data	1 (0.3)	1 (0.3)	0	0	1 (0.5)	1 (0.5)
WHO grade — no. (%)‡						
1	168 (48.4)	166 (47.7)	76 (48.4)	83 (50.0)	92 (48.4)	83 (45.6)
2	178 (51.3)	182 (52.3)	81 (51.6)	83 (50.0)	97 (51.1)	99 (54.4)
Missing data	1 (0.3)	0	0	0	1 (0.5)	0
Gleason score of biopsy specimen — no. (%)§						
2–4	45 (13.0)	46 (13.2)	25 (15.9)	27 (16.3)	20 (10.5)	19 (10.4)
5 or 6	165 (47.6)	166 (47.7)	69 (43.9)	81 (48.8)	96 (50.5)	85 (46.7)
7	77 (22.2)	82 (23.6)	33 (21.0)	32 (19.3)	44 (23.2)	50 (27.5)
8 or 9	14 (4.0)	21 (6.0)	5 (3.2)	10 (6.0)	9 (4.7)	11 (6.0)
Missing data¶	46 (13.3)	33 (9.5)	25 (15.9)	16 (9.6)	21 (11.1)	17 (9.3)
Method of detection — no. (%)						
Screening‖	18 (5.2)	18 (5.2)	9 (5.7)	7 (4.2)	9 (4.7)	11 (6.0)
Coincidental**	87 (25.1)	91 (26.1)	41 (26.1)	46 (27.7)	46 (24.2)	45 (24.7)
TURP	40 (11.5)	56 (16.1)	19 (12.1)	29 (17.5)	21 (11.1)	27 (14.8)
Symptoms	152 (43.8)	138 (39.7)	68 (43.3)	66 (39.8)	84 (44.2)	72 (39.6)
Other	49 (14.1)	44 (12.6)	20 (12.7)	17 (10.2)	29 (15.3)	27 (14.8)
Missing data	1 (0.3)	1 (0.3)	0	1 (0.6)	1 (0.5)	0
PSA level — no. (%)						
<4 ng/ml	43 (12.4)	63 (18.1)	27 (17.2)	32 (19.3)	16 (8.4)	31 (17.0)
4–6.9 ng/ml	60 (17.3)	60 (17.2)	33 (21.0)	24 (14.5)	27 (14.2)	36 (19.8)
7–10 ng/ml	68 (19.6)	67 (19.3)	23 (14.6)	28 (16.9)	45 (23.7)	39 (21.4)

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10.1–20 ng/ml	100 (28.8)	95 (27.3)	43 (27.4)	51 (30.7)	57 (30.0)	44 (24.2)
>20 ng/ml	69 (19.9)	60 (17.2)	30 (19.1)	28 (16.9)	39 (20.5)	32 (17.6)
Missing data	7 (2.0)	3 (0.9)	1 (0.6)	3 (1.8)	6 (3.2)	0
Surgery — no. (%)						
Radical prostatectomy††	289 (83.3)	17 (4.9)	140 (89.2)	9 (5.4)	149 (78.4)	8 (4.4)
Lymph node dissection only	23 (6.6)	4 (1.1)	7 (4.5)	2 (1.2)	16 (8.4)	2 (1.1)
No surgery††	35 (10.1)	327 (94.0)	10 (6.4)	155 (93.4)	25 (13.2)	172 (94.5)
Positive margins — no./total no. (%)§§						
0 mm	184/284 (64.8)	—	100/137 (73.0)	—	84/147 (57.1)	—
1–9 mm	50/284 (17.6)	—	18/137 (13.1)	—	32/147 (21.8)	—
10–19 mm	25/284 (8.8)	—	11/137 (8.0)	—	14/147 (9.5)	—
≥20 mm	24/284 (8.5)	—	8/137 (5.8)	—	16/147 (10.9)	—
Missing data	1/284 (0.4)	—	0	—	1/147 (0.7)	—
Extracapsular extension — no./total no. (%)						
0 mm	151/284 (53.2)	—	84/137 (61.3)	—	67/147 (45.6)	—
1–9 mm	46/284 (16.2)	—	19/137 (13.9)	—	27/147 (18.4)	—
10–19 mm	38/284 (13.4)	—	14/137 (10.2)	—	24/147 (16.3)	—
≥20 mm	48/284 (16.9)	—	20/137 (14.6)	—	28/147 (19.0)	—
Missing data	1/284 (0.4)	—	0	—	1/147 (0.7)	—
Gleason score of prostatectomy specimen — no./total no. (%)§						
3–6	88/284 (31.0)	—	46/137 (33.6)	—	42/147 (28.6)	—
3+4	87/284 (30.6)	—	40/137 (29.2)	—	47/147 (32.0)	—
4+3	70/284 (24.6)	—	35/137 (25.5)	—	35/147 (23.8)	—
8 or 9	38/284 (13.4)	—	15/137 (10.9)	—	23/147 (15.6)	—
Missing data	1/284 (0.4)	—	1/137 (0.7)	—	0	—

* Percentages may not total 100 because of rounding. TURP denotes transurethral resection of the prostate.
† Tumors that are found incidentally during surgery are classified as stage T1a (if ≤5% of resected tissue is cancerous) or stage T1b (if >5% of resected tissue is cancerous); stage T1c tumors are nonpalpable and are found by biopsy, and stage T2 tumors are palpable but are completely confined within the prostate gland.
‡ World Health Organization (WHO) grade is an indication of the degree of glandular differentiation present in a tumor, with lower grades indicating greater degrees of differentiation.
§ Gleason scores range from 2 to 10 and are calculated as the sum of two scores (each ranging from 1 to 5) indicating the aggressiveness of the two most common histologic patterns in a prostate tumor, with higher scores indicating more aggressive cancer. For scores expressed as the sum of the two separate scores, the first number indicates the more common pattern found in the tumor. No men in this trial had a Gleason score of 10.
¶ Diagnosis was made only by cytologic examination in 55 patients; a biopsy specimen could not be retrieved in 24 patients.
‖ Prostate-specific antigen (PSA) levels were assayed during opportunistic screening among asymptomatic men.
** Detection was coincidental during rectal examination being performed because of other symptoms.
†† Category pertains to the year after randomization.
‡‡ A radical-prostatectomy specimen was not retrieved for 5 men.

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investigated end points: in the younger age group, overall mortality was 15.0 percentage points lower, mortality due to prostate cancer was 15.1 percentage points lower, and the risk of metastasis was 18.6 percentage points lower in the radical-prostatectomy group than in the watchful-waiting group. Among men 65 years of age or older at diagnosis, the between-group differences were smaller for all investigated end points. (Figs. 1 and 2 and Tables 1 and 2).

PER-PROTOCOL ANALYSES

The cumulative incidence of the end points and corresponding relative risks according to treatment received within the first year is shown in Table S2 in the Supplementary Appendix. The relative risk of death from any cause was 0.70 (95% CI, 0.59 to 0.83) in the overall trial population, 0.57 (95% CI, 0.44 to 0.75) among men younger than 65 years of age, and 0.83 (95% CI, 0.66 to 1.04) among men 65 years of age or older. The corresponding relative risks of death due to prostate cancer were 0.45 (95% CI, 0.33 to 0.61), 0.41 (95% CI, 0.27 to 0.62), and 0.47 (95% CI, 0.29 to 0.76), and those for distant metastases were 0.43 (95% CI, 0.33 to 0.57), 0.41 (95% CI, 0.28 to 0.59), and 0.45 (95% CI, 0.30 to 0.67).

LONG-TERM PROGNOSIS BASED ON HISTOPATHOLOGICAL MEASURES IN THE RADICAL-PROSTATECTOMY GROUP

A positive surgical margin was present in 99 (35%) of the 283 prostatectomy specimens that could be evaluated. A positive margin was associated with a poorer prognosis in the statistical model that had adjustment only for age, but when we adjusted for extracapsular extension, PSA level, and Gleason score, the relative risk of death from prostate cancer associated with positive margins as compared with clear margins was small (1.16; 95% CI, 0.62 to 2.15).

Extracapsular extension was present in 132 (47%) of 283 reviewed specimens in the radical-prostatectomy group. A total of 38 of the men (29%) with extracapsular extension died from prostate cancer, as compared with 9 of the men (6%) without extracapsular extension, which corresponded to a relative risk of 5.21 (95% CI, 2.42 to 11.22). As compared with men who had a Gleason score of 3 to 6, the risk of death from prostate cancer among men with a Gleason score of 3+4 was similar (relative risk, 0.99; 95% CI, 0.23 to 4.33), but the risk among men with a Gleason score of 4+3 was 5 times as high (relative risk, 5.73; 95% CI, 1.59 to 20.67). Among men with a Gleason score of 8 or 9 in the radical-prostatectomy group (no men had a score of 10), the risk of death from prostate cancer was 10 times as high as that among men with a score of 3 to 6 (relative risk, 10.63; 95% CI, 3.03 to 37.30) (Table 3).

DISCUSSION

After 29 years of follow-up, at a time when 80% of all the participants had died, lower overall mortality, lower mortality due to prostate cancer, and a lower risk of metastasis prevailed in the radical-prostatectomy group. The findings from a per-protocol analysis with adjustment for nonadherence to the assigned treatment did not differ from the main findings from the intention-to-treat analysis. At 23 years of follow-up, radical prostatectomy resulted in a mean of 2.9 years of life gained. Extracapsular extension and a Gleason score of 8 or 9 in the radical-prostatectomy group were strong predictors of death from prostate cancer.

In our trial, the absolute benefit associated with radical prostatectomy increased by a factor of more than 2 between 10 and 23 years of follow-up for both overall mortality (from 5.0 to 12.0 percentage points) and disease-specific mortality (from 5.5 to 11.7 percentage points), whereas the relative risks remained stable during this period for both overall mortality (0.75 to 0.74) and disease-specific mortality (0.56 to 0.54).[2] In the Prostate Cancer Intervention versus Observation Trial (PIVOT), at 19 years of follow-up, the relative risk of death from prostate cancer was 0.65 and thus similar to our results, but the absolute difference in risk was only 4 percentage points, reflecting the low baseline risk.[14] The difference in risk in PIVOT is similar to that in the SPCG-4 10-year follow-up analysis. Only long-term follow-up can reveal whether the PIVOT results will catch up with the SPCG-4 results after passing of the lead time associated with PSA testing or whether they will remain unchanged as a result of a substantial overdiagnosis of nonlethal prostate cancer.

In the Prostate Testing for Cancer and Treatment (ProtecT) trial, which involved only PSA-detected prostate cancers, the relative risk of death from prostate cancer at 10 years associated with radical prostatectomy as compared with

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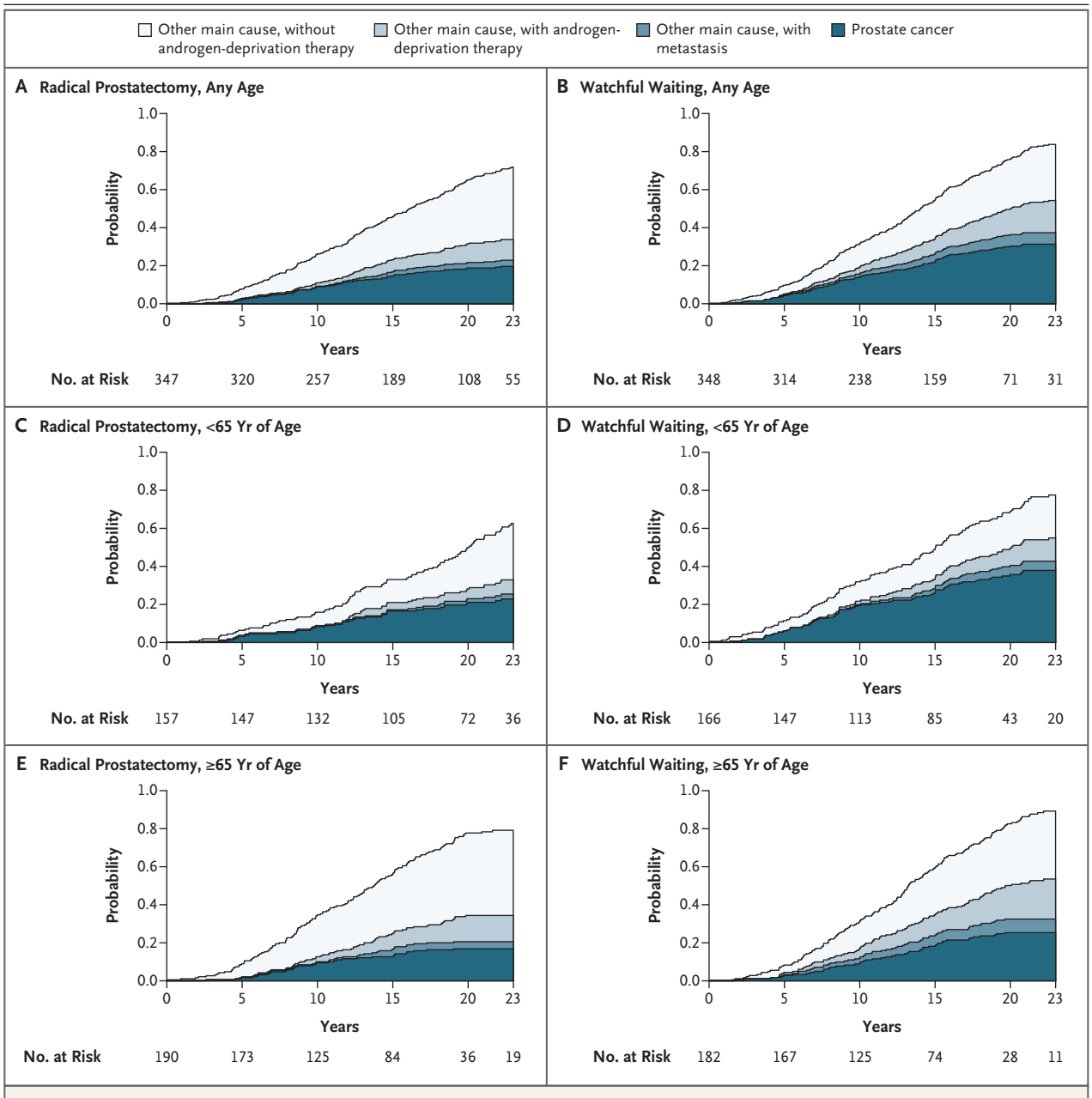

Figure 1. Stacked Cumulative Incidence of Causes of Death According to Treatment and Age Group.

active monitoring was 0.63.[15] In that trial, the comparison group is not watchful waiting but active monitoring, and therefore the goal is to compare immediate radical treatment with delayed curative treatment in patients for whom it is indicated; in theory, this should reduce the possibility of finding any substantial effect from radical prostatectomy. The event rate is still low in the ProtecT trial, and only approximately 1% of the participants died from prostate cancer within 10 years, which suggests an even longer lead time and possibly a greater degree of overdiagnosis than in PIVOT.

The length of time for a more substantial benefit to occur even among men with more advanced tumors, as in our trial, highlights the importance of carefully selecting men who might benefit from curative treatment and not treating the small, low-risk tumors often diagnosed today, unless they show signs of progression during

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Table 2. End-Point Estimates at 23 Years and Relative Risk Over the 29-Year Trial Period.*

End Point	Radical Prostatectomy		Watchful Waiting		Absolute Difference in Risk at 23 Yr (95% CI)	No. Needed to Treat to Prevent End Point at 23 Yr (95% CI)	Relative Risk, Radical Prostatectomy vs. Watchful Waiting (95% CI)†	P Value‡
	No. of Events/ Total No.§	Cumulative Incidence at 23 Yr¶	No. of Events/ Total No.§	Cumulative Incidence at 23 Yr¶				
		%		%	*percentage points*			
Death from any cause								
All patients	261/347	71.9 (67.0–77.0)	292/348	83.8 (79.8–88.1)	12.0 (5.5–18.4)	8.4 (5.4–18.2)	0.74 (0.62–0.87)	<0.001
Patients <65 yr of age	105/157	62.6 (55.1–71.2)	129/166	77.6 (71.1–84.7)	15.0 (4.4–25.5)	6.7 (3.9–22.6)	0.62 (0.48–0.80)	—
Patients ≥65 yr of age	156/190	79.2 (73.4–85.4)	163/182	89.3 (84.6–94.3)	10.1 (2.4–17.8)	9.9 (5.6–41.4)	0.86 (0.69–1.07)	—
Death from prostate cancer‖								
All patients	71/347	19.6 (15.8–24.4)	110/348	31.3 (26.8–36.6)	11.7 (5.2–18.2)	8.6 (5.5–19.3)	0.55 (0.41–0.74)	<0.001
Patients <65 yr of age	39/157	22.8 (17.0–30.6)	63/166	37.9 (31.1–46.3)	15.1 (5.0–25.2)	6.6 (4.0–20.0)	0.50 (0.34–0.75)	—
Patients ≥65 yr of age	32/190	16.9 (12.3–23.1)	47/182	25.3 (19.7–32.6)	8.5 (0.2–16.8)	11.8 (6.0–601.0)	0.63 (0.40–0.99)	—
Distant metastasis**								
All patients	92/347	26.6 (22.3–31.7)	150/348	43.3 (38.3–48.9)	16.7 (9.6–23.7)	6.0 (4.2–10.4)	0.54 (0.42–0.70)	<0.001
Patients <65 yr of age	48/157	30.8 (24.3–39.0)	81/166	49.4 (42.2–57.8)	18.6 (7.9–29.2)	5.4 (3.4–12.7)	0.49 (0.34–0.70)	—
Patients ≥65 yr of age	44/190	23.2 (17.9–30.0)	69/182	37.7 (31.2–45.6)	14.6 (5.2–23.9)	6.9 (4.2–19.2)	0.59 (0.41–0.86)	—

* The widths of the confidence intervals have not been adjusted for multiplicity.
† Relative risk values are based on a Cox regression of data from the entire 29-year follow-up period.
‡ Since no adjustments were planned for multiplicity, P values are not shown for comparisons within age groups.
§ Data are the numbers of events at 29 years (through December 31, 2017).
¶ Values are estimates of cumulative incidence at 23 years.
‖ Death from other causes was considered as a competing risk in the analysis.
** Death from other causes without previous metastasis was considered as a competing risk in the analysis.

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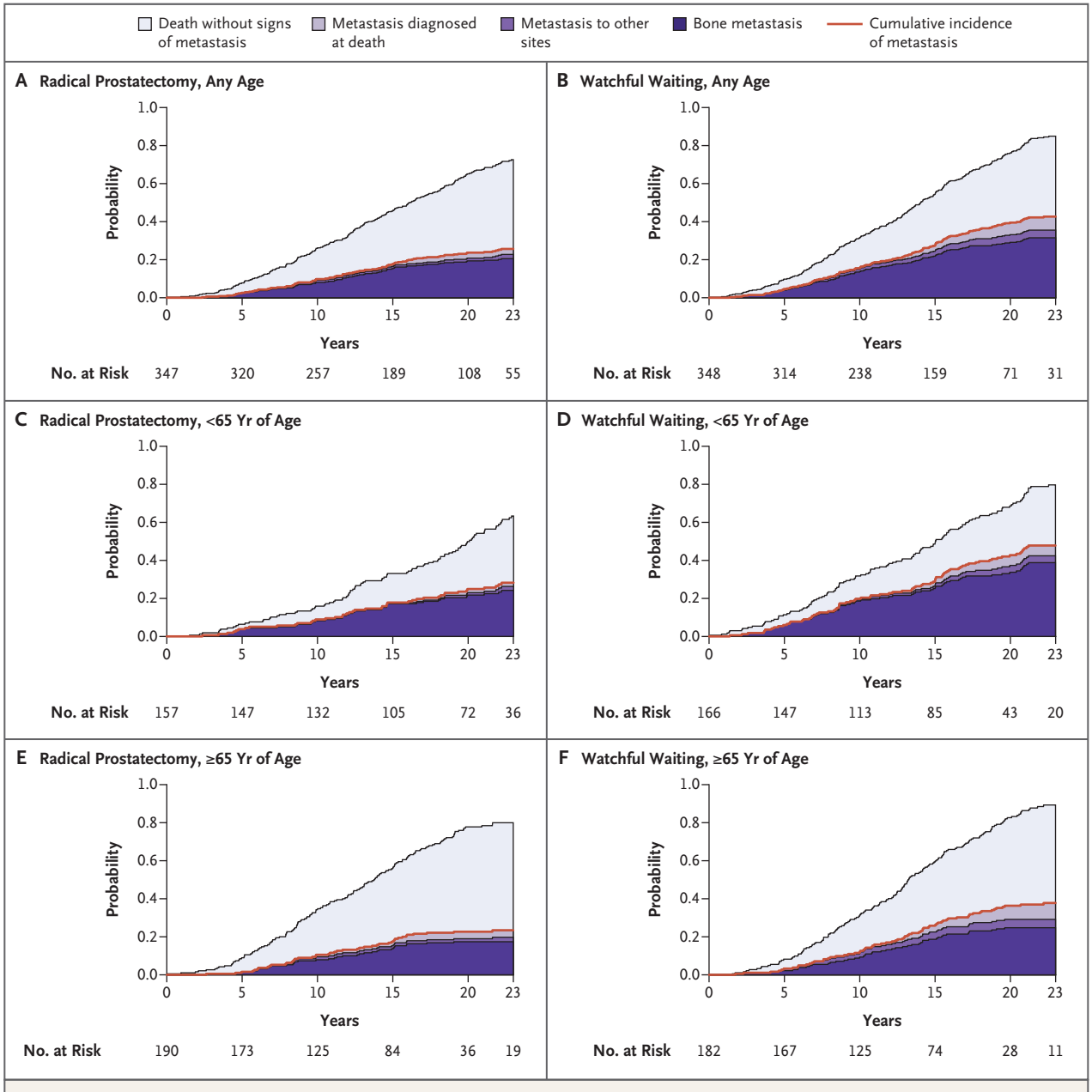

Figure 2. Stacked Cumulative Incidence of Sites of Metastasis According to Treatment and Age Group.

active surveillance. At this follow-up, neither the analysis stratified according to age nor the per-protocol analysis could corroborate that age per se plays a major role in the response to radical prostatectomy. However, the long latency period before effects become tangible and our estimates of years of life gained point toward the importance of taking the expected remaining lifetime into account when recommending treatment. Both our trial and PIVOT required participants to have at least 10 years of expected survival. However, in our trial, at 10.8 years of follow-up, 42% of the patients had died, and at 10 years in the PIVOT trial, 48% had died, reflecting the difficulty of estimating life expectancy.[2,16] In the ProtecT trial, only 5% of the patients had died by 10 years, which partly reflects the steady increase in life expectancy in high-income countries.[15,17]

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Table 3. Univariate and Multivariate Cox Regression Analyses of Histopathological Risk Factors Based on Tumor Specimens from Radical Prostatectomy.

End Point and Risk Factor	No. of Men	No. of Events	Relative Risk with Adjustment for Age Group (95% CI)*	Relative Risk with Adjustment for Age Group and Additional Factors (95% CI)†
Distant metastasis				
Margins				
Negative	184	29	Reference	Reference
Positive	99	32	2.73 (1.63–4.57)	1.26 (0.73–2.20)
Extracapsular extension				
Absent	151	13	Reference	Reference
Present	132	47	6.59 (3.54–12.27)	4.50 (2.34–8.64)
Gleason score of prostatectomy specimen				
3–6	88	4	Reference	Reference
7	157	37	6.27 (2.23–17.59)	3.10 (1.05–9.11)
8 or 9	38	20	17.82 (6.08–52.28)	9.44 (3.09–28.84)
Death from prostate cancer				
Margins				
Negative	184	24	Reference	Reference
Positive	99	24	2.55 (1.42–4.56)	1.16 (0.62–2.15)
Extracapsular extension				
Absent	151	9	Reference	Reference
Present	132	38	7.61 (3.66–15.84)	5.21 (2.42–11.22)
Gleason score of prostatectomy specimen				
3–6	88	3	Reference	Reference
3+4	87	5	1.91 (0.46–7.99)	0.99 (0.23–4.33)
4+3	70	21	11.78 (3.51–39.55)	5.73 (1.59–20.67)
8 or 9	38	19	20.06 (5.93–67.91)	10.63 (3.03–37.30)

* The model was adjusted for age group (<65 vs. ≥65 years).
† The model was adjusted for age group (<65 vs. ≥65 years), PSA level, margins, capsular extension, and Gleason score.

In a trial with a drastic difference between the interventions, there is always a risk that the reasons for nonadherence will differ considerably according to trial group, which may bias the comparison. The per-protocol analysis in our trial showed results similar to those in the intention-to-treat analysis. Thus, our main results do not reflect the possible effects of systematic patterns of nonadherence.

A mean of 2.9 years of life were gained with radical prostatectomy. The mean number of years gained is a crude measure, since any given man who is randomly assigned to undergo the procedure either might not benefit at all or might have a much greater benefit than the mean number for the whole group indicates. However, the measure puts in perspective what is risked by delaying intervention. We have previously found similar quality of life after radical prostatectomy and watchful waiting.[18] In a recent publication, however, we investigated the effect of hormonal therapy and found that men whose prostate cancer is managed by watchful waiting without hormonal treatment reported the highest quality of life, which was similar to that among younger men without prostate cancer. In contrast, men who had disease progression while undergoing watchful waiting, which necessitated initiation of hormonal therapy, reported the lowest quality of life.[19] These findings help with individual counseling and shared decision making about the advantages and disadvantages of curative treatment.

Extracapsular extension and a high Gleason score in the prostatectomy specimen were strong predictors of death from prostate cancer; the majority of men who died from prostate cancer

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in the radical-prostatectomy group had extracapsular extension. More studies of adjuvant treatment are needed, but the strategies for the selection of patients and interventions are not self-evident: at 29 years of follow-up in our trial, only one third of the men with extracapsular extension had died from prostate cancer.

The strengths of our trial are the randomized design, the completeness of the long-term follow-up data, and the blinded evaluation of causes of death. Adherence to the assigned treatment was high, and a per-protocol analysis did not alter our main conclusions. Our interpretation of the data relies on estimates and trends consistent over an extended follow-up period. The limitations of our trial are that the analyses according to age were not prespecified in the protocol, were exploratory, and were, among other caveats, sensitive to chance findings and not adjusted for multiple testing. Furthermore, the diagnostic procedures used today differ drastically from those used during the period of enrollment in our trial. As a result of widespread PSA testing today, most men have nonpalpable, PSA-detected tumors, whereas in our trial the majority of the men had clinically detected, palpable tumors. Today, men undergo multiple biopsies or multiparametric magnetic resonance imaging with targeted biopsies, whereas the participants in our trial had only cytologic or sextant biopsies, with few cores investigated as compared with current standards. Today, the clinical domain of localized prostate cancer is different, and the sensitivity for the detection of high-grade cancers during our trial was considerably lower than it is today.

In clinically detected prostate cancer, the benefit of radical prostatectomy in otherwise healthy men can be substantial, with a mean gain of almost 3 years of life after 23 years of follow-up. The remaining expected lifetime is important in decision making, with the reservation that it is hard to predict. When our results are applied to inform current practice, several issues have to be considered: the lead time induced by screening, the addition to modern cohorts of overdiagnosed nonlethal cancers, and the influence of modern diagnostics on the definition of risk groups. Furthermore, even if the relative risks in our trial were fully applicable to modern studies, the amount of absolute benefit is highly dependent on baseline risk.

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

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