ORIGINAL ARTICLE

Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer

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ABSTRACT

BACKGROUND

In 2008, we reported that radical prostatectomy, as compared with watchful waiting, reduces the rate of death from prostate cancer. After an additional 3 years of follow-up, we now report estimated 15-year results.

METHODS

From October 1989 through February 1999, we randomly assigned 695 men with early prostate cancer to watchful waiting or radical prostatectomy. Follow-up was complete through December 2009, with histopathological review of biopsy and radical-prostatectomy specimens and blinded evaluation of causes of death. Relative risks, with 95% confidence intervals, were estimated with the use of a Cox proportional-hazards model.

RESULTS

During a median of 12.8 years, 166 of the 347 men in the radical-prostatectomy group and 201 of the 348 in the watchful-waiting group died (P=0.007). In the case of 55 men assigned to surgery and 81 men assigned to watchful waiting, death was due to prostate cancer. This yielded a cumulative incidence of death from prostate cancer at 15 years of 14.6% and 20.7%, respectively (a difference of 6.1 percentage points; 95% confidence interval [CI], 0.2 to 12.0), and a relative risk with surgery of 0.62 (95% CI, 0.44 to 0.87; P=0.01). The survival benefit was similar before and after 9 years of follow-up, was observed also among men with low-risk prostate cancer, and was confined to men younger than 65 years of age. The number needed to treat to avert one death was 15 overall and 7 for men younger than 65 years of age. Among men who underwent radical prostatectomy, those with extracapsular tumor growth had a risk of death from prostate cancer that was 7 times that of men without extracapsular tumor growth (relative risk, 6.9; 95% CI, 2.6 to 18.4).

CONCLUSIONS

Radical prostatectomy was associated with a reduction in the rate of death from prostate cancer. Men with extracapsular tumor growth may benefit from adjuvant local or systemic treatment. (Funded by the Swedish Cancer Society and the National Institutes of Health.)

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THE RANDOMIZED SCANDINAVIAN PROS-
tate Cancer Group Study Number 4 (SPCG-4)
showed that radical prostatectomy de-
creased the risk of metastases, the rate of death
from prostate cancer, and the rate of death from
any cause.[1-3] Although the participants in SPCG-4
were predominantly men whose cancers were
detected on the basis of symptoms, rather than
by elevated prostate-specific antigen (PSA) levels,
prostate-cancer events have also accumulated dur-
ing an extended follow-up period in a subgroup
of men with low-risk disease. Determining wheth-
er there is a survival benefit for men with low-
risk disease is relevant in light of the risk of over-
diagnosis resulting from PSA testing and the
adverse events associated with therapy.[4] Whether
the previously observed lack of benefit in men
older than 65 years of age and the absence of
increased benefit after 9 years of follow-up per-
sist is also of interest. We now present estimates
of 15-year results, with a median follow-up peri-
od of 12.8 years.

METHODS

SUBJECTS

Between October 1989 and December 1999, at 14
centers in Sweden, Finland, and Iceland, we ran-
domly assigned 695 men with newly diagnosed,
localized prostate cancer to radical prostatectomy
or watchful waiting, as described in detail in a
previous report[1] and in the study protocol (avail-
able with the full text of this article at NEJM.org).
The study was approved by the regional ethics
committee for each participating center. Oral in-
formed consent was obtained from all eligible
patients.

Men were eligible for inclusion in the study if
they were younger than 75 years of age and had
a life expectancy of more than 10 years, had no
other known cancers, and had a localized tumor
of stage T0d (later named T1b), T1, or T2, as
assessed according to the 1978 criteria of the
International Union against Cancer. After revi-
sion of the staging criteria in 1987, T1c tumors
were also included starting in 1994.[5] On the
basis of the results of a core biopsy or fine-nee-
dle aspiration, the tumor had to be well differen-
tiated to moderately well differentiated accord-
ing to the World Health Organization (WHO)
classification. All patients included in the study
were required to have a serum PSA level of less
than 50 ng per milliliter and a negative bone scan.

STUDY DESIGN

For men assigned to the radical-prostatectomy
group, the surgical procedure started with a lymph-
adenectomy of the obturator fossa[6]; if no nodal
metastases were found in frozen sections, the
radical prostatectomy was performed.[7] Radical
excision of the tumor was given priority over
nerve-sparing surgery. Men who were assigned to
the watchful-waiting group did not receive any
immediate treatment.

If signs of local recurrence (a palpable nodule
or histologically confirmed recurrence) devel-
oped in a patient in the radical-prostatectomy
group, hormonal therapy was initiated. Men in
the watchful-waiting group who had signs of
obstructive voiding disorders were treated with
transurethral resection. Metastases detected by
bone scan were managed with hormonal therapy.
In 2003, after the introduction of antiandrogens,
clinicians were allowed to initiate hormonal treat-
ment if there were signs of tumor progression,
including elevations in PSA level, and if they be-
lieved that hormonal treatment would be benefi-
cial to the patient.

In 1999, all core biopsy specimens were re-
viewed by four uropathologists and graded with
the use of Gleason scores.[8] (The Gleason score is
the sum of the two most common histologic pat-
terns or grades in a prostate tumor, each of which
is graded on a scale of 1 to 5, with 5 indicating
the most aggressive pattern.) The pathologists
were unaware of the patient's study assignment
and of the outcome of the cancer. In 2006, the
same four pathologists and one additional pa-
thologist reviewed all radical-prostatectomy spec-
imens, graded them with the use of Gleason
scores, evaluated extracapsular tumor growth,
and examined the surgical margins. Seminal ves-
icle involvement was assessed as extracapsular
tumor growth. For 256 of the specimens, con-
cordance between the preoperative and the post-
operative Gleason scores could be evaluated. Full
concordance was noted in the scores for 32% of
the specimens, and postoperative Gleason scores
were lower in 10%, one step higher in 30%, and
two or more steps higher in 28%.

Patients were followed every 6 months for
2 years and annually thereafter. Initially, bone
scans were obtained annually; after 2003, they
were obtained every second year. Metastases were
defined as metastatic lesions that were visible on
a bone scan or histologically confirmed soft-
tissue metastases outside the pelvic area. In the

radical-prostatectomy group, local recurrence was defined as the presence of a palpable mass on digital rectal examination or a histologically confirmed tumor on rectal biopsy. In the watchful-waiting group, tumor progression was defined as palpable extracapsular extension or symptoms of obstructive voiding necessitating intervention. All medical records were reviewed for information on events related to prostate cancer as well as on side effects of surgery reported by the attending urologist.

In the case of patients who died, an end-point committee, whose members were unaware of the treatment assignments, determined the cause of death on the basis of information extracted from the patient's medical records, using a protocol that defined disease progression according to increased elevations in PSA levels, development of metastases, and the need for hormonal treatments and palliative treatments. All participants were followed through December 31, 2009, and no patient was lost to follow-up. The three members of the end-point committee (see the Supplementary Appendix, available at NEJM.org) determined the cause of death individually; for cases in which there was disagreement among the members regarding the cause of death, the group met to reach consensus.

STATISTICAL ANALYSIS

Analyses have been performed every third year according to the protocol. We analyze three different end points: death from any cause, death from prostate cancer (with death from other causes treated as a competing risk), and the risk of metastases (with death from all causes treated as a competing risk). Relative risks and 95% confidence intervals, as well as differences in cumulative incidence (with 95% confidence intervals) are reported for each end point. Relative risks were estimated with the use of Cox proportional-hazards models. Proportionality was verified by means of visual inspection of the parallelisms of the logarithms of the estimated cumulative hazards and was further tested with an analysis conditioned on 9-year survival. Cumulative incidence was assessed to account for competing risks.[9] We used Gray's test to assess differences in cumulative incidence.[10] The effect of radical prostatectomy on nonfatal end points was estimated by calculating the difference between the study groups

in the cumulative incidence of local progression and of the initiation of hormonal and other palliative treatments, including palliative radiation, cytotoxic drugs, and laminectomy.

To assess the possible modification of the treatment effect according to patient characteristics, analyses were performed in subgroups according to age (<65 vs. ≥65 years), PSA level at the time of diagnosis (<10 vs. ≥10 ng per milliliter), and Gleason score (<7 vs. ≥7). These three subgroup analyses were not included in the main protocol but were specified before any data were seen. Any modification of the effect of radical prostatectomy was tested in the Cox proportional-hazards model by including an interaction term between subgroup category and randomization group. We further explored the interaction by including the three possible effect modifiers (age, PSA level, and Gleason score) as continuous variables in the model. When there was evidence of effect modification, we further controlled for age, PSA level, tumor stage (T1b, T1c, or T2), Gleason score, and year of enrollment.

We similarly explored the effect of radical prostatectomy in a low-risk group, which was defined as men with a PSA level of less than 10 and a tumor with either a Gleason score less than 7 or a WHO grade of 1 (in the case of tumors that were diagnosed only by cytologic assessment). We also assessed the prognostic ability of three histopathological characteristics of the radical-prostatectomy specimens: margins (positive vs. negative), extracapsular tumor growth (not present vs. any extension), and Gleason score (2 to 6, 7, or 8 to 10). One model included the histopathological characteristic of interest with adjustment for age group. Another model included the histopathological characteristic of interest with adjustment for the two other histopathological characteristics and age group.

RESULTS

SUBJECTS

A total of 347 men were assigned to the radical-prostatectomy group, and 348 to the watchful-waiting group. The baseline characteristics of the two groups were similar; the mean age of the men in both groups was 65 years. Only 12% of the patients had nonpalpable T1c tumors at the time of enrollment in the study. The mean PSA level

was approximately 13 ng per milliliter (Table 1 in the Supplementary Appendix). By December 31, 2009, a total of 294 men in the radical-prostatectomy group had undergone a radical prostatectomy, and 302 men in the watchful-waiting group had not undergone curative treatment (Fig. 1 in the Supplementary Appendix). The median follow-up time was 12.8 years (range, 3 weeks to 20.2 years).

MORTALITY

A total of 367 of the 695 men enrolled in the study had died by the end of 2009 — 166 in the radical-prostatectomy group and 201 in the watchful-waiting group. The cumulative incidence of death at 15 years was 46.1% in the radical-prostatectomy group and 52.7% in the watchful-waiting group (a difference of 6.6 percentage points; 95% confidence interval [CI], −1.3 to 14.5), corresponding to a relative risk of death in the radical-prostatectomy group of 0.75 (95% CI, 0.61 to 0.92; $P=0.007$) (Fig. 1A and Tables 1 and 2) and a number needed to treat of 15. One man in the radical-prostatectomy group died postoperatively.

By the end of 2009, a total of 55 men in the radical-prostatectomy group and 81 men in the watchful-waiting group had died of prostate cancer. The cumulative incidence of death at 15 years was 14.6 in the radical-prostatectomy group and 20.7 in the watchful-waiting group (a difference of 6.1 percentage points; 95% CI, 0.2 to 12.0), corresponding to a relative risk of death in the radical-prostatectomy group of 0.62 (95% CI, 0.44 to 0.87; $P=0.01$) (Fig. 1B and Tables 1 and 2). The Cox proportional-hazards analysis conditioned on 9-year survival showed differences in survival patterns that were similar to those in the main analysis (data not shown).

DISTANT METASTASES

Distant metastases were diagnosed in 81 men in the radical-prostatectomy group and 123 men in the watchful-waiting group by the end of 2009. The cumulative incidence of distant metastases at 15 years was 21.7% in the radical-prostatectomy group and 33.4% in the watchful-waiting group (a difference of 11.7 percentage points; 95% CI, 4.8 to 18.6), corresponding to a relative risk of distant metastases in the radical-prostatectomy group of 0.59 (95% CI, 0.45 to 0.79; $P<0.001$) (Fig. 1C and Tables 1 and 2).

NONFATAL END POINTS

Local progression occurred in 74 men in the radical-prostatectomy group and 169 men in the watchful-waiting group. The cumulative incidence of local progression at 15 years was 21.5% and 49.3%, respectively (a difference of 27.9 percentage points; 95% CI, 20.9 to 34.8), corresponding to a relative risk of local progression in the radical-prostatectomy group of 0.34 (95% CI, 0.26 to 0.45). A total of 139 men in the radical-prostatectomy group, as compared with 223 men in the watchful-waiting group, received hormonal therapy; the cumulative incidence was 39.6% and 63.4%, respectively (a difference of 23.8 percentage points; 95% CI, 16.4 to 31.2).

Table 3 shows the 1-year cumulative incidence of postoperative complications as noted in the medical records. The most common symptom reported was impotence (58% of patients), followed by urinary leakage (32%).

SUBGROUP ANALYSES

The PSA level at the time of diagnosis (<10 vs. ≥10 ng per milliliter) and the Gleason score (<7 vs. ≥7) did not alter the effect of radical prostatectomy ($P=0.72$ and $P=0.36$, respectively, for the interaction with respect to overall survival, and $P=0.30$ and $P=0.52$, respectively, for the interaction with respect to cause-specific survival). The interaction term between age at randomization (<65 years vs. ≥65 years) and treatment was significant with respect to overall mortality ($P=0.003$) and remained so when age was considered as a continuous variable ($P=0.001$). The P value for the interaction between age and treatment with respect to death from prostate cancer was 0.16. There was a significant reduction in all three investigated end points among men who were younger than 65 years of age. The relative risk reduction ranged from 48% to 53%, and the absolute risk reduction ranged from 9 percentage points to 18 percentage points at 15 years; the number needed to treat was seven (Fig. 1G, 1H, and 1I and Table 1). Among men 65 years of age or older, there was no significant reduction in any of the three investigated end points (Fig. 1D, 1E, and 1F and Table 1). However, more men in the watchful-waiting group than in the radical-prostatectomy group died from causes other than prostate cancer, but with metastases present (Tables 1 and 2).
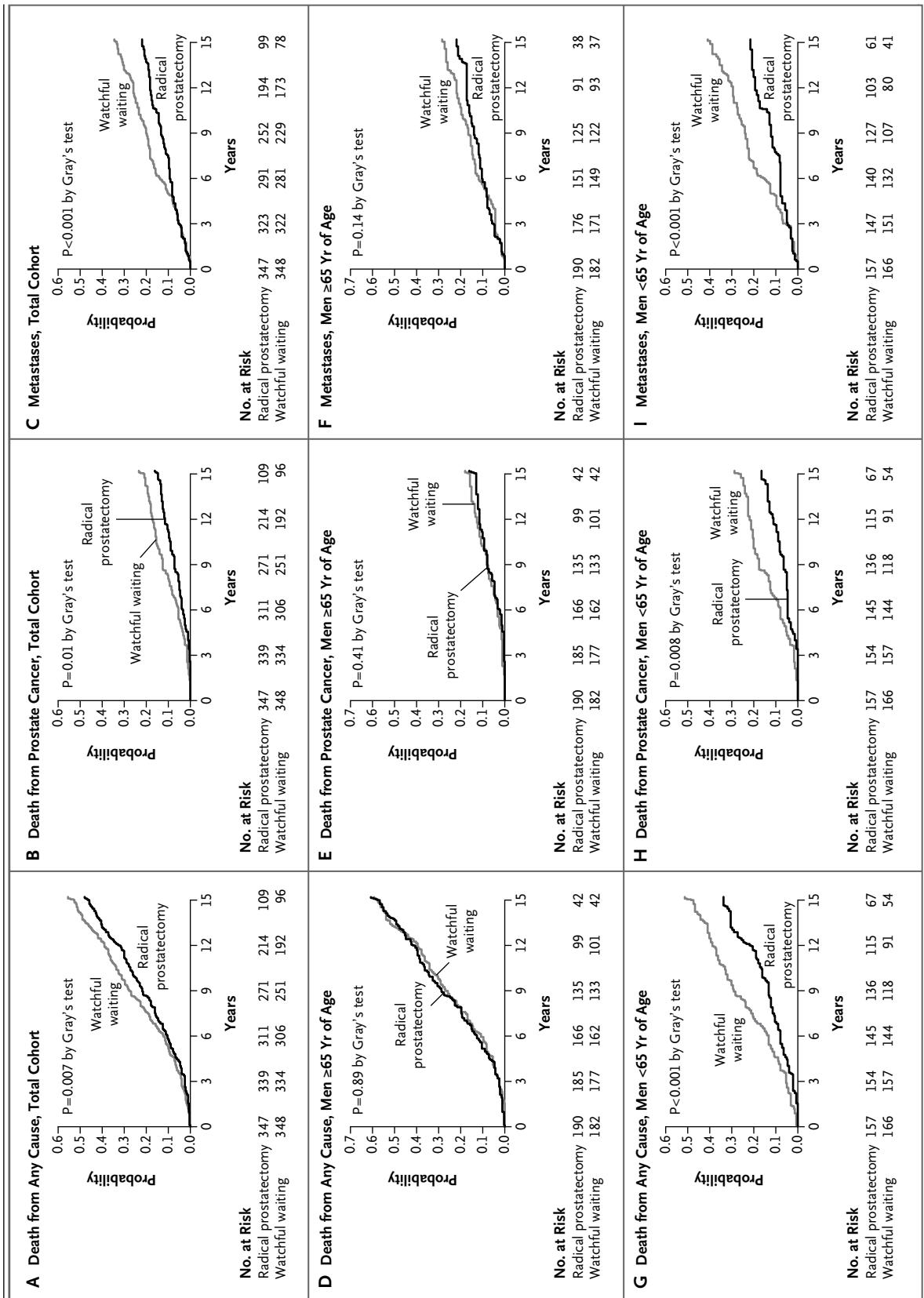
A Death from Any Cause, Total Cohort

P=0.007 by Gray's test

Probability

Watchful waiting

Radical prostatectomy

Years

No. at Risk

	0	3	6	9	12	15
Radical prostatectomy	347	339	311	271	214	109
Watchful waiting	348	334	306	251	192	96

B Death from Prostate Cancer, Total Cohort

P=0.01 by Gray's test

Probability

Radical prostatectomy

Watchful waiting

Years

No. at Risk

	0	3	6	9	12	15
Radical prostatectomy	347	339	311	271	214	109
Watchful waiting	348	334	306	251	192	96

C Metastases, Total Cohort

P<0.001 by Gray's test

Probability

Watchful waiting

Radical prostatectomy

Years

No. at Risk

	0	3	6	9	12	15
Radical prostatectomy	347	323	291	252	194	99
Watchful waiting	348	322	281	229	173	78

D Death from Any Cause, Men ≥65 Yr of Age

P=0.89 by Gray's test

Probability

Watchful waiting

Radical prostatectomy

Years

No. at Risk

	0	3	6	9	12	15
Radical prostatectomy	190	185	166	135	99	42
Watchful waiting	182	177	162	133	101	42

E Death from Prostate Cancer, Men ≥65 Yr of Age

P=0.41 by Gray's test

Probability

Watchful waiting

Radical prostatectomy

Years

No. at Risk

	0	3	6	9	12	15
Radical prostatectomy	190	185	166	135	99	42
Watchful waiting	182	177	162	133	101	42

F Metastases, Men ≥65 Yr of Age

P=0.14 by Gray's test

Probability

Watchful waiting

Radical prostatectomy

Years

No. at Risk

	0	3	6	9	12	15
Radical prostatectomy	190	176	151	125	91	38
Watchful waiting	182	171	149	122	93	37

G Death from Any Cause, Men <65 Yr of Age

P<0.001 by Gray's test

Probability

Watchful waiting

Radical prostatectomy

Years

No. at Risk

	0	3	6	9	12	15
Radical prostatectomy	157	154	145	136	115	67
Watchful waiting	166	157	144	118	91	54

H Death from Prostate Cancer, Men <65 Yr of Age

P=0.008 by Gray's test

Probability

Watchful waiting

Radical prostatectomy

Years

No. at Risk

	0	3	6	9	12	15
Radical prostatectomy	157	154	145	136	115	67
Watchful waiting	166	157	144	118	91	54

I Metastases, Men <65 Yr of Age

P<0.001 by Gray's test

Probability

Watchful waiting

Radical prostatectomy

Years

No. at Risk

	0	3	6	9	12	15
Radical prostatectomy	157	147	140	127	103	61
Watchful waiting	166	151	132	107	80	41

Figure 1 (facing page). Cumulative Incidence of Death from Any Cause, Death from Prostate Cancer, and Development of Metastases.

The cumulative incidence of death from any cause, death from prostate cancer, and development of metastases in the radical-prostatectomy group and the watchful-waiting group is shown in the total cohort (Panels A, B, and C), in men 65 years of age or older (Panels D, E, and F), and in men younger than 65 years of age (Panels G, H, and I).

MEN WITH LOW-RISK PROSTATE CANCER

A total of 124 men in the radical-prostatectomy group and 139 in the watchful-waiting group had a PSA level of less than 10 ng per milliliter and a tumor with a Gleason score of less than 7 or a WHO of grade 1 in the preoperative biopsy specimens. Among them, 42 in the radical-prostatectomy group and 68 in the watchful-waiting group died. The 15-year estimates in an intention-to-treat analysis showed that there was an absolute between-group difference of 13.2 percentage points with respect to the rate of death from any cause, corresponding to a relative risk with radical prostatectomy of 0.62 (95% CI, 0.42 to 0.92; P=0.02) (Fig. 2 and Table 1) and a number needed to treat of 8, although with a broad confidence interval. However, 3 of the men in the radical-prostatectomy group did not undergo surgery. With respect to death from prostate cancer, the absolute between-group difference at 15 years was 4.2 percentage points, corresponding to a relative risk of 0.53 (95% CI, 0.24 to 1.14; P=0.14) (Fig. 2 and Table 1). The absolute between-group difference with respect to distant metastases was 11.4 percentage points (95% CI, 2.6 to 20.2), corresponding to a relative risk of 0.43 (95% CI, 0.23 to 0.79; P=0.008) (Fig. 2 and Table 1). When the Gleason grading of the operative specimens was compared with the preoperative grading of the core biopsy specimens in the 7 men who underwent surgery and died from prostate cancer, the tumors in 6 of the 7 patients were upgraded to a score of 7 or 8 from a score of 6 or lower.

HISTOPATHOLOGICAL CHARACTERISTICS IN THE RADICAL-PROSTATECTOMY GROUP

Positive surgical margins, which were present in 99 of the 283 prostatectomy specimens that could be evaluated, were associated with a poor prognosis in a model that adjusted only for age. However in a multivariate analysis that included extracapsular tumor growth, PSA level at randomization, and Gleason score, the relative risk associated with positive surgical margins was not significantly increased (data not shown).

Extracapsular tumor growth was found in 132 of the 284 radical-prostatectomy specimens (46%); tumors with extracapsular growth, as compared with those without extracapsular growth, were associated with a risk of death from prostate cancer that was increased by a factor of 7 (relative risk, 6.92; 95% CI, 2.6 to 18.4). Gleason score was also highly predictive of the risk of death from prostate cancer; among 129 men who had tumors with Gleason scores of 2 to 6, only 5 died from prostate cancer (data not shown).

DISCUSSION

As of the current follow-up analysis, there continues to be a significant reduction in the rate of death from any cause, the rate of death from prostate cancer, and the risk of metastases in the radical-prostatectomy group as compared with the watchful-waiting group. The benefit is obvious among men younger than 65 years of age, but it is still unclear whether the benefit extends to older men. The risk of death from prostate cancer after radical prostatectomy among men who had tumors with extracapsular growth, as compared with men who had tumors without extracapsular growth, was increased by a factor of 7. We also observed a benefit of radical prostatectomy among men with low-risk tumors.

The data on mortality are in accordance with our previous follow-up reports. However, in the current analysis, the number needed to treat to avert one death was 15, as compared with 19 in a previous analysis, in the case of the whole cohort, and the number was 7 in the case of men younger than 65 years of age. A previous analysis indicated that the difference between the two groups remained constant after 9 years. In the current analysis, a continuing benefit with radical prostatectomy was observed also after 9 years of follow-up.

The finding that the effect of radical prostatectomy is modified by age has not been confirmed in other studies of radical prostatectomy or external-beam radiation.[11,12] The SPCG-4 data show that men younger than 65 years of age in whom

Table 1. Cumulative Incidence, Absolute Risk Reduction, and Relative Risk for Death from Any Cause, Death from Prostate Cancer, and Development of Distant Metastases.

End Point	Cumulative Incidence		Absolute Risk Reduction with Radical Prostatectomy	Relative Risk with Radical Prostatectomy (95% CI)	P Value
	Radical Prostatectomy*	Watchful Waiting†			
	% (95% CI)		*percentage points (95% CI)*		
Death from any cause					
All	46.1 (40.8 to 52.0)	52.7 (47.4 to 58.6)	6.6 (−1.3 to 14.5)	0.75 (0.61 to 0.92)	0.007
Low-risk cancer	31.4 (23.9 to 41.3)	44.6 (36.6 to 54.4)	13.2 (0.9 to 25.5)	0.62 (0.42 to 0.92)	0.02
Age <65 yr	33.9 (26.9 to 42.6)	47.4 (40.0 to 56.1)	13.5 (2.4 to 24.7)	0.52 (0.37 to 0.73)	<0.001
Age <65 yr and low-risk cancer	16.9 (9.5 to 30.1)	36.2 (26.1 to 50.2)	19.3 (4.0 to 34.7)	0.36 (0.18 to 0.70)	0.002
Age ≥65 yr	56.7 (49.5 to 65.0)	57.4 (50.2 to 65.8)	0.7 (−10.3 to 11.7)	0.98 (0.75 to 1.28)	0.89
Age ≥65 yr and low-risk cancer	46.8 (35.1 to 62.3)	52.9 (41.3 to 67.6)	6.1 (−12.6 to 24.8)	0.92 (0.57 to 1.49)	0.74
Death from prostate cancer					
All	14.6 (11.2 to 19.1)	20.7 (16.7 to 25.6)	6.1 (0.2 to 12.0)	0.62 (0.44 to 0.87)	0.01
Low-risk cancer	6.8 (3.5 to 13.5)	11.0 (6.8 to 17.8)	4.2 (−2.9 to 11.2)	0.53 (0.24 to 1.14)	0.14
Age <65 yr	16.4 (11.3 to 23.8)	25.8 (19.7 to 33.7)	9.4 (0.2 to 18.6)	0.49 (0.31 to 0.79)	0.008
Age <65 yr and low-risk cancer	7.1 (2.7 to 18.6)	11.6 (6.0 to 22.4)	4.5 (−5.7 to 14.8)	0.41 (0.14 to 1.17)	0.14
Age ≥65 yr	13.0 (8.9 to 18.9)	16.0 (11.4 to 22.6)	3.0 (−4.3 to 10.4)	0.83 (0.50 to 1.39)	0.41
Age ≥65 yr and low-risk cancer	6.6 (2.5 to 17.1)	10.3 (5.1 to 21.0)	3.8 (−5.9 to 13.4)	0.76 (0.25 to 2.32)	0.58
Distant metastases					
All	21.7 (17.6 to 26.7)	33.4 (28.6 to 39.0)	11.7 (4.8 to 18.6)	0.59 (0.45 to 0.79)	<0.001
Low-risk cancer	9.9 (5.8 to 17.1)	21.4 (15.4 to 29.6)	11.4 (2.6 to 20.2)	0.43 (0.23 to 0.79)	0.008
Age <65 yr	21.5 (15.9 to 29.2)	39.8 (32.6 to 48.5)	18.3 (8.0 to 28.5)	0.47 (0.32 to 0.70)	0.001
Age <65 yr and low-risk cancer	9.5 (4.4 to 20.4)	20.6 (12.8 to 33.0)	11.1 (−1.0 to 23.2)	0.41 (0.18 to 0.95)	0.06
Age ≥65 yr	22.1 (16.6 to 29.4)	27.5 (21.5 to 35.1)	5.4 (−3.9 to 14.6)	0.77 (0.51 to 1.15)	0.14
Age ≥65 yr and low-risk cancer	10.5 (4.8 to 23.0)	21.8 (13.9 to 34.3)	11.3 (−1.6 to 24.1)	0.46 (0.19 to 1.11)	0.06

* A total of 166 men in the radical-prostatectomy group died, of whom 42 had low-risk prostate cancer; 55 men, of whom 10 had low-risk cancer, died from prostate cancer. Distant metastases developed in 81 men, of whom 15 had low-risk prostate cancer.

† A total of 201 men in the watchful-waiting group died, of whom 68 had low-risk prostate cancer; 81 men, of whom 19 had low-risk cancer, died from prostate cancer. Distant metastases developed in 123 men, of whom 34 had low-risk prostate cancer.

the tumor is left in situ have a worse outcome than do all other subgroups. The apparent lack of effect in men older than 65 years of age should be interpreted with caution because, owing to a lack of power, the subgroup analyses may falsely dismiss differences. At 15 years, there was a trend toward a difference between the two groups in the development of metastases, and more men in the watchful-waiting group than in the radical-prostatectomy group died from causes other than

prostate cancer, but with metastases present. Current hormonal treatments might induce remissions long enough for older patients to die from other diseases. Therefore, competing risks of death may blur the long-term effects of treatment, and different classification rules of disease-free survival will influence survival estimates.

The cumulative incidence in our study of death from prostate cancer among men treated with radical prostatectomy was high as compared with

Table 2. Cause of Death According to Treatment Group and Age at Diagnosis.*

Cause of Death	Radical Prostatectomy (N = 347)			Watchful Waiting (N = 348)		
	All Men	<65 Yr of Age	≥65 Yr of Age	All Men	<65 Yr of Age	≥65 Yr of Age
			number			
Prostate cancer	55	28	27	81	49	32
Other cause	111	27	84	120	42	78
With metastases	6	2	4	16	5	11
Without metastases but with local progression or recurrence	12	2	10	26	8	18
With unknown status regarding metastases but with local progression	3	0	3	8	4	4
With no evidence of metastases or local progression or recurrence	89	23	66	69	24	45
Within first month after randomization	1	0	1	1	1	0
Any cause	166	55	111	201	91	110

* All events were evaluated by the independent end-point committee.

the incidence in other studies[13,14]; nearly 80% of the men enrolled in our study had palpable tumors, with extracapsular tumor growth in 46% of the radical-prostatectomy specimens. All but five men who died of prostate cancer in the radical-prostatectomy group had extracapsular tumor growth. Although extracapsular growth is not a perfect predictor of lethal disease, our findings indicate that these men could be a group for which adjuvant local or systemic therapy would be beneficial.[15,16] In studies of active surveillance, a high proportion of patients with extracapsular growth among those who were switched to radical prostatectomy could be an indication that the trigger point for active treatment is too late.

In men with low-risk disease, the absolute benefit of surgery with respect to death from prostate cancer and the risk of metastases was similar to that in the whole cohort. We caution that our low-risk group cannot be compared directly with men who are currently included in active-surveillance protocols because few of the men in our low-risk group had a tumor that was detected by means of a screening test.[17,18] Furthermore, the biopsy protocol in this study entails a lower sensitivity for diagnosing high-risk disease than the extensive protocol in a more recent study[19]; the lower sensitivity in our study is highlighted by the reclassification of the diagnostic Gleason score in
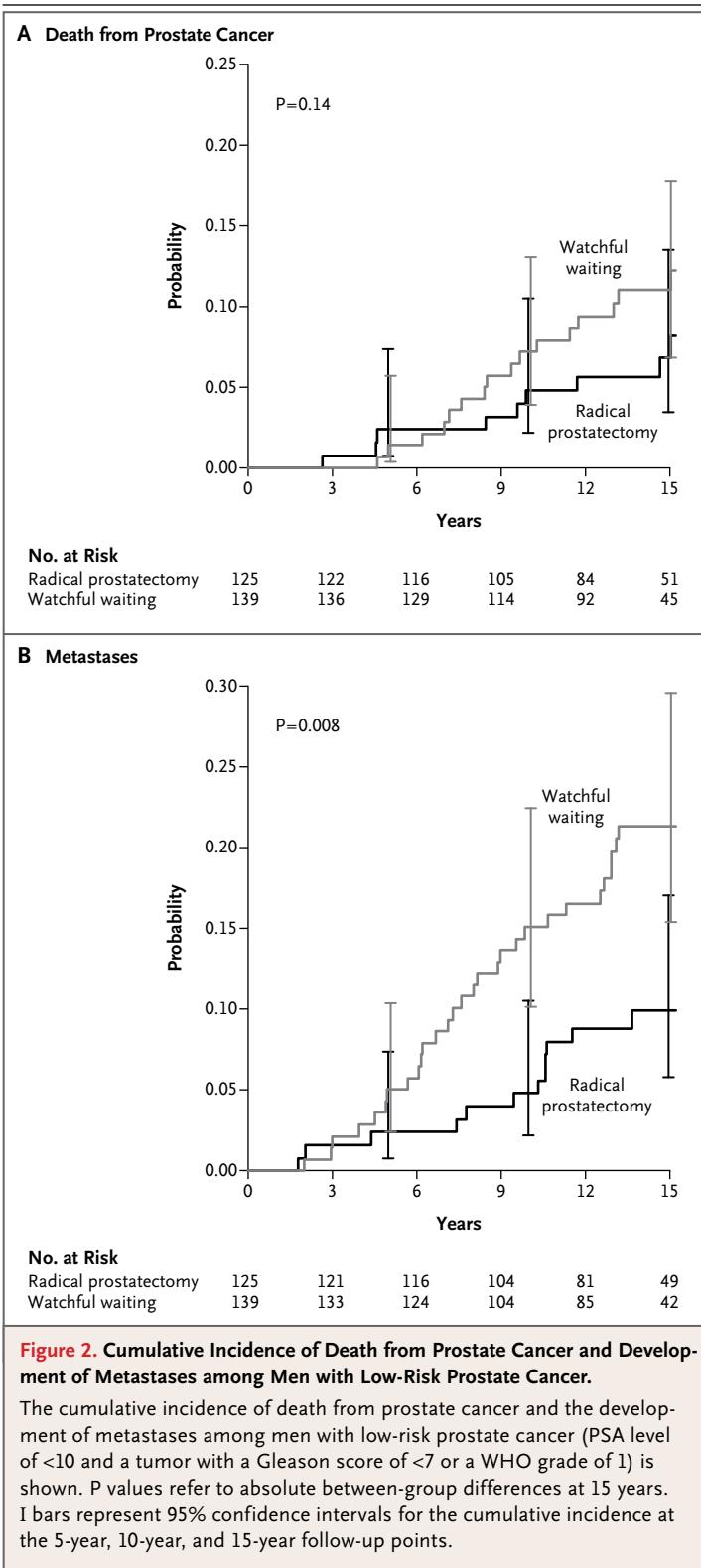
the radical-prostatectomy specimens. However, our findings show that some tumors that are considered to be low-risk at diagnosis do pose a threat to life, especially if they are not surgically removed.

The cumulative incidence of side effects of surgery reflects a situation in which, historically, the need for radical excision of the tumor dictated extensive surgery more often than is the case today. Furthermore, the surgical techniques were not as well developed, and the number of surgeries performed was far from today's levels. The data

Table 3. Nonfatal Surgical Complications within 1 Year after Surgery among Men in the Radical-Prostatectomy Group.*

Complication	No. of Events	1-Year Cumulative Incidence (95% CI)
Urinary leakage	93	32.2 (27.2–38.1)
Urinary obstruction	6	2.1 (0.9–4.6)
Impotence	168	58.1 (52.7–64.1)
Pulmonary embolism	4	1.4 (0.5–3.7)
Deep-vein thrombosis	3	1.0 (0.3–3.2)
Myocardial infarction	0	NA

* A total of 289 men in the radical-prostatectomy group underwent surgery within the first year; 1 man died postoperatively. CI denotes confidence interval, and NA not applicable.

A Death from Prostate Cancer

B Metastases

Figure 2. Cumulative Incidence of Death from Prostate Cancer and Development of Metastases among Men with Low-Risk Prostate Cancer.

The cumulative incidence of death from prostate cancer and the development of metastases among men with low-risk prostate cancer (PSA level of <10 and a tumor with a Gleason score of <7 or a WHO grade of 1) is shown. P values refer to absolute between-group differences at 15 years. I bars represent 95% confidence intervals for the cumulative incidence at the 5-year, 10-year, and 15-year follow-up points.

in the current analysis are based on information from medical records. We have previously shown that a complete understanding of the complex balance in effects between surgery and watchful waiting also requires obtaining patient-reported data on the severity of symptoms and on how much the patient is bothered by them.[20,21]

The strengths of our study include the randomized design, the completeness of follow-up, and the independent and blinded evaluation of the cause of death. Adherence to the assigned treatment was high despite the diversity of the two interventions. Our interpretation relies on stable long-term quantitative estimates, as illustrated in the cumulative-incidence curves and the consistency of the results over an extended follow-up period. The subgroup analyses were not prespecified in the protocol and lack the power to rule out a treatment difference. We emphasize that these results should be interpreted with caution and should be viewed as hypothesis-generating for other studies.

The current analysis adds to our knowledge in several areas. The benefit of radical prostatectomy continued to be seen beyond 9 years, which contradicts the notion that there is only a distinct subpopulation that responds to radical surgery with an early reduction in risk. The accruing numbers of events for the older age group indicate that in our study, a reduction in disease-specific mortality is unlikely ever to become apparent in this age group, owing to competing causes of death. The finding that some low-risk tumors will progress and become lethal emphasizes the importance of protocols with well-defined end points at which men in active surveillance switch to curative treatment. With continued follow-up, data from the SPCG-4 study may allow us to identify prognostic markers in men assigned to watchful waiting that can serve as trigger points for active treatment; the prognostic value of these markers can then be validated in cohorts that are under active surveillance.

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