

ORIGINAL ARTICLE

Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer

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ABSTRACT

BACKGROUND

In 2002, we reported the initial results of a trial comparing radical prostatectomy with watchful waiting in the management of early prostate cancer. After three more years of follow-up, we report estimated 10-year results.

METHODS

From October 1989 through February 1999, 695 men with early prostate cancer (mean age, 64.7 years) were randomly assigned to radical prostatectomy (347 men) or watchful waiting (348 men). The follow-up was complete through 2003, with blinded evaluation of the causes of death. The primary end point was death due to prostate cancer; the secondary end points were death from any cause, metastasis, and local progression.

RESULTS

During a median of 8.2 years of follow-up, 83 men in the surgery group and 106 men in the watchful-waiting group died ($P=0.04$). In 30 of the 347 men assigned to surgery (8.6 percent) and 50 of the 348 men assigned to watchful waiting (14.4 percent), death was due to prostate cancer. The difference in the cumulative incidence of death due to prostate cancer increased from 2.0 percentage points after 5 years to 5.3 percentage points after 10 years, for a relative risk of 0.56 (95 percent confidence interval, 0.36 to 0.88; $P=0.01$ by Gray's test). For distant metastasis, the corresponding increase was from 1.7 to 10.2 percentage points, for a relative risk in the surgery group of 0.60 (95 percent confidence interval, 0.42 to 0.86; $P=0.004$ by Gray's test), and for local progression, the increase was from 19.1 to 25.1 percentage points, for a relative risk of 0.33 (95 percent confidence interval, 0.25 to 0.44; $P<0.001$ by Gray's test).

CONCLUSIONS

Radical prostatectomy reduces disease-specific mortality, overall mortality, and the risks of metastasis and local progression. The absolute reduction in the risk of death after 10 years is small, but the reductions in the risks of metastasis and local tumor progression are substantial.

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*The participants in the Scandinavian Prostate Cancer Group Study No. 4 are listed in the Appendix.

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RADICAL PROSTATECTOMY IS BECOMING one of the most common major surgical procedures in many Western countries. In the United States alone, an estimated 60,000 men undergo this operation each year. However, to our knowledge, only one randomized trial quantified the benefit of radical prostatectomy.¹

In 2002, we presented the results of a clinical trial in which radical prostatectomy was compared with watchful waiting in the management of early prostate cancer.¹ Our analysis was based on a mean follow-up time of 6.2 years, a relatively short period in relation to the often long natural history of early prostate cancer.² We found that, as compared with watchful waiting, radical prostatectomy reduced the risk of death due to prostate cancer by 50 percent and the risk of distant metastasis by 37 percent, but there was no statistically significant reduction in overall mortality.

We now present a second analysis after an additional three years of follow-up, in accordance with the study protocol. Our main purpose was to analyze two hypotheses: first, that the relative reduction in the risk of death due to prostate cancer after surgery increases over time because removal of the primary tumor prevents metastasis and, second, that radical prostatectomy significantly improves overall survival.

METHODS

STUDY DESIGN

Details concerning study design and methods have been published previously.¹ The protocol, defined in 1988, is available with the full text of this article at www.nejm.org.

From 1989 to 1999, 695 men from 14 centers in Sweden, Finland, and Iceland were enrolled. The eligibility criteria included an age under 75 years; the presence of newly diagnosed, untreated, localized prostate cancer, as verified by cytologic or histologic examination, with a tumor stage of T0d (later changed to T1b), T1, or T2 (T1c was included in 1994)^{3,4} (Table 1); a health status that would permit radical prostatectomy; and a life expectancy of more than 10 years. The tumor had to be well differentiated to moderately well differentiated, according to the definition established by the World Health Organization.⁵ Patients had to have a bone scan that showed no abnormalities and a prostate-specific antigen (PSA) level of less than 50 ng per milliliter. If the diagnosis had been established

after transurethral resection, at least six blocks of prostate tissue should have been examined. After oral informed consent was received from eligible patients, they were randomly assigned to undergo either radical prostatectomy or watchful waiting through a telephone service outside the clinics. Stratification was made according to tumor grade and randomization center.

For men assigned to the radical-prostatectomy group, surgery started with dissection of the pelvic lymph nodes.⁶ If there were no signs of metastasis in frozen sections, the operation was continued with retropubic radical prostatectomy.⁷ The men in the watchful-waiting group received no initial treatment other than the transurethral resection some of them had already undergone.

Hormonal treatment was recommended for men with symptomatic local progression in the radical-prostatectomy group and for those with disseminated disease in both groups. Transurethral resection was recommended as the initial treatment for men with urinary obstruction in the watchful-waiting group. In January 2003, an amendment to the protocol allowed men in both groups to begin hormonal therapy if their physicians advised it.

FOLLOW-UP AND DEFINITION OF CLINICAL EVENTS

The participants were seen every six months during the first two years and then annually for a clinical examination and blood tests (to evaluate hemoglobin, PSA, alkaline phosphatase, and creatinine levels). A bone scan and a chest radiograph were obtained annually until 1997; thereafter, chest radiographs were obtained only once a year for the first two years after randomization. The clinical follow-up continued for all patients except nine, who underwent blood tests (including tests for PSA levels) and bone scanning when possible but who did not have clinical visits owing to old age and co-existing illnesses. Beginning in 2003, bone scans were allowed every second year if the patient had no biochemical or clinical signs of progression. In 2001, a pathological review of cytologic and histologic data that were available at inclusion was carried out. For the purpose of this analysis, all patient records were retrieved and individually reviewed for new events.

An independent end-point committee determined the cause of death on the basis of standardized extractions from the patient files; for this determination, the treatment group was not revealed.

The committee used six categories of cause of death: prostate cancer; another main cause but with distant metastases, regardless of local status; another main cause but with local progression, without distant metastases; another main cause, but with local progression and unknown status concerning distant metastases; another main cause, with no evidence of tumor recurrence, tumor progression, or metastases; and another main cause within the first month after randomization.

In the radical-prostatectomy group, local progression was defined as the presence of a histologically confirmed local tumor. In the watchful-waiting group, men with palpable transcapsular tumor growth or with symptoms of urinary obstruction that necessitated intervention were classified as having local progression. Distant metastases were considered present when bone scans, skeletal radiographs, computed tomographic scans, or chest radiographs revealed metastases or if lymph nodes at sites other than the regional sites showed cytologic or histologic evidence of prostate cancer.

STATISTICAL ANALYSIS

There were four main end points: disease-specific death, with death due to prostate cancer (the first cause-of-death category) considered the event and death from other causes treated as a competing risk; distant metastasis, with its diagnosis considered the event and death from other causes treated as a competing risk; local progression, with death treated as a competing risk; and death from any cause.

All analyses were carried out in accordance with the intention-to-treat principle. Relative risks (with 95 percent confidence intervals) and differences in cumulative incidence (with 95 percent confidence intervals) were used as measures of effect for each end point. Gray's test⁸ was used to test the hypothesis that there was no difference between the treatment groups; a P value of less than 0.05 (two-sided) was considered to indicate statistical significance. The relative risks were estimated from the Cox proportional-hazards model. Cumulative incidence (calculated in terms of integrated subdensity) rather than cumulative hazard (integrated subhazard) was used in the acknowledgment that the end points constitute competing events.⁹ The results presented here and in the previous report¹ involved low absolute risks for disease-specific death and death from any cause, with no sensitivity to whether cumulative incidence rates or cumulative hazard rates were used.

Table 1. Baseline Characteristics of the 695 Men Enrolled in the Study.*

Characteristic	Radical-Prostatectomy Group (N=347)	Watchful-Waiting Group (N=348)
Age — yr	64.7±5.1.	64.7±5.1
Mean PSA — ng/ml	13.5	12.3
Tumor stage — no. (%)†		
T1b	33 (9.5)	50 (14.4)
T1c	43 (12.4)	38 (10.9)
T2	270 (77.8)	259 (74.4)
Unknown	1 (0.3)	1 (0.3)
WHO grade — no. (%)		
1	168 (48.4)	166 (47.7)
2	178 (51.3)	182 (52.3)
Unknown	1 (0.3)	0
Gleason score — no. (%)‡		
2–4	45 (13.0)	46 (13.2)
5–6	165 (47.6)	166 (47.7)
7	77 (22.2)	82 (23.6)
8–10	14 (4.0)	21 (6.0)
Unknown§	46 (13.3)	33 (9.5)
Method of detection — no. (%)		
Screening	18 (5.2)	18 (5.2)
Coincidental	87 (25.1)	91 (26.1)
TURP	40 (11.5)	56 (16.1)
Symptoms	152 (43.8)	138 (39.7)
Other	49 (14.1)	44 (12.6)
Unknown	1 (0.3)	1 (0.3)
PSA level — no. (%)		
<4 ng/ml	43 (12.4)	63 (18.1)
4–6.9 ng/ml	60 (17.3)	60 (17.2)
7–10 ng/ml	68 (19.6)	67 (19.3)
10.1–20 ng/ml	100 (28.8)	95 (27.3)
>20 ng/ml	69 (19.9)	60 (17.2)
Unknown	7 (2.0)	3 (0.9)

* Plus-minus values are means ±SE. PSA denotes prostate-specific antigen, WHO World Health Organization, and TURP transurethral resection of the prostate.

† Tumor stage T1b indicates an incidental histologic finding in more than 5 percent of resected tissue (in 1978, this finding was classified as stage T0d); stage T1c indicates a tumor identified by a needle biopsy that was performed because of elevated serum PSA levels (in 1978, this classification did not exist). In palpable carcinoma, stage T2 indicates a tumor confined within the prostate (in 1978, this finding was classified as stage T1 or T2). Tumor classifications are from Harmer³ and Hermanek and Sobin.⁴

‡ The Gleason score, which rates tumor growth on a scale of 2 to 10, with 10 indicating the most poorly differentiated tumors, was assigned during histopathological examination.

§ The diagnosis of prostate cancer was made on the basis of cytologic examination only in 55 patients; a biopsy specimen was not available for 24 patients.

Effect modification was first investigated through simple stratified analyses. For all end points, three prespecified subgroup analyses were carried out: analysis according to age at diagnosis — less than 65 years of age as compared with 65 years of age or older; analysis according to PSA level at diagnosis — 10 ng per milliliter or lower as compared with more than 10 ng per milliliter; and analysis according to the Gleason score of the pre-randomization biopsy specimen — lower than 7 as compared with 7 or more (on a scale of 2 to 10, with 10 indicating the most poorly differentiated tumors). Any modification of the effect of radical prostatectomy according to subgroup was tested by a Cox proportional-hazards model, which included an interaction term between subgroup category and randomization group. In a second step, we further explored the interaction by including the possible effect modifier (age, PSA level at diagnosis, or Gleason score) as a continuous variable. When there was an indication of effect modification, we further controlled for the PSA level at diagnosis, the tumor stage, the Gleason score, and the year at inclusion by adding these as additional covariates in the Cox proportional-hazards model.

Table 2. Causes of Death, According to the Final Consensus of the End-Point Committee.

Cause of Death	Radical-Prostatectomy Group	Watchful-Waiting Group
	no. of patients	
Prostate cancer	30*	50†
Other causes	53	56
Other main cause, with metastases	1	8
Other main cause, without metastases but with local progression or recurrence	6	13
Other main cause, with unknown status regarding metastases but with local progression	0	0
Other main cause, with no evidence of metastases or local progression or recurrence	45	34
Other main cause, within first month after randomization	1	1
Any cause	83	106

* One of these patients did not have prior metastases as verified by scintigraphy, but his prostate-specific antigen (PSA) level had risen to more than 70 ng per milliliter after hormonal treatment.

† Two of these men did not have prior metastases as verified by scintigraphy; one had a PSA level of more than 1000 ng per milliliter and died with uremia before having a response to hormonal treatment, and in the other patient, the PSA level had risen to more than 70 ng per milliliter after hormonal treatment.

RESULTS

We randomly assigned 347 men to radical prostatectomy and 348 to watchful waiting. Relevant characteristics at the time of inclusion were similar in the two groups. Most patients (76 percent) had stage T2 tumors (i.e., the tumor was confined within the prostate), and in only 12 percent were T1c (nonpalpable) tumors detected by means of PSA testing (Table 1). At the end of 2003, 21 men assigned to radical prostatectomy had not undergone surgery, and 43 assigned to watchful waiting had undergone curative treatment. Lymph-node metastases, which precluded surgery, were found in frozen sections from 23 men in the radical-prostatectomy group.

During follow-up, fewer men in the radical-prostatectomy group than in the watchful-waiting group died of prostate cancer (30 vs. 50, $P=0.01$). As for causes of death other than prostate cancer, the numbers were similar in the two groups (53 and 56, respectively). However, among men who died from causes other than prostate cancer, a larger number in the watchful-waiting group had metastases or local progression. In terms of death from any cause, 23 more men in the watchful-waiting group than in the radical-prostatectomy group died (106 vs. 83, $P=0.04$) (Table 2).

DISEASE-SPECIFIC MORTALITY

The difference between the two groups in the cumulative incidence of death from prostate cancer increased over time, from 2 percentage points (95 percent confidence interval, -0.6 to 4.7) after five years of follow-up to 5.3 percentage points (95 percent confidence interval, -0.3 to 11.0) after 10 years, in favor of radical prostatectomy. The relative risk among men assigned to radical prostatectomy, as compared with those assigned to watchful waiting, was 0.56 (95 percent confidence interval, 0.36 to 0.88) (Fig. 1A and Table 3).

DISTANT METASTASES

The cumulative incidence of distant metastases was similar in the two groups during the first five years (8.1 percent in the radical-prostatectomy group and 9.8 percent in the watchful-waiting group, $P=0.42$). However, a difference emerged after that time: at the second follow-up, 50 of the 347 men in the radical-prostatectomy group had distant metastases, as compared with 79 of the 348 men in the watchful-waiting group. In the radical-prostatectomy group, the absolute risk reduction at 10 years was 10.2 per-

centage points (95 percent confidence interval, 3.1 to 17.2), corresponding to a relative risk of 0.60 (95 percent confidence interval, 0.42 to 0.86) (Fig. 2A and Table 3).

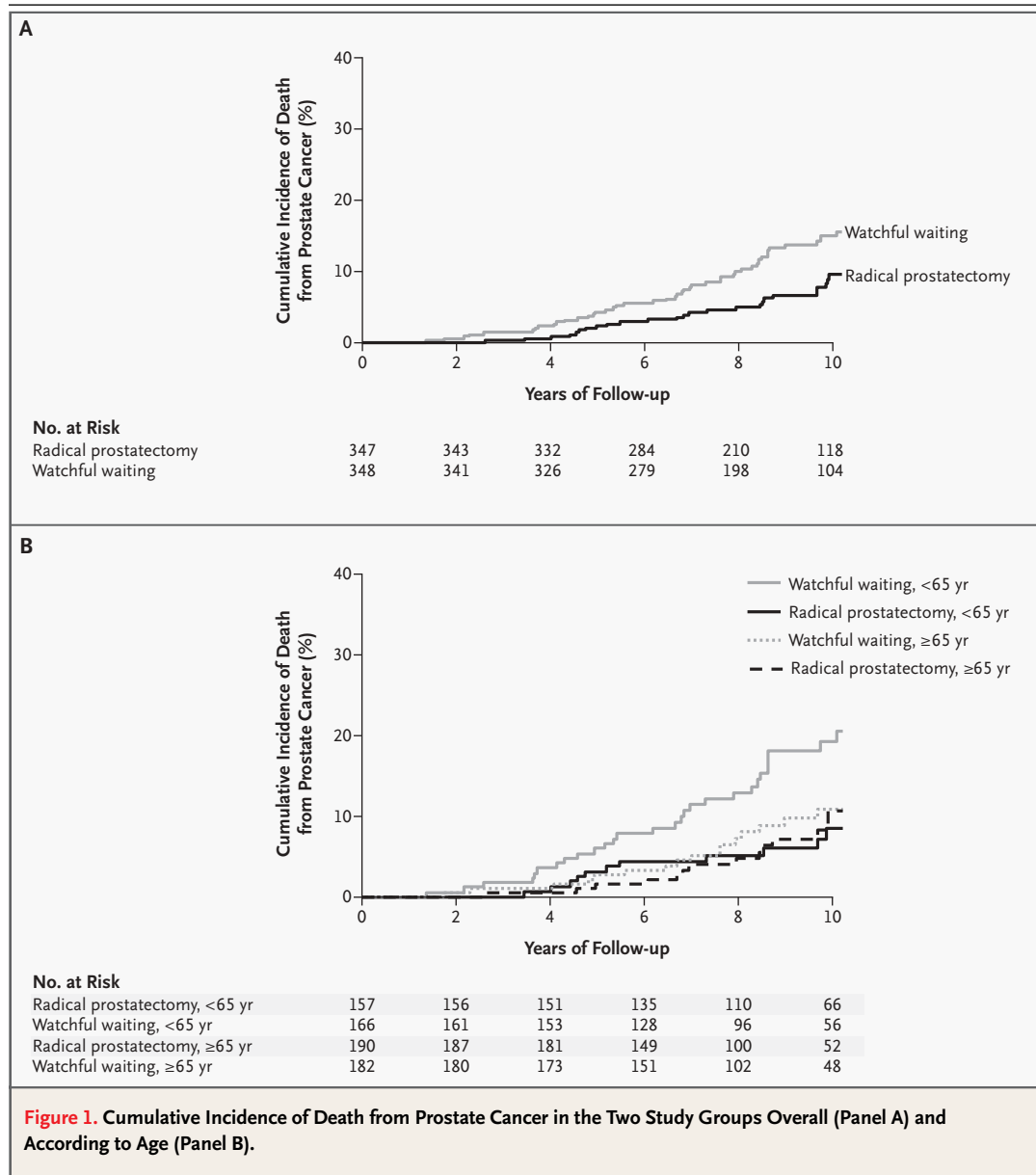
LOCAL PROGRESSION

The difference between the two groups in the cumulative incidence of local progression was statistically significant after five years of follow-up (8.1 percent in the radical-prostatectomy group vs. 27.2 percent in the watchful-waiting group, $P < 0.01$); the difference increased over time, to 64 men with lo-

cal progression among the 347 in the prostatectomy group, as compared with 149 men among the 348 in the watchful-waiting group, at the second follow-up. The difference in the absolute risk reduction after 10 years was 25.1 percentage points (19.2 percent vs. 44.3 percent), corresponding to a relative risk in the radical-prostatectomy group of 0.33 (95 percent confidence interval, 0.25 to 0.44) (Table 3).

OVERALL MORTALITY

The cumulative incidence of death from any cause was similar in the two groups during the first five



years (7.8 percent for radical prostatectomy vs. 9.8 percent for watchful waiting). At the last follow-up, 83 of 347 men in the radical-prostatectomy group and 106 of 348 in the watchful-waiting group had died. After randomization to radical prostatectomy, the absolute reduction in the risk of death from any cause after 10 years was 5.0 percentage points, corresponding to a relative risk of 0.74 (95 percent confidence interval, 0.56 to 0.99; $P=0.04$ by Gray's test) (Fig. 2B and Table 3).

OTHER TREATMENTS

Hormonal treatment was administered less often in the radical-prostatectomy group than in the watchful-waiting group (110 of 347 patients vs. 177 of 348, $P<0.01$). The mean time to hormonal treatment was 4.5 years in the radical-prostatectomy group and 4.8 years in the watchful-waiting group. Palliative radiation was also administered less often in the radical-prostatectomy group than in the watchful-waiting group (29 patients vs. 38 patients, $P=0.30$), as was laminectomy (4 patients vs. 11 patients, $P=0.04$).

SUBGROUP ANALYSES

In planned, simple stratified analyses, we found that the benefit of radical prostatectomy in terms of

disease-specific mortality differed according to age group but not according to the PSA level at diagnosis or the Gleason score. A further investigation of disease-specific mortality with the use of a Cox proportional-hazards model that included the randomization group, the patient's age as a continuous variable, and an interaction term showed that the interaction term was statistically significant ($P=0.03$). When the same model was augmented with the PSA level at diagnosis, the tumor stage, the Gleason score, and the year at inclusion, the P value for the interaction term shifted to 0.08. For overall mortality, the P value for the interaction term in the corresponding two analyses shifted only marginally and remained less than 0.01. The cumulative incidence of death from prostate cancer in men under 65 years of age in the watchful-waiting group was 19.2 percent at 10 years. This was markedly higher than the cumulative incidence of death in the other subgroups defined according to randomization group and age, for which the incidence varied from 8.5 percent to 11.5 percent (Fig. 1B).

DISCUSSION

In this comparison of radical prostatectomy with watchful waiting for patients with prostate cancer,

Table 3. Cumulative Incidence of the Main End Points and Corresponding Relative Risks.*

End Point	Cumulative Incidence				Absolute Risk Reduction (95% CI)	Relative Risk (95% CI)	P Value
	Radical-Prostatectomy Group		Watchful-Waiting Group				
	total no.	% (95% CI)	total no.	% (95% CI)			
Disease-specific mortality	30		50				
At 5 yr		2.3 (1.2 to 4.6)		4.3 (2.6 to 7.1)	2.0 (-0.6 to 4.7)		
At 10 yr		9.6 (6.5 to 14.2)		14.9 (11.2 to 19.8)	5.3 (-0.3 to 11.0)	0.56 (0.36 to 0.88)	0.01
Distant metastases	50		79				
At 5 yr		8.1 (5.7 to 11.6)		9.8 (7.1 to 13.5)	1.7 (-2.5 to 6.0)		
At 10 yr		15.2 (11.4 to 20.3)		25.4 (20.4 to 31.5)	10.2 (3.1 to 17.2)	0.60 (0.42 to 0.86)	0.004
Local progression	64		149				
At 5 yr		8.1 (5.7 to 11.5)		27.2 (22.8 to 32.3)	19.1 (13.6 to 24.6)		
At 10 yr		19.2 (15.0 to 24.6)		44.3 (38.8 to 50.5)	25.1 (17.6 to 32.6)	0.33 (0.25 to 0.44)	<0.001
Overall mortality	83		106				
At 5 yr		7.8 (5.4 to 11.2)		9.8 (7.1 to 13.5)	2.0 (-2.2 to 6.2)		
At 10 yr		27.0 (21.9 to 33.1)		32.0 (26.9 to 38.2)	5.0 (-2.8 to 13.0)	0.74 (0.56 to 0.99)	0.04

* Analysis of the cumulative incidence was performed with the method of Kalbfleisch and Prentice,⁹ and relative risks were calculated with the use of the Cox proportional-hazards model. The absolute risk reduction and relative risk are for radical prostatectomy as compared with watchful waiting. Gray's test was used to determine P values. The mean follow-up period was 8.5 years in the radical-prostatectomy group and 8.8 years in the watchful-waiting group. CI denotes confidence interval.

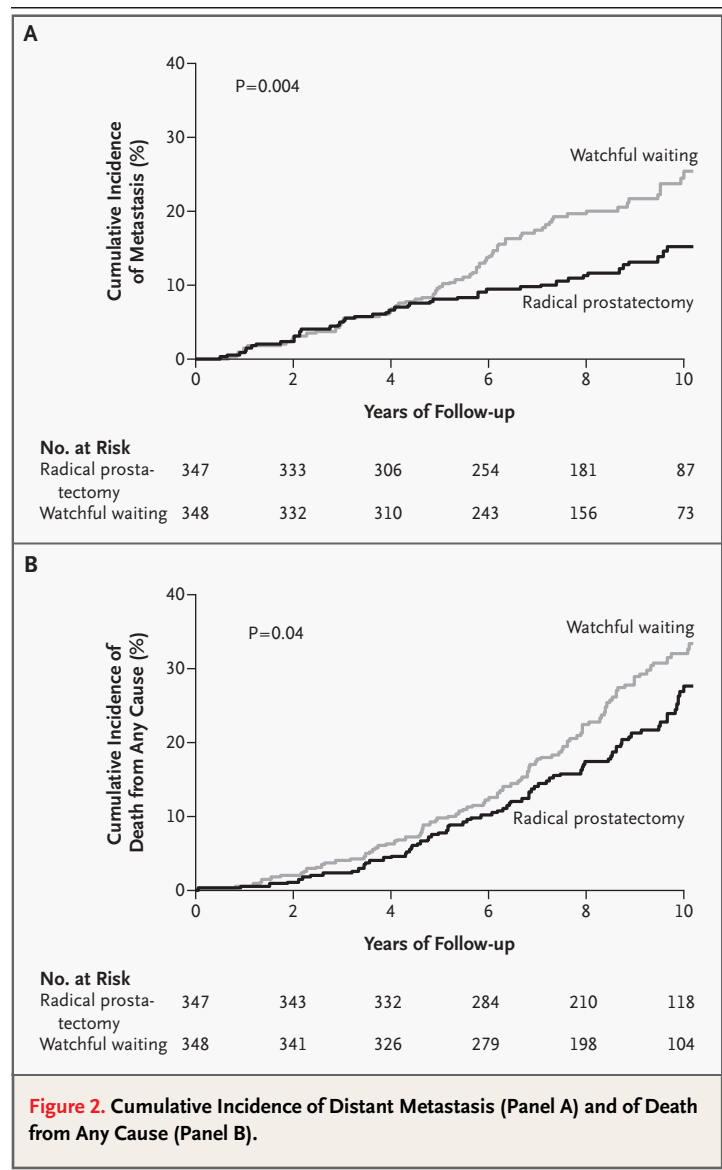
the 10-year absolute differences in disease-specific and overall mortality were statistically significant, by 5.3 (P=0.01) and 5.0 (P=0.04) percentage points, respectively, in favor of radical prostatectomy. In addition, the cumulative incidence of distant metastasis was 10.2 percentage points lower in the surgery group than in the watchful-waiting group. Because clinical manifestations of disseminated disease virtually always precede death,² this finding might herald a further lowering of the risk of death due to prostate cancer in the radical-prostatectomy group after a longer period of follow-up. We found no evidence that the benefit of radical prostatectomy was exaggerated by more frequent administration of hormonal treatment, since hormonal therapy was given less often in the radical-prostatectomy group than in the watchful-waiting group (110 patients vs. 177 patients).

We found that the reduction in disease-specific mortality as a result of radical prostatectomy was greatest among, or even limited to, patients younger than 65 years. The multivariate analyses indicated that this finding was attributable, only to a limited extent, to differences between younger and older men in the distribution of PSA levels or Gleason scores; however, there may have been other differences in characteristics between younger and older men at the time of inclusion. These results have limited interpretability for two additional reasons: they were based on small numbers, since the study was not powered to analyze subgroups, and the analysis was exploratory rather than based on any a priori biologic hypothesis. Therefore, the results of the subgroup analyses should be an incentive to conduct further research rather than to introduce an immediate change in clinical practice.

Observational cohort studies have analyzed survival rates among patients whose cancer was managed by watchful waiting. After 10 years of follow-up, such studies yielded disease-specific survival rates of 87 percent,¹⁰ 86 percent,¹¹ and 83 percent.¹² In our trial, the corresponding 10-year figure was 85 percent. The similar prognosis among patients randomly assigned to watchful waiting in our trial and those analyzed in observational studies indicates that our findings are generalizable to patients in similar settings. If watchful waiting with curative intervention in patients with rising PSA levels (as detected with active monitoring) yields better survival than does traditional watchful waiting, the difference between watchful waiting and primary surgery should diminish. As yet, however,

there is no evidence from a randomized trial that the monitoring of PSA levels with accompanying curative intervention will yield better results than will watchful waiting as used in this trial and in the observational studies.

In this follow-up period, we found a substantial absolute difference between the two groups in terms of local progression (which can cause problems with the micturition, pain, and anxiety). Moreover, the need for hormonal treatment increased in frequency in the watchful-waiting group, as did the need for palliative radiation; both types of treatment were associated with side effects that influenced patients' quality of life and well-being. Thus,



the more immediate, though stable, side effects associated with surgery¹³ (predominantly, impotence and incontinence) and reported previously for this study,¹⁴ should be weighed against the increasing incidence of symptoms and use of treatments after the progression of disease in the watchful-waiting group. However, for several reasons, a reevaluation of the costs and benefits of radical prostatectomy in the era of widespread screening is necessary: the number of patients needed to treat may be high, and the lead time to the onset of symptoms and treatment may be long in those undergoing monitoring, but the removal of small tumors may facilitate surgery and result in fewer side effects.

Our 10-year estimates show that radical prosta-

tectomy is associated with a statistically significant reduction in all the end points that we investigated, with a relative reduction of 44 percent in mortality due to prostate cancer, of 26 percent in overall mortality, of 40 percent in the risk of distant metastasis, and of 67 percent in local progression. Since, in absolute terms, the reduction in mortality is moderate, clinical decision making and patient counseling will remain difficult. The additional finding that radical prostatectomy substantially reduces the risk of metastasis and symptomatic local tumor growth may, however, be of some help in guiding therapy, and we expect that the benefits of this surgery will increase during longer periods of follow-up.

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APPENDIX

The participants in the Scandinavian Prostate Cancer Group Study No. 4 were as follows: *Protocol Committee*—H.-O. Adami and J.-E. Johansson; *Steering Committee*—H.-O. Adami, A. Bill-Axelsson, L. Holmberg, J.-E. Johansson (principal investigator), and B.-J. Norlén; *Statistical Analysis*—L. Holmberg, H. Garmo, and J. Palmgren; *Manuscript Preparation*—H.-O. Adami, A. Bill-Axelsson, and L. Holmberg; *Monitoring*—A. Bill-Axelsson and B. Gobén; *Study Group, Recruitment, and Data Collection*: Borås, Sweden—S. Bratell; Eskilstuna, Sweden—T. Lindeborg; Helsinki—M. Ruutu and J. Salo; Linköping, Sweden—A. Spångberg; Lund, Sweden—P. Elfving; Reykjavik, Iceland—G. Einarsson; Stockholm—J. Adolfsson, P. Ekman, P.-O. Hedlund, and H. Wikström; Uleåborg, Finland—O. Lukkarinen; Uppsala, Sweden—A. Bill-Axelsson, M. Häggman, and B.-J. Norlén; Västerås, Sweden—L. Karlberg; Växjö, Sweden—G. Hagberg; Örebro, Sweden—S.-O. Andersson and J.-E. Johansson; *Reference Pathologists*—C. Busch (chair), M. de la Torre, A. Lindgren, and S. Nordling; *End Point Committee*—J.-E. Damber, Department of Urology, University Hospital, Göteborg, Sweden; A. Lindgren, Department of Pathology, University Hospital, Uppsala, Sweden; E. Varenhorst (chair), Department of Urology, University Hospital, Linköping, Sweden; *External Review Committee*—P.F. Schellhammer, Department of Urology, Eastern Virginia Medical School, Norfolk, Va.; U.E. Studer, Department of Urology, University of Bern, Bern, Switzerland; and R. Sylvester, European Organization for Research and Treatment of Cancer, Brussels.

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CLINICAL TRIAL REGISTRATION

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