

The New England Journal of Medicine

Copyright © 2002 by the Massachusetts Medical Society

VOLUME 347

SEPTEMBER 12, 2002

NUMBER 11



A RANDOMIZED TRIAL COMPARING RADICAL PROSTATECTOMY WITH WATCHFUL WAITING IN EARLY PROSTATE CANCER

LARS HOLMBERG, M.D., PH.D., ANNA BILL-AXELSON, M.D., FRED HELGESEN, M.D., JAAKKO O. SALO, M.D., PH.D.,
PER FOLMERZ, M.D., MICHAEL HÄGGMAN, M.D., PH.D., SWEN-OLOF ANDERSSON, M.D., PH.D., ANDERS SPÅNGBERG, M.D.,
CHRISTER BUSCH, M.D., PH.D., STEG NORDLING, M.D., PH.D., JUNI PALMGREN, PH.D., HANS-OLOV ADAMI, M.D., PH.D.,
JAN-ERIK JOHANSSON, M.D., PH.D., AND BO JOHAN NORLÉN, M.D., PH.D.,
FOR THE SCANDINAVIAN PROSTATIC CANCER GROUP STUDY NUMBER 4*

ABSTRACT

Background Radical prostatectomy is widely used in the treatment of early prostate cancer. The possible survival benefit of this treatment, however, is unclear. We conducted a randomized trial to address this question.

Methods From October 1989 through February 1999, 695 men with newly diagnosed prostate cancer in International Union against Cancer clinical stage T1b, T1c, or T2 were randomly assigned to watchful waiting or radical prostatectomy. We achieved complete follow-up through the year 2000 with blinded evaluation of causes of death. The primary end point was death due to prostate cancer, and the secondary end points were overall mortality, metastasis-free survival, and local progression.

Results During a median of 6.2 years of follow-up, 62 men in the watchful-waiting group and 53 in the radical-prostatectomy group died ($P=0.31$). Death due to prostate cancer occurred in 31 of 348 of those assigned to watchful waiting (8.9 percent) and in 16 of 347 of those assigned to radical prostatectomy (4.6 percent) (relative hazard, 0.50; 95 percent confidence interval, 0.27 to 0.91; $P=0.02$). Death due to other causes occurred in 31 of 348 men in the watchful-waiting group (8.9 percent) and in 37 of 347 men in the radical-prostatectomy group (10.6 percent). The men assigned to surgery had a lower relative risk of distant metastases than the men assigned to watchful waiting (relative hazard, 0.63; 95 percent confidence interval, 0.41 to 0.96).

Conclusions In this randomized trial, radical prostatectomy significantly reduced disease-specific mortality, but there was no significant difference between surgery and watchful waiting in terms of overall survival. (N Engl J Med 2002;347:781-9.)

Copyright © 2002 Massachusetts Medical Society.

THE management of early prostate cancer is controversial. Radical prostatectomy has become widely used, but its possible benefit has not been adequately documented in a randomized trial. Early studies indicated a lower rate of progression after surgery than after external radiotherapy,¹ but no gain in overall survival after more than 20 years of follow-up, as compared with primary expectant management (watchful waiting).^{2,3} Systematic overviews of observational studies reveal a lack of reliable data to support any specific recommendation for the treatment of early prostate cancer.⁴⁻⁷

We conducted a randomized trial in 695 men with early prostate cancer, who were assigned to either watchful waiting or radical prostatectomy. The median follow-up was 6.2 years. Our presentation follows the revised CONSORT recommendations.⁸

METHODS

The protocol (available at <http://www.roc.se>) was defined in 1988. Our main purpose was to determine whether mortality from

From the Regional Oncologic Center (L.H.) and the Department of Urology (A.B.-A., M.H., B.J.N.), University Hospital, Uppsala, Sweden; the Center for Assessment of Medical Technology (E.H., J.-E.J.) and the Department of Urology (S.-O.A., J.-E.J.), Örebro University Hospital, Örebro, Sweden; the Department of Urology, Helsinki University Hospital, Helsinki, Finland (J.O.S.); the Department of Urology, Borås Hospital, Borås, Sweden (P.E.); the Department of Urology, University Hospital, Linköping, Sweden (A.S.); the Department of Pathology, University Hospital, Tromsø, Norway (C.B.); the Department of Pathology, Haartman Institute, University of Helsinki, Helsinki, Finland (S.N.); the Department of Medical Epidemiology, Karolinska Institute, Stockholm, Sweden (J.P., H.-O.A.); and the Department of Epidemiology and the Harvard Center for Cancer Prevention, Harvard School of Public Health, Boston (H.-O.A.). Address reprint requests to Dr. Bill-Axelsson at the Department of Urology, University Hospital, SE-751 85 Uppsala, Sweden, or at anna.bill-axelsson@urologi.uas.lul.se.
Drs. Johansson and Norlén contributed equally to the article.

*Members of the Scandinavian Prostatic Cancer Group Study Number 4 are listed in the Appendix.

prostate cancer was lower among patients treated with radical prostatectomy than among patients treated with watchful waiting. Secondary aims were to measure metastasis-free survival and the risk of local tumor progression. In March 1999, we added an analysis of deaths from all causes.⁹

Enrollment Criteria

Men under the age of 75 years with a primary, previously untreated, and newly diagnosed adenocarcinoma of the prostate verified by cytologic examination, histologic examination, or both were eligible. Further prerequisites were a general condition and mental status that were expected to permit a radical prostatectomy and follow-up for at least 10 years. Patients with other cancers were excluded.

To be eligible, the participants had to have a tumor in stage T0d, T1, or T2.¹⁰ After 1994, men with T1c tumors — according to the revised 1987 International Union against Cancer classification¹¹ — were also eligible. All of these are early stages; the prostate cancer was either clinically inapparent (T0d, T1), confined to the prostate (T2), or diagnosed by needle biopsy performed because of an elevated prostate-specific antigen level (T1c). If the tumor was detected through transurethral resection only, at least six blocks of prostatic tissue had to have been studied. The tumor had to be graded as well- or moderately well differentiated, as judged according to the World Health Organization classification.¹² Men with a poorly differentiated tumor were not eligible. Patients whose condition was diagnosed with an extended biopsy protocol were accepted if less than 25 percent of the tumor was Gleason grade 4 and less than 5 percent was Gleason grade 5. It was further required that a preoperative bone scan show no signs of metastases, that a bone scan or a urographic examination show no signs of obstruction of the upper urinary tract, and that the prostate-specific antigen level be less than 50 ng per milliliter.

Randomization

Patients were randomly assigned to two parallel groups, the watchful-waiting group and the radical-prostatectomy group, with stratification according to degree of differentiation and center. The randomization was performed through a telephone service at offices outside the clinical units. The urologist responsible for the patient's care informed the patient and completed the case-record forms.

Interventions

Men assigned to watchful waiting received no immediate treatment apart from the transurethral resection some had already undergone. In the radical-prostatectomy group, surgery started with a dissection of the pelvic lymph nodes.¹³ If no nodal metastases were found in a frozen section, a Walsh–Lepor radical prostatectomy¹⁴ was carried out. The radical nature of the surgery was given priority over preservation of potency.

Adjuvant local or systemic treatment was not given. Transurethral resection was recommended in the watchful-waiting group as a treatment for local progression. For men with symptomatic local progression in the radical-prostatectomy group, orchidectomy or treatment with gonadotropin-releasing hormone analogues was recommended. Treatment for disseminated disease was the same for the two groups within each center.

Histopathological Review

Four pathologists who were unaware of the patients' outcomes reviewed the inclusion cytologic evidence (55 men had a cytologic examination only) and core-biopsy material (which was missing for 24 men). Each pathologist reviewed the samples from 150 to 200 men, with a similar number from each study group. The review re-evaluated the diagnosis of cancer and scored the tumors according to the method of Gleason.¹⁵ In 48 randomly selected specimens, the

rate of agreement among the pathologists was 60 percent for the classification of tumors as having Gleason scores less than, equal to, or more than 7, where a score of less than or equal to 7 indicates a well- or moderately well differentiated tumor.

Follow-up

Routine follow-up examination of all patients occurred twice a year for the first two years and then annually. On each occasion, a clinical examination was performed, and determination of hemoglobin, creatinine, prostate-specific antigen, and alkaline phosphatase levels was recommended. A bone scan and chest radiograph were obtained one year after randomization and then annually. After 1996, chest x-ray films were obtained annually for the first two years after randomization. From 1998 through March 2001, the records of all patients from the urology and oncology departments were reviewed, and an extended search for all available medical information for men who had died was carried out.

Outcomes and Definitions of Clinical Events

Cause of Death

Two of the investigators extracted data relevant to the clinical course of prostate cancer in a standardized format for all deceased participants. The group assignment and primary treatment mode were not revealed. An independent end-point committee of two urologists and one pathologist individually classified all deaths in one of six categories: 1, death from prostate cancer; 2, death from another main cause but with distant metastases present, regardless of local status; 3, death from another main cause with local progression but without distant metastases; 4, death from another main cause with local progression but with unknown status concerning distant disease; 5, death without evidence of tumor recurrence; and 6, death from another cause within the first month after randomization.

The end-point committee, whose members were unaware of the study results, used the following guidelines.⁹ If the autopsy determined that death was due to prostate cancer or there were distant metastases that had progressed or had not responded to treatment, then the patient's death was attributed to prostate cancer. If the patient had distant recurrence that had responded to treatment with no or only minimal residual disease at autopsy, or if the patient had local tumor progression (watchful-waiting group) or a local recurrence (radical-prostatectomy group) without metastases, the patient was considered to have died with but not directly from prostate cancer and was assigned to category 2, 3, or 4 as appropriate. Otherwise, the patient was deemed to have died from a cause other than prostate cancer without recurrence.

Distant Metastases

Metastases were diagnosed when a bone scintigram or skeletal radiograph was positive, when a computed tomographic scan or pulmonary x-ray film demonstrated metastases, and when lymph nodes beyond the regional nodes showed cytologic or histologic evidence of prostate cancer.

Local Progression and Local Recurrence

In the watchful-waiting group, a patient was classified as having local progression if a transcapsular tumor growth was palpable, if he had symptoms of obstruction of the flow of urine that necessitated intervention, or both. In the radical-prostatectomy group, the criterion for progression and local recurrence was a histologically confirmed local tumor.

Definition of End Points

Three end points were used. The first, disease-specific mortality, was defined by the time to death from prostate cancer (category 1), with deaths from other causes treated as censoring events. The sec-

ond, the rate of distant metastasis, was defined by the time to diagnosis of distant metastases, with deaths from causes other than prostate cancer treated as censoring events. For patients assigned to categories 1, 2, and 4, but without a prior clinical diagnosis of metastases, the date of death was considered the date of diagnosis of distant metastases. Overall mortality was defined by the time to death, regardless of cause.

Sample Size

Initially, the five-year, disease-specific survival rate in the watchful-waiting group was assumed to be 85 percent,¹⁶ and we aimed to detect a reduction in mortality from prostate cancer due to radical prostatectomy that would yield a disease-specific survival of at least 95 percent. With the risk of a type I error at 5 percent (two-sided test) and the risk of a type II error at 20 percent, the initial target sample size was 520 patients. We planned two interim analyses, one after the enrollment of 300 patients and the other after the enrollment of 520. We decided to break the code and discuss the results in the steering committee if the P value was greater than 0.01 and less than or equal to 0.05 and to consider an early cessation for all patients if the P value was less than 0.01.

In the interim analyses, none of the prestipulated P values for breaking the code and revealing the results to the steering committee were reached; however, the overall mortality rate was lower than anticipated. Therefore, after the analysis of 520 patients, the target sample size was increased to 700 patients. With that sample size and the same risks of type I and type II errors, we would be able to detect an absolute difference in the survival rate of 6 percent between the two groups if the disease-specific survival rate was 95 percent in one group.

Ethical Considerations

The ethics committees at all participating centers approved the initial protocol and the increased target sample size. In all but two centers, a modified version of Zelen's randomization model¹⁷ was allowed from 1988 to 1990, which implied that only men in the experimental group received complete information about the study before randomization, but that all patients were informed that they were taking part in a clinical study and gave their oral consent to participate. From 1990, when 68 men had been enrolled at these centers (with 33 assigned to watchful waiting), it became clear that Zelen's model was not necessary for randomization, and thus all men were fully informed thereafter.

Statistical Analysis

All analyses were prespecified, were performed according to the intention-to-treat principle, and were based on complete follow-up of all enrolled eligible men (Fig. 1). At the end of follow-up on December 31, 2000, 520 men had been followed for at least five years, when the first open analysis was to be undertaken according to the protocol. To acknowledge the presence of competing risks, we calculated cumulative cause-specific hazard rates¹⁸ with the use of the negative log transformation of the Kaplan–Meier estimator for each end point. The 95 percent confidence intervals for the difference between the point estimates at five and eight years for the cumulative hazard rates for the study groups are reported.

The log-rank test was used for comparisons between groups, with a P value of less than 0.05 (two-sided) considered to indicate statistical significance. Relative hazards with 95 percent confidence intervals were estimated with the use of Cox proportional-hazards models. The influence of any imbalance in age, distribution of tumor stage, Gleason score as determined by the review, or prostate-specific antigen level was checked in a multivariate Cox model for disease-specific mortality. In the multivariate model, the tumor stage and Gleason grade were represented with dummy variables, and age was entered as a continuous variable. SAS statistical software was used for all calculations. No adjustments of P values or confidence intervals were made for the interim analysis.

RESULTS

Participation

Fourteen centers enrolled 2 to 182 patients each from October 1989 to February 1999. A total of 698 men were enrolled (Fig. 1), with 349 assigned to watchful waiting and 349 to radical prostatectomy. After the exclusion of 2 men wrongly given a diagnosis of prostate cancer and of 1 man with a prior diagnosis of Hodgkin's disease, 348 and 347 men (assigned to watchful waiting and prostatectomy, respectively) were included. During follow-up, 30 men in the watchful-waiting group were treated with curative intent and 25 men in the radical-prostatectomy group were followed without radical treatment (Fig. 1). No patient was lost to follow-up, and the median duration of follow-up was 6.2 years in both groups.

Characteristics at Base Line

The characteristics at base line were similar in the two study groups, with the exception of a somewhat higher proportion of men with stage T1b tumors in the watchful-waiting group (Table 1); however, most of the men had stage T2 tumors.

Number of Events

During follow-up, 115 men died (Table 2); 62 had been assigned to watchful waiting and 53 to radical prostatectomy. Before its consensus meeting, the end-point committee was unanimous in its classification of the causes of deaths of 94 men (53 in the watchful-waiting group and 41 in the radical-prostatectomy group). At a joint meeting, the committee reached a consensus about all causes of death.

Of the 115 men who died, 47 died of prostate cancer, only 1 of whom had no prior clinical diagnosis of distant metastatic disease; all had received hormonal treatment. There were 31 deaths related to prostate cancer in the watchful-waiting group and 16 in the radical-prostatectomy group. There were 37 deaths from other causes in the radical-prostatectomy group and 31 in the watchful-waiting group. Of the 23 men who died from other cancers (Table 2), 17 had a second cancer verified during surgery or at autopsy, and 2 had myeloma verified and treated before death.

Disease-Specific Mortality

The cumulative hazard functions for death from prostate cancer (Fig. 2) and the corresponding five-year and eight-year point estimates (Table 3) showed a difference that increased over time. The absolute difference, in favor of radical prostatectomy, was 2.0 percent (95 percent confidence interval, -0.8 to 4.8) at five years and 6.6 percent (95 percent confidence interval, 2.1 to 11.1) at eight years. The relative hazard for men assigned to prostatectomy as compared with

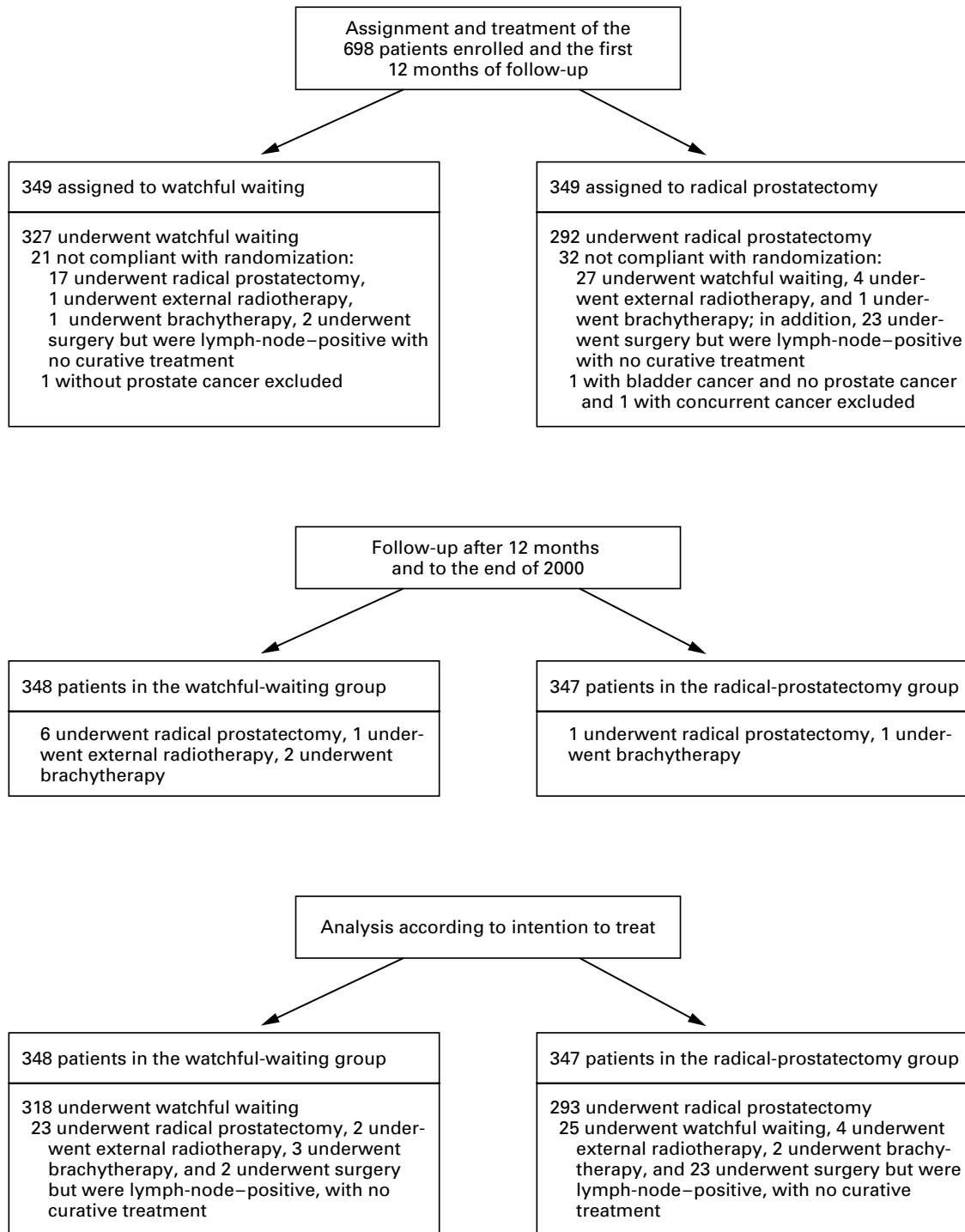


Figure 1. Flow Diagram of Treatment Assignment and Follow-up.

RADICAL PROSTATECTOMY VERSUS WATCHFUL WAITING

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 695 MEN ENROLLED IN THE STUDY.

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

*Plus-minus values are means ±SE.

†In incidental prostate cancer, stage T1b indicates an incidental histologic finding in more than 5 percent of tissue resected (in 1978, this was classified as stage T0d); stage T1c indicates a tumor identified by needle biopsy because of elevated serum prostate-specific antigen levels (in 1978, this classification did not exist). In palpable or visible carcinoma confined to the prostate, stage T2 indicates a tumor confined within the prostate (in 1978, this was classified as stage T1 or T2).

‡This score was assigned during histopathological review.

§Diagnosis was made by cytologic examination only in 55 patients; a biopsy specimen could not be retrieved in 24 patients.

those assigned to watchful waiting was 0.50 (95 percent confidence interval, 0.27 to 0.91). A multivariate analysis that adjusted for age at randomization, tumor stage, and Gleason score according to the pathologists' review yielded a relative hazard of 0.45 (95 percent confidence interval, 0.25 to 0.84).

Rate of Development of Distant Metastases

Analyses of the cumulative hazard rate for distant metastases (Fig. 3 and Table 3) also showed a time-

TABLE 2. CAUSE OF DEATH ACCORDING TO THE FINAL CONSENSUS MEETING OF THE END-POINT COMMITTEE.

CAUSE OF DEATH	WATCHFUL WAITING (N=348)	RADICAL PROSTATECTOMY (N=347)
	number	
Prostate cancer	31	16
Other causes	31	37
Other main cause with metastases	3*	1†
Other main cause without metastases but with local progression or recurrence	8*	6†
Other main cause with no evidence of metastases or local progression or recurrence	19‡	29§
Other main cause within first mo after randomization	1	1
All causes	62	53

*Of these 11 men, 3 died from another cancer.

†Of these 7 men, 3 died from another cancer.

‡Of these 19 men, 5 died from another cancer.

§Of these 29 men, 12 died from another cancer.

dependent pattern, with similar results in the two groups at five years but an absolute difference at eight years of about 14 percent in favor of prostatectomy. The results of log-rank tests were statistically significant (P=0.03), and the relative hazard was 0.63 (95 percent confidence interval, 0.41 to 0.96).

Rate of Local Progression

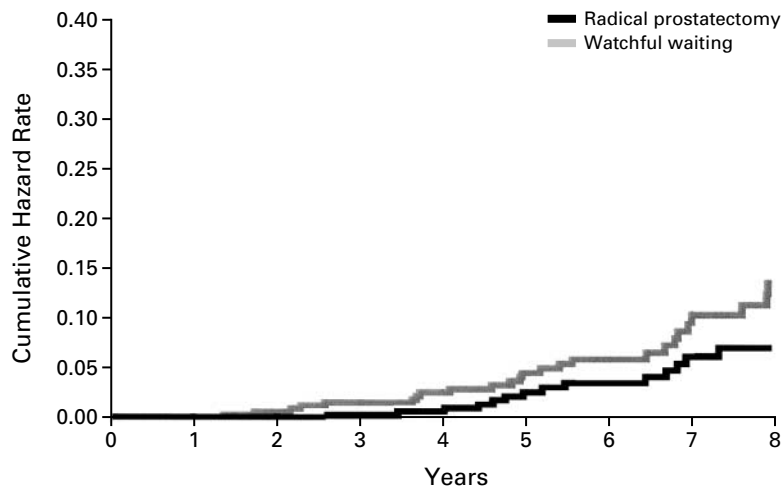
The cumulative hazard rate of local progression (Table 3) was significantly different in the two groups at five years. At eight years, the risk of a local recurrence verified by biopsy was almost 20 percent in the prostatectomy group but was approximately 60 percent in the watchful-waiting group.

Overall Mortality

Two men died within one month after randomization. One man assigned to watchful waiting died at home without signs of progression. One man in the radical-prostatectomy group died postoperatively. If his death is classified as due to prostate cancer, the absolute difference in disease-specific end points changes marginally (Table 3). Sixty-two men in the watchful-waiting group and 53 in the radical-prostatectomy group died; this corresponded to a relative hazard of death from any cause of 0.83 (95 percent confidence interval, 0.57 to 1.2; P=0.31) (Fig. 4).

Hormonal Treatment, Palliative Irradiation, and Laminectomy

Overall, 116 men in the watchful-waiting group (24.7 percent) and 80 men in the radical-prostatecto-



No. AT RISK		0	1	2	3	4	5	6	7	8
Radical prostatectomy	347	343	339	308	281	233	185	134	89	
Watchful waiting	348	346	337	302	275	231	185	121	82	

Figure 2. Cumulative Hazard Rate of Death from Prostate Cancer.

TABLE 3. CUMULATIVE HAZARD RATES, DIFFERENCE BETWEEN THE CUMULATIVE HAZARD RATES, AND RELATIVE HAZARDS FROM COX MODELS FOR THE MAIN END POINTS.*

VARIABLE	WATCHFUL WAITING (N=348)	RADICAL PROSTATECTOMY (N=347)	DIFFERENCE
Disease-specific mortality			
Total no. of events	31	16	
Mean follow-up — yr	6.1	6.2	
Five years of follow-up — % (95% CI)	4.6 (2.1 to 7.2)	2.6 (0.7 to 4.6)	2.0 (−0.8 to 4.8)
Eight years of follow-up — % (95% CI)	13.6 (7.9 to 19.7)	7.1 (3.3 to 11.0)	6.6 (2.1 to 11.1)
Relative hazard — % (95% CI)			0.50 (0.27 to 0.91)†
P value by log-rank test			0.02
Rate of development of distant metastases			
Total no. of events	54	35	
Mean follow-up — yr	5.8	6.0	
Five years of follow-up — % (95% CI)	11.0 (7.1 to 15.0)	8.6 (5.3 to 12.0)	2.3 (−2.1 to 6.8)
Eight years of follow-up — % (95% CI)	27.3 (19.4 to 36.0)	13.4 (8.6 to 18.5)	13.9 (8.0 to 19.8)
Relative hazard — % (95% CI)			0.63 (0.41 to 0.96)‡
P value by log-rank test			0.03
Rate of local progression			
Total no. of events	108	40	
Mean follow-up — yr	4.4	5.2	
Five years of follow-up — % (95% CI)	35.5 (28.0 to 43.7)	9.4 (5.8 to 13.1)	26.2 (20.3 to 32.0)
Eight years of follow-up — % (95% CI)	61.1 (47.8 to 76.4)	19.3 (12.7 to 26.4)	41.8 (35.2 to 48.4)
Relative hazard — % (95% CI)			0.31 (0.22 to 0.44)
P value by log-rank test			<0.001
Overall mortality			
Total no. of events	62	53	
Mean follow-up — yr	6.1	6.2	
Five years of follow-up — % (95% CI)	10.3 (6.6 to 14.0)	8.7 (5.3 to 12.2)	1.5 (−2.8 to 5.9)
Eight years of follow-up — % (95% CI)	28.3 (20.2 to 37.1)	22.0 (15.3 to 29.1)	6.3 (−0.2 to 12.7)
Relative hazard — % (95% CI)			0.83 (0.57 to 1.2)
P value by log-rank test			0.31

*CI denotes confidence interval.

†This estimate changes to 0.53 if one postoperative death is defined as due to prostate cancer.

‡This estimate changes to 0.64 if one postoperative death is defined as due to prostate cancer.

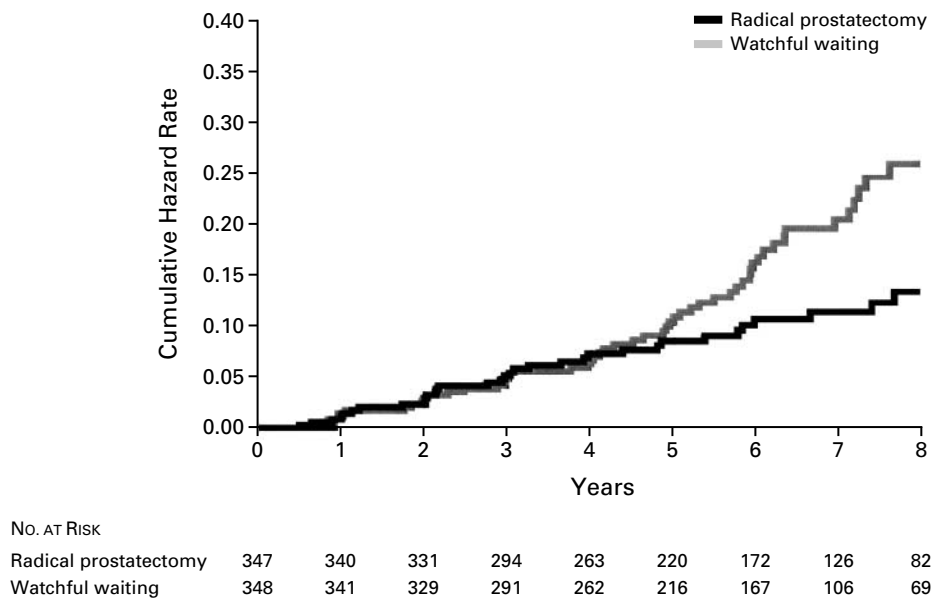


Figure 3. Cumulative Hazard Rate of Development of Distant Metastasis.

my group (17.3 percent) had received hormonal treatment. Palliative irradiation was carried out in 22 men in the watchful-waiting group and in 13 men in the radical-prostatectomy group, and laminectomy was carried out in 8 men and 1 man, respectively.

DISCUSSION

This trial was designed to determine whether radical prostatectomy reduces the risk of death due to prostate cancer. We found a statistically significant difference in the risk of death due to prostate cancer after radical prostatectomy as compared with watchful waiting, yet there was no significant difference between the two groups in the overall survival rate. There were 37 deaths from other causes in the radical-prostatectomy group and 31 in the watchful-waiting group. This difference could be due to chance or to long-term but hitherto unknown adverse effects of prostatectomy. Differences in the management of coexisting conditions between the two groups would, theoretically, confer a disadvantage on the men in the watchful-waiting group, since they had an untreated cancer. The difference could also have been due to misclassification of some deaths in the prostatectomy group, but this is unlikely, since the end-point committee was unaware of the group assignments throughout the process. Indeed, all but one of the men who were classified as dying from prostate cancer had clinically verified metastases, and all men received palliative hormonal treatment before death.

At eight years after radical prostatectomy, the absolute reduction in both overall and disease-specific mortality rates was approximately 6 percent. For distant metastasis, the absolute reduction at eight years was 14 percent. The absolute difference of 6 percent at eight years implies that 17 patients would need to be treated in order to prevent one death from prostate cancer over an eight-year period. The total of 47 critical events indicates a power of 90 percent to detect the level of difference stipulated in the protocol at a level of significance of 5 percent (two-tailed test).

This trial was designed and initiated before the era of screening for prostate-specific antigen began. The study was closed shortly before the target of 700 participants was reached, because of the increasing difficulty of finding patients without a treatment preference. We stress that our results were obtained in a group of men with clinically detected, well-differentiated or moderately well differentiated prostate cancer.

The initial protocol stipulated an estimation of disease-specific mortality rates. However, we also show all causes of death together with the analyses of all end points. The smaller confidence intervals of the estimates of the rates of development of distant metastases and overall mortality indicate that these rates are at least as informative as those for disease-specific mortality.¹⁹

We found only a small difference between the two groups within the first five years after radical prostatectomy. The most likely explanation is that the pro-

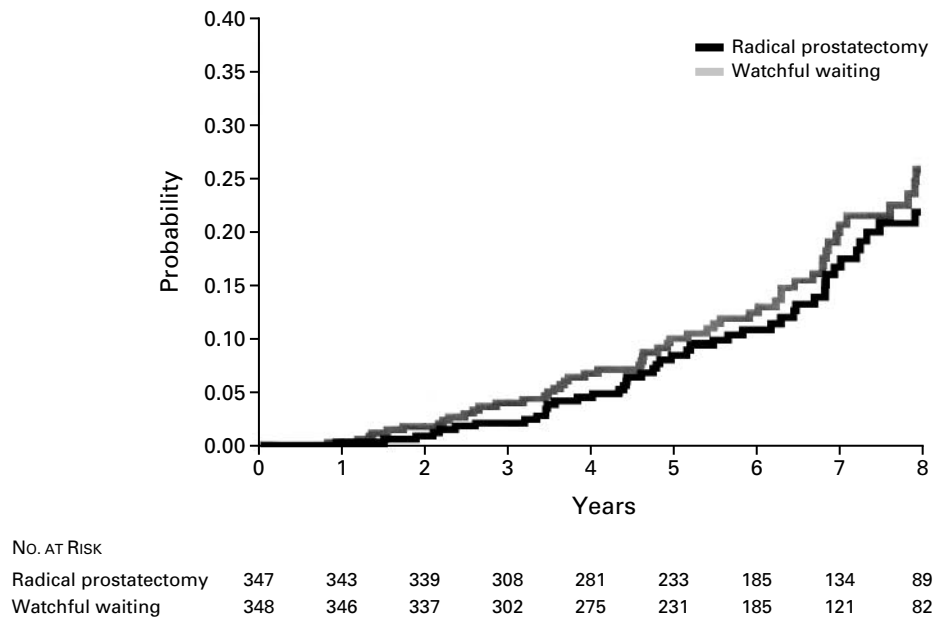


Figure 4. Cumulative Probability of Death.

portion of patients with undetectable, disseminated disease at the time of diagnosis and randomization was similar in the two groups and that these patients account for the majority of deaths from prostate cancer during early follow-up. Surgical removal of the primary tumor will prevent spread and provide cure only in men with localized disease at diagnosis; our findings indicate that this effect will be tangible beyond five years after surgery. By necessity, the definition of local progression differed in the two groups. In the watchful-waiting group, there was an element of subjectivity; for example, obstruction due to benign prostatic hyperplasia could be attributed to malignant progression. This end point is therefore not reliable. Our study has not had a long enough follow-up to determine whether the benefit of surgery will increase further at 10 years and beyond.

Even a relative hazard of 0.5 implies that the absolute benefit associated with radical prostatectomy is limited in men who have the same risk of dying from prostate cancer as the men in this study. This benefit has to be weighed against the well-documented side effects of surgery, such as impotence and incontinence,^{20,21} and the lack of a demonstrated difference in overall survival. As an accompanying article in this issue of the *Journal* about quality of life in a subgroup of this study population shows,²² there were effects on quality of life in both study groups. Erectile dysfunction and urinary leakage are important

sources of decreased well-being after radical prostatectomy, and obstructed voiding and possibly fecal leakage are important after watchful waiting. Moreover, the level of distress varies considerably among subjects, and men give different priorities to survival and to the avoidance of therapy-induced distressful symptoms. Thus, in early prostate cancer, the choice of therapy is complex, and patients need complete information about the alternatives; in addition, physicians need to know about individual patients' concerns. Furthermore, our results indicate that it takes several years for the survival benefit to emerge. In men with cancer detected by screening, the baseline risk of death from prostate cancer may be even lower, and thus the absolute benefit of radical treatment may be even less pronounced than in this study. Moreover, the lead time in screening — which may be many years²³ — would add to the time before the benefit emerges.

Supported by the Swedish Cancer Society.

APPENDIX

The members of the Scandinavian Prostatic Cancer Group Study Number 4 were as follows: *Steering Committee*: H.-O. Adami, A. Bill-Axelsson, E. Helgesen, L. Holmberg, J.-E. Johansson, and B.J. Nørén (principal investigator); *Statisticians*: L. Holmberg, J. Nilsson, and J. Palmgren; *Monitoring Committee*: A. Bill-Axelsson, B. Gobén, and F. Helgesen; *Study Group*: Borås, Sweden: S. Bratell, P. Folmerz, and B. Zackrisson; Eskilstuna, Sweden: T. Lindeborg; Helsinki, Finland: M. Ruutu and J. Salo; Linköping, Sweden: A. Spångberg; Lund, Sweden: P. Elfving; Reykjavik, Iceland: G. Einarsson;

Stockholm, Sweden: J. Adolfsson, P. Ekman, P.O. Hedlund, and H. Wikström; Uleåborg, Sweden: O. Lukkariinen; Uppsala, Sweden: A. Bill-Axelsson, M. Häggman, M. Norberg, and B.J. Norlén; Västerås, Sweden: L. Karlberg; Växjö, Sweden: G. Hagberg; and Örebro, Sweden: S.-O. Andersson and J.-E. Johansson; *Reference Pathologists*: C. Busch (chairman), 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; and E. Varenhorst (chairman), 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, Belgium.

REFERENCES

- Paulson DF, Lin GH, Hinshaw W, Stephani S. Radical surgery versus radiotherapy for adenocarcinoma of the prostate. *J Urol* 1982;128:502-4.
- Graversen PH, Nielsen KT, Gasser TC, Corle DK, Madsen PO. Radical prostatectomy versus expectant primary treatment in stages I and II prostatic cancer: a fifteen-year follow-up. *Urology* 1990;36:493-8.
- Iversen P, Madsen PO, Corle DK. Radical prostatectomy versus expectant treatment for early carcinoma of the prostate: twenty-three year follow-up of a prospective randomized study. *Scand J Urol Nephrol Suppl* 1995;172:65-72.
- Chodak GW, Thisted RA, Gerber GS, et al. Results of conservative management of clinically localized prostate cancer. *N Engl J Med* 1994;330:242-8.
- Gerber GS, Thisted RA, Scardino PT, et al. Results of radical prostatectomy in men with clinically localized prostate cancer. *JAMA* 1996;276:615-9.
- Middelton RG, Thompson IM, Austenfeld MS, et al. Prostate Cancer Clinical Guidelines Panel summary report on the management of clinically localized prostate cancer. *J Urol* 1995;154:2144-8.
- Fleming C, Wasson JH, Albertsen PC, Barry MJ, Wennberg JE. A decision analysis of alternative treatment strategies for clinically localized prostate cancer. *JAMA* 1993;269:2650-8.
- Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001;357:1191-4.
- Schellhammer P, Cockett A, Boccon-Gibod L, et al. Assessment of end-points for clinical trials for localized prostate cancer. *Urology* 1997;49: Suppl 4A:27-38.
- Harmer MH, ed. TNM classification of malignant tumours. 3rd ed. Geneva: International Union against Cancer, 1978.
- Hermanek PH, Sobin LH, eds. TNM classification of malignant tumors. 4th ed. rev. Berlin, Germany: Springer-Verlag, 1992.
- Mostofi FK, Sesterhenn I, Sobin LH. Histological typing of prostate tumors. In: International histological classification of tumors. World Health Organization monograph series no. 22. Geneva: World Health Organization, 1980.
- Brendler CB, Cleeve LK, Anderson EE, Paulson DF. Staging pelvic lymphadenectomy for carcinoma of the prostate risk versus benefit. *J Urol* 1980;124:849-50.
- Walsh PC, Lepor H. The role of radical prostatectomy in the management of prostatic cancer. *Cancer* 1987;60:526-37.
- Gleason DF. Histologic grading and clinical staging of prostatic carcinoma. In: Tannenbaum M, ed. Urologic pathology: the prostate. Philadelphia: Lea & Febiger, 1977:171-98.
- Johansson JE, Adami HO, Andersson S-O, Bergström R, Krusemo UB, Kraaz W. Natural history of localised prostatic cancer: a population-based study in 223 untreated patients. *Lancet* 1989;1:799-803.
- Zelen M. A new design for randomized clinical trials. *N Engl J Med* 1979;300:1242-5.
- Massaro J. Competing risks. In: Armitage P, Colton T, eds. Encyclopedia of biostatistics. New York: John Wiley, 1998:824-35.
- Poole C. Low P-values or narrow confidence intervals: which are more durable? *Epidemiology* 2001;12:291-4.
- Stanford JL, Feng Z, Hamilton AS, et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer. *JAMA* 2000;283:354-60.
- Siegel T, Moul JW, Spevak M, Alvord G, Costabile RA. The development of erectile dysfunction in men treated for prostate cancer. *J Urol* 2001;165:430-5.
- Steineck G, Helgesen F, Adolfsson J, et al. Quality of life after radical prostatectomy or watchful waiting. *N Engl J Med* 2002;347:790-6.
- Pearson JD, Luderer AA, Metter EJ, et al. Longitudinal analysis of serial measurements of free and total PSA among men with and without prostatic cancer. *Urology* 1996;48:Suppl:4-9.

Copyright © 2002 Massachusetts Medical Society.