

Competing Risk Analysis of Men Aged 55 to 74 Years at Diagnosis Managed Conservatively for Clinically Localized Prostate Cancer

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Context.—The appropriate therapy for men with localized prostate cancer is uncertain. Until results of clinical trials are available, men and their physicians need guidance.

Objective.—To estimate survival based on a competing risk analysis stratified by age at diagnosis and histologic findings for men diagnosed as having clinically localized prostate cancer and who were managed conservatively.

Design.—Retrospective cohort study.

Setting.—Connecticut Tumor Registry.

Patients.—A total of 767 men with localized prostate cancer diagnosed between 1971 and 1984, aged 55 to 74 years at diagnosis, either not treated or treated with immediate or delayed hormonal therapy, and followed up for 10 to 20 years after diagnosis.

Main Outcome Measures.—Estimates of the probability of dying from prostate cancer or other competing hazards.

Results.—Men with tumors that have Gleason scores of 2 to 4, 5, 6, 7, and 8 to 10 face a 4% to 7%, 6% to 11%, 18% to 30%, 42% to 70%, and 60% to 87% chance, respectively, of dying from prostate cancer within 15 years of diagnosis depending on their age at diagnosis.

Conclusions.—Men whose prostate biopsy specimens show Gleason score 2 to 4 disease face a minimal risk of death from prostate cancer within 15 years of diagnosis. Conversely, men whose biopsy specimens show Gleason score 7 to 10 disease face a high risk of death from prostate cancer when treated conservatively, even when cancer is diagnosed as late as age 74 years. Men with Gleason score 5 or 6 tumors face a modest risk of death from prostate cancer that increases slowly over at least 15 years of follow-up.

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RESEARCHERS ESTIMATE that in 1998, physicians will diagnose prostate cancer in approximately 200 000 American men.¹ Many of these men will be offered treatments designed to cure or control progression of their disease. Unfortunately, the absence of data from large randomized trials compromises the ability of these patients and their physicians to assess the relative efficacy of aggressive

treatment alternatives compared with the more conservative approach of watchful waiting followed by androgen suppression for symptomatic metastatic disease. Previous studies concerning long-term outcomes associated with conservatively managed disease have focused primarily on older men and have documented relatively modest disease-specific mortality among men with low-grade and moderate-grade²⁻⁴ tumors. Clinicians have criticized these studies, however, because they contain little information concerning the long-term outcomes of younger men, who are the targets of current screening efforts.⁵⁻⁷

Many patients select their initial treatment following a discussion with their physicians and a review of data from tertiary medical centers that provide infor-

mation concerning the outcomes of men treated by radical prostatectomy, external beam radiation therapy, and brachytherapy.⁸⁻¹¹ Unfortunately, these studies suffer from known and unknown selection biases that prevent direct comparisons between studies. Furthermore, many of these studies provide little information concerning competing medical risks that become increasingly important as men age.

See also pp 969 and 1008.

This study was designed to estimate survival based on a competing risk analysis for men diagnosed as having clinically localized prostate cancer who did not receive surgery, external beam radiation, or brachytherapy. The primary objective of the analysis was to estimate the probability of dying from prostate cancer or other competing causes given a patient's tumor histology and age at diagnosis. Patients were selected to meet several criteria: (1) long-term follow-up extending from 10 to 20 years after diagnosis to capture the impact of prostate cancer and competing medical hazards; (2) men aged 55 to 74 years at diagnosis to identify a series of men who have an average life expectancy of more than 10 years; (3) availability of original histology material to permit contemporary grading using the Gleason scoring system; and (4) a sample size sufficiently large to permit stratification by the biopsy Gleason score and age at diagnosis, factors known to be important determinants of outcome.

METHODS

Patient Identification and Data Collection

Connecticut Tumor Registry (CTR) files were searched to identify male Connecticut residents diagnosed as having prostate cancer between 1971 and 1984 and aged 55 to 74 years at diagnosis. Pa-

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Table 1.—Characteristics of 767 Patients With Putative Localized Prostate Cancer

| | |
|---|------|
| Age at diagnosis, mean, y | 68 |
| Year of diagnosis, mean | 1979 |
| Time from diagnosis to death or last contact, mean, y | 8.6 |
| White, % | 94 |
| Follow-up, % | |
| Until death | 80 |
| Alive for >15 y | 10 |
| Alive for 10-15 y | 10 |
| Information available concerning cause of death | 91 |
| Digital rectal examination, % | |
| Not indicative of cancer | 51 |
| Indicative, confined within prostate | 15 |
| Indicative, extending through capsule | 5 |
| Indicative, no further information | 24 |
| Not done or result unknown | 5 |
| Method of diagnosis, % | |
| Transurethral resection of prostate | 60 |
| Simple open prostatectomy | 11 |
| Needle biopsy of prostate | 26 |
| Other or unknown | 3 |
| Total acid phosphatase, % | |
| Normal | 53 |
| Elevated, ≤ 2 times the upper limit of normal | 6 |
| Elevated, > 2 times the upper limit of normal | 3 |
| Elevated, magnitude unknown | 2 |
| Done, but result unknown | 3 |
| Not done | 33 |
| Bone scan performed, no metastases, % | 30 |
| Metastatic survey performed, no metastases, % | 27 |
| No test for metastatic disease performed, % | 21 |
| Treatment within 6 mo of diagnosis, % | |
| None | 58 |
| Orchiectomy | 16 |
| Estrogen therapy | 22 |
| Both orchiectomy and estrogen therapy | 4 |
| Concurrent medical conditions (if $> 5\%$), % | |
| Myocardial infarction | 12 |
| Congestive heart failure | 8 |
| Peripheral vascular disease | 6 |
| Cerebrovascular disease | 7 |
| Chronic pulmonary disease | 20 |
| Diabetes | 10 |
| Peptic ulcer disease | 11 |
| Vital status at last contact, % | |
| Alive | 21 |
| Deceased because of other causes | 46 |
| Deceased because of prostate cancer | 26 |
| Deceased, unable to ascertain cause | 7 |

tients who were noted to have metastases were excluded. After obtaining appropriate institutional review board approvals, we attempted to locate hospital medical records for these patients at each of the 36 acute care hospitals and 2 Veterans Affairs medical centers located throughout the state during the study period. Charts were abstracted on-site to confirm the date of diagnosis and obtain additional information concerning the method of diagnosis, metastatic evaluations completed, method of treatment, and any associated comorbidities. Patients undergoing surgery or receiving either radiation therapy or brachytherapy were excluded. In addition, patients with concomitant cancers and those surviving less than 6 months, the time needed for most patients to select therapy, were also excluded. Study per-

sonnel performing chart abstraction were blinded to the long-term outcome of the patients as recorded by the CTR. Original histology slides that were used to secure the patient's diagnosis were located in hospital pathology departments for as many patients as possible and mailed to a referee pathologist, who was also blinded to the long-term outcome, for grading using the Gleason classification system.¹²

Data collected from the hospital record included the method of case finding (needle biopsy, transurethral resection, or simple open prostatectomy), the results of procedures performed to exclude metastases, if completed, and any treatment initiated within 6 months of diagnosis. The presence of other concomitant diseases was measured using an instrument developed and validated by Charlson et al.¹³

Vital status of each patient as of March 1, 1997, was obtained from the CTR and the Vital Statistics Bureau of the Connecticut State Department of Health. The CTR is the oldest state cancer registry and has functioned as 1 of the 11 sites of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program since 1973. The CTR uses a variety of sources to obtain follow-up data for registered patients, including hospital tumor registrars who rely on hospital records and physician and patient contact. There are several reciprocal reporting agreements with surrounding states, as well as with Florida, where many Connecticut men reside during the winter. Every year the CTR links the files of the Health Care Financing Administration with the CTR files to determine the vital status of those men older than 65 years and, if alive, the date of their last medical claim. The National Death Index is linked to the CTR files every 2 years, and the Connecticut Department of Motor Vehicles files are linked twice a year.

For all patients who were deceased, an attempt was made to retrieve the original death certificate. A patient was determined to have died from prostate cancer if any 1 of the 3 causes listed on the death certificate reported prostate cancer. If prostate cancer did not appear on 1 of these 3 lines, the patient's death was attributed to competing medical conditions. In some instances only information concerning the date of death was available. Patients not followed up until death were considered alive until the date of last contact and their subsequent follow-up was censored.

Study Population

A total of 767 men were identified for whom we were able to verify or obtain

the following information: date of diagnosis between 1971 and 1984, age at diagnosis between 55 and 74 years, method of diagnosis, the Gleason score of the original prostate biopsy, and no evidence of therapy beyond either immediate or delayed hormonal therapy. Of these men, 610 died before March 1, 1997. Of the 157 patients lost to follow-up or known to be alive as of March 1, 1997, the mean follow-up was 15.4 years. Only 2 men were followed up for less than 10 years, 76 men were followed up for 10 to 14 years, and the remaining 79 men were followed up for 15 years or more. Of the 610 patients who died, we were able to determine the date of death for all patients and the cause of death for 553. A description of the study population is provided in Table 1.

Unfortunately, accurate staging information was lacking for many patients. Bone scans were performed on only 30% of patients and a serum acid phosphatase was confirmed as normal in only 53% of patients. No evidence of any testing for metastatic disease ranged from 33% for men with Gleason score 2 to 4 disease to 15% for men with Gleason score 7 and 8 to 10 disease. No information was available concerning prostate-specific antigen (PSA) levels at diagnosis, because this population of men had prostate cancer diagnosed prior to the clinical application of this test.

Statistical Methods

The primary outcomes for this study were estimates of the probability of dying from prostate cancer or other competing causes given a patient's age at diagnosis and tumor histology. For the competing risk analysis, we tabulated the numbers of men with each of the 3 outcomes of interest (alive, deceased from prostate cancer, and deceased from other causes) for each of the 20 age-histology combinations (Table 2). Because of the variable length of follow-up and the small numbers in some cells, we also performed a second competing risk analysis. This second analysis was based on 2 inputs, the rate of death from prostate cancer and the rate of death from other causes, both fitted as smooth functions of age at diagnosis, Gleason score, and year of follow-up (Table 3).¹⁴ These smoothed estimates were derived from regression models and incorporated the duration of follow-up and the patterns of outcomes in neighboring cells to allow more stable estimates for all cells.¹⁵ A separate figure showing patient outcomes during the 15 years following diagnosis was constructed for each age-histology stratum (Figure).

Because the regression models used to construct the smoothed competing risk analysis required information con-

cerning both the date of death and the cause of death for all patients, and because only date of death was available for 57 of the 610 men who died, we imputed the cause of death for each of these 57 men separately for each histology score category according to the ratio of the deaths of known causes for the other men with the same histology scores. For example, among men with Gleason score 2 to 4 tumors, there were 72 deaths from competing hazards and 8 deaths from prostate cancer (ratio, 9:1). The 8 deaths of undetermined cause in this category were therefore each counted as 0.9 of a death from competing hazards and 0.1 of a death from prostate cancer. The regression models were based on 218.6 deaths (198 known + 20.6 imputed) from prostate cancer and 391.4 deaths (355 known + 36.4 imputed) from competing medical hazards. To test the magnitude of the impact of these assumptions on the smoothed competing risk analysis, we performed a sensitivity analysis in which the cause of death for all of the 57 patients lacking this information was first assumed to be the result of prostate cancer and then assumed to be the result of a competing medical hazard. Results of the sensitivity analysis were compared with the data shown in Table 3. In most cases results varied in either direction by no more than 2% to 3%; in no case was the variation more than 5%. We chose to impute cause of death according to the ratio of the other cases found in each cell because imputation provides more realistic histology-specific outcome statistics than we would have obtained by other alternatives, such as indiscriminately partitioning the deaths as either the result of prostate cancer or the result of competing hazards, 2 very unlikely extremes, or censoring the observations at the time the patient died, an approach that would bias results toward more favorable outcomes.¹⁴

The rates of death from prostate cancer and from competing medical hazards were estimated respectively using separate Poisson regression analyses from the 6626 man-years of follow-up using the Poisson link in the GENMOD procedure in SAS statistical software (SAS Institute Inc, Cary, NC), which allows noninteger numbers of events. To estimate the proportions of men who died from prostate cancer, died from competing medical hazards, or were still alive 15 years following diagnosis, we applied the 2 fitted rates to the proportion of men still alive at the beginning of each successive follow-up interval.¹⁵

RESULTS

The distribution and outcomes of 767 patients treated conservatively for puta-

Table 2.—Distribution, Comorbidity Scores, and 15-Year Outcome of Patients With Putative Localized Prostate Cancer

| | Age at Diagnosis, y | | | | Total |
|-----------------------------------|---------------------|-------|-------|-------|-------|
| | 55-59 | 60-64 | 65-69 | 70-74 | |
| Gleason Score 2-4 | | | | | |
| Sample size | 11 | 35 | 42 | 50 | 138 |
| Charlson score, No. | | | | | |
| 0-1 | 10 | 30 | 29 | 35 | 104 |
| ≥2 | 1 | 5 | 13 | 15 | 34 |
| No. alive as of March 1, 1997 | 5 | 15 | 14 | 16 | 50 |
| No. deceased from other causes | 6 | 16 | 22 | 28 | 72 |
| No. deceased from unknown causes | 0 | 4 | 3 | 1 | 8 |
| No. deceased from prostate cancer | 0 | 0 | 3 | 5 | 8 |
| Gleason Score 5 | | | | | |
| Sample size | 8 | 24 | 43 | 43 | 118 |
| Charlson score, No. | | | | | |
| 0-1 | 8 | 19 | 7 | 33 | 96 |
| ≥2 | 0 | 5 | 36 | 10 | 22 |
| No. alive as of March 1, 1997 | 8 | 13 | 16 | 4 | 41 |
| No. deceased from other causes | 0 | 9 | 22 | 29 | 60 |
| No. deceased from unknown causes | 0 | 0 | 1 | 6 | 7 |
| No. deceased from prostate cancer | 0 | 2 | 4 | 4 | 10 |
| Gleason Score 6 | | | | | |
| Sample size | 25 | 45 | 84 | 140 | 294 |
| Charlson score, No. | | | | | |
| 0-1 | 18 | 37 | 65 | 103 | 223 |
| ≥2 | 7 | 8 | 19 | 37 | 71 |
| No. alive as of March, 1 1997 | 12 | 15 | 20 | 8 | 55 |
| No. deceased from other causes | 6 | 16 | 37 | 87 | 146 |
| No. deceased from unknown causes | 2 | 5 | 5 | 10 | 22 |
| No. deceased from prostate cancer | 5 | 9 | 22 | 35 | 71 |
| Gleason Score 7 | | | | | |
| Sample size | 8 | 22 | 43 | 64 | 137 |
| Charlson score, No. | | | | | |
| 0-1 | 6 | 17 | 33 | 48 | 104 |
| ≥2 | 2 | 5 | 10 | 16 | 33 |
| No. alive as of March 1, 1997 | 1 | 2 | 3 | 2 | 8 |
| No. deceased from other causes | 1 | 3 | 23 | 31 | 58 |
| No. deceased from unknown causes | 2 | 0 | 5 | 5 | 12 |
| No. deceased from prostate cancer | 4 | 17 | 12 | 26 | 59 |
| Gleason Score 8-10 | | | | | |
| Sample size | 2 | 15 | 30 | 33 | 80 |
| Charlson score, No. | | | | | |
| 0-1 | 2 | 13 | 17 | 27 | 59 |
| ≥2 | 0 | 2 | 13 | 6 | 21 |
| No. alive as of March 1, 1997 | 0 | 0 | 2 | 1 | 3 |
| No. deceased from other causes | 0 | 1 | 10 | 8 | 19 |
| No. deceased from unknown causes | 1 | 3 | 1 | 3 | 8 |
| No. deceased from prostate cancer | 1 | 11 | 17 | 21 | 50 |
| Total | | | | | |
| Sample size | 54 | 141 | 242 | 330 | 767 |
| Charlson score, No. | | | | | |
| 0-1 | 44 | 116 | 180 | 246 | 586 |
| ≥2 | 10 | 25 | 62 | 84 | 181 |
| No. alive as of March 1, 1997 | 26 | 45 | 55 | 31 | 157 |
| No. deceased from other causes | 13 | 45 | 114 | 183 | 355 |
| No. deceased from unknown causes | 5 | 12 | 15 | 25 | 57 |
| No. deceased from prostate cancer | 10 | 39 | 58 | 91 | 198 |

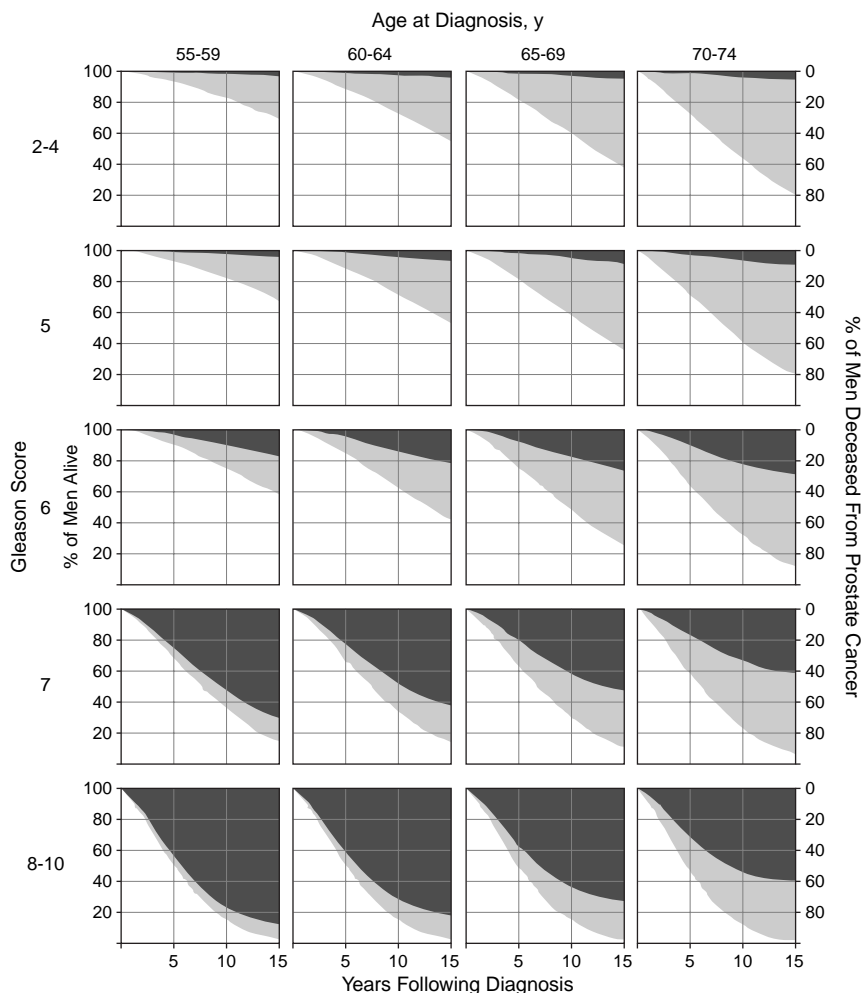
tively localized prostate cancer and whose original histology slides were available for review are presented in Table 2. The table stratifies patients by 2 important factors that influence long-term survival, age at diagnosis and the histology of the biopsy specimen classified according to the Gleason system. To

standardize the follow-up and provide more stable estimates, particularly for the small groups of patients younger than 60 years, smoothed estimates of the probability of dying from either prostate cancer or other causes are presented as a 15-year outcome in Table 3 and as a function of time since diagnosis in the Figure.

Table 3.—Estimated Percentages of Patients With Putatively Localized Cancer Managed Conservatively by Age and Gleason Score at Diagnosis With Each Outcome After 15 Years*

| Gleason Score | Age at Diagnosis, y | | | | | | | | | | | |
|---------------|---------------------|--------------------------------|----------------------------------|----------|--------------------------------|----------------------------------|----------|--------------------------------|----------------------------------|----------|--------------------------------|----------------------------------|
| | 55-59 | | | 60-64 | | | 65-69 | | | 70-74 | | |
| | Alive, % | Deceased From Other Disease, % | Deceased From Prostate Cancer, % | Alive, % | Deceased From Other Disease, % | Deceased From Prostate Cancer, % | Alive, % | Deceased From Other Disease, % | Deceased From Prostate Cancer, % | Alive, % | Deceased From Other Disease, % | Deceased From Prostate Cancer, % |
| 2-4 | 69 | 27 | 4 | 55 | 40 | 5 | 38 | 56 | 6 | 20 | 73 | 7 |
| 5 | 67 | 27 | 6 | 53 | 39 | 8 | 35 | 55 | 10 | 18 | 71 | 11 |
| 6 | 57 | 25 | 18 | 41 | 36 | 23 | 25 | 48 | 27 | 11 | 59 | 30 |
| 7 | 15 | 15 | 70 | 14 | 24 | 62 | 11 | 36 | 53 | 7 | 51 | 42 |
| 8-10 | 3 | 10 | 87 | 3 | 16 | 81 | 3 | 25 | 72 | 2 | 38 | 60 |

*Data derived from regression-based competing risks model.



Survival (white lower band) and cumulative mortality from prostate cancer (dark gray upper band) and other causes (light gray middle band) up to 15 years after diagnosis stratified by age at diagnosis and Gleason score. Percentage of men alive can be read from the left-hand scale, and percentage of men who have died from prostate cancer or from other causes during this interval can be read from the right-hand scale.

The Figure demonstrates that few men with Gleason 2 to 4 tumors identified by prostate biopsy had progression leading to death from prostate cancer within 15 years. A majority of the younger men are still alive but face a possibility of death from prostate cancer in the future. In contrast, most older men with Gleason 2 to 4 tumors identified by

biopsy have died from competing medical hazards rather than prostate cancer.

Compared with men with well-differentiated tumors, men with Gleason score 5 and 6 tumors identified by prostate biopsy experienced a somewhat higher risk of death from prostate cancer when managed conservatively. More than half of the younger men with Gleason 5 and

6 tumors are still alive after 15 years, whereas a majority of the older men have died from competing medical hazards.

Men with Gleason scores 7 and 8 to 10 tumors identified by prostate biopsy experienced a very high rate of death from prostate cancer regardless of their age at diagnosis. Very few of these men of any age are still alive. Most have died from prostate cancer, except for approximately one third of the oldest men, who died from competing medical hazards.

To determine the impact of comorbidities on patient outcome, we analyzed the survival of the 181 patients who were noted to have several comorbidities (Charlson score, ≥ 2) compared with the 586 who were found to have few or no comorbidities (Charlson score, 0-1). As expected, patients with significant comorbidities had a worse survival outcome (mortality rate ratio, 1.9; 95% confidence interval [CI], 1.6-2.2 after adjustment for age compared with patients who had few or no comorbidities). The probability of dying from prostate cancer, however, was comparable between these 2 groups of patients (mortality rate ratio, 1.26; 95% CI, 0.95-1.69). The number of patients with Charlson scores of 0 to 1 and 2 or more is listed by patient age and Gleason score in Table 2.

Preliminary analysis of the data also revealed a significant impact on cause-specific and overall survival associated with the timing of antiandrogen therapy. Men who received immediate treatment (42%) had a significantly worse survival compared with men who received no immediate antiandrogen therapy (58%). Some of this latter group may have received hormonal therapy at a later date. After adjusting for age and comorbidity, the mortality rate ratio for men with delayed or no antiandrogen treatment compared with men with immediate treatment was 1.63 (95% CI, 1.42-1.87) for overall survival and 2.81 (95% CI, 2.19-3.60) for cause-specific survival. Men receiving immediate antiandrogen therapy either started taking estrogen-containing compounds or underwent bilateral orchiectomy within 6 months of

diagnosis. No information was available concerning why hormone therapy was initiated immediately following diagnosis in some patients and not in others. To our knowledge, none of the men in this study received radical prostatectomy or radiation therapy.

COMMENT

Considerable controversy and confusion surround the appropriate treatment of newly diagnosed localized prostate cancer. Many clinicians recommend aggressive treatments such as radical prostatectomy, external beam radiation therapy, or brachytherapy because of the presumed risk of disease progression and eventual death from prostate cancer. Unfortunately, few data are available concerning the natural history of this disease in younger men, and virtually no information is available concerning the temporal progression of tumors identified as a result of testing with serum PSA.

Comparison With Other Studies of Conservative Management

Several authors have reported long-term outcomes associated with conservative management of this disease. In 1997, Johansson et al² published a 15-year analysis of a population-based cohort of 642 men who received no immediate therapy for newly diagnosed prostate cancer. Of this group, only 300 had disease localized to the prostate and only 85 were younger than 70 years. Approximately half of the men had well-differentiated tumors. Although the numbers of patients followed up with moderate-grade or high-grade tumors were small, their results demonstrated that 6% of the patients with well-differentiated disease, 17% with moderately differentiated disease, and 56% with poorly differentiated disease died from prostate cancer. Chodak et al³ published a pooled analysis of 828 men included in 6 nonrandomized studies describing the natural history of clinically localized prostate cancer. They found that men with well-differentiated and moderately differentiated tumors had an 87% 10-year disease-specific survival compared with a 34% 10-year disease-specific survival for men with poorly differentiated tumors. We previously reported results based on a cohort of 411 men aged 65 to 75 years at diagnosis between 1971 and 1976.⁴ Men in this series had a 15-year cumulative mortality from prostate cancer of 9%, 28%, and 51% with Gleason score 2 to 4, 5 to 7, and 8 to 10 tumors, respectively. Of these men, 334 satisfied the requirements for this study and were included in this analysis.

The present study was designed to provide younger patients with better estimates of their risk of dying from pros-

tate cancer or competing causes given the histology of their prostate biopsy specimen. Our data are remarkably consistent with those reported by Johansson et al² and Chodak et al.³ After 15 years, men diagnosed as having low-grade disease (Gleason score, 2-4) had a small risk of dying from prostate cancer. Men with moderate-grade disease (Gleason score, 5 or 6) had a higher risk of dying from prostate cancer, whereas men with high-grade disease (Gleason score, 7-10) had a substantial risk of dying from their disease. Men with Gleason score 2 to 6 disease identified by biopsy appeared to have a slightly higher mortality rate from prostate cancer the older they were at the time of diagnosis, whereas men with Gleason score 7 to 10 disease identified by biopsy appeared to have a slightly lower mortality rate from prostate cancer the older they were at the time of diagnosis. These findings may simply be an artifact of the case series selection, since other investigators have suggested that the risk of death from prostate cancer is independent of the age of diagnosis.^{2,12,16}

Our results are at odds with a controversial retrospective analysis by Aus et al.¹⁷ In this study the authors assembled a group of 301 Swedish men originally diagnosed as having localized prostate cancer who died between 1988 and 1990. By sampling only men who had died, the authors enriched their sample with men who had moderately or poorly differentiated disease. The distribution of men by Gleason score (2-5, 6-7, 8-10) in their study was 33%, 39%, and 28%, respectively, whereas in our study this distribution was 33%, 56%, and 10%, respectively. The 10% of patients with Gleason score 8 to 10 tumors in our series were responsible for 25% of the cancer deaths. As a consequence of their sampling technique, the estimates by Aus et al of 15-year mortality from prostate cancer more closely approximate the figures for men with high-grade disease than those with low-grade to moderate-grade disease. From their data, Aus et al¹⁷ and Hugosson et al¹⁸ suggest that the disease-specific survival of patients who survive longer than 10 years following diagnosis of prostate cancer is 55%. Our analysis found that 23% of men died from prostate cancer and 39% died from competing hazards within 10 years of diagnosis. Of those patients surviving at least 10 years, 11% subsequently died from prostate cancer within the next 5 years, 30% died from competing hazards, and 56% were still alive.

Comparability With Patients Whose Tumor Was Identified by PSA Testing

Testing with PSA has dramatically altered the apparent incidence of recog-

nized prostate cancer in recent years, identifying cancer in a large number of patients whose disease previously would have gone undiagnosed for many additional years and identifying cancers in some patients that might never have been discovered.¹ The magnitude of the lead time introduced by PSA testing is considerable. Gann et al¹⁹ estimated that a single elevated PSA measurement can detect nearly 80% of all aggressive cancers diagnosed 5 years before their clinical appearance and approximately 50% of all aggressive cancers diagnosed 9 to 10 years before their clinical appearance. Whether the cancers found by contemporary PSA screening are comparable with those identified in our patient series is unclear. The possibility exists that cancers identified by PSA screening may progress more rapidly than the cancers identified in the men in our series, but the effect of any lead-time bias would result in contemporary patients having a longer survival following diagnosis compared with our study population.

Modern imaging studies such as computed tomography, transrectal ultrasound, and magnetic resonance coil imaging have changed the staging of patients presenting for prostate cancer therapy and introduced another potential confounding effect. Before the advent of transrectal ultrasound and the use of serum PSA as a staging tool, 40% of patients with newly diagnosed disease had clinical evidence of extracapsular extension of disease.²⁰ Catalona et al²¹ have shown that more than half of all patients presenting with a serum PSA level greater than 10 ng/mL have pathologic evidence of extracapsular extension. Because none of the patients included in this series underwent PSA testing, there is a high probability that this series contains a number of patients with extracapsular disease. By including these men in our analysis, the long-term estimates presented in the Figure more likely underestimate rather than overestimate survival.

Finally, the modern practice of initiating antiandrogen therapy to treat a rising serum PSA level raises concerns about the comparability of this series with the outcomes associated with contemporary management. Some researchers suggest that early antiandrogen therapy improves patient survival, especially among patients with minimal disease.²² Because of the changes in screening, staging, and the use of antiandrogen therapy over the past 2 decades, contemporary patients with clinically localized prostate cancer are likely to have survival outcomes that are superior to our study population.

Walsh and Brooks⁵ suggested that the lead-time bias associated with early de-

tection is greater for cancers detected by transurethral resection than by contemporary screening efforts using PSA testing.⁵

To evaluate this hypothesis, we compared the survival of the 26% of men with prostate cancer diagnosed following needle biopsy of the prostate with the 71% of men with prostate cancer diagnosed following transurethral resection or open prostatectomy. After adjusting for Gleason score and patient age, we found no significant difference in the survival of these 2 groups of patients ($P > .90$). Since patients with palpable disease on rectal examination generally have a higher tumor burden compared with men with T1c disease, patients diagnosed as having T1c disease following contemporary screening efforts and managed conservatively would probably have survival curves that are better, not worse, than those displayed in the Figure.

Study Limitations

There are several limitations to our analysis. Many of the men included in the study sample had inadequate staging evaluations. As a result, men with regional or metastatic disease are probably included in the analysis as suggested by the statistically different survival curves for men receiving immediate vs delayed antiandrogen therapy. Although we were able to locate hospital records and original histology slides for many patients, many others were excluded because of incomplete or absent records, absent histology slides, or documentation of aggressive treatments such as surgery, radiation, or brachytherapy. How these selection biases affect the construct of this case

series is impossible to assess. As part of our preliminary analysis, we evaluated office medical records for a subset of the patients included in this analysis. We did not find any cases of aggressive interventions that were not also identified in the hospital medical record. The possibility exists, however, that some of these patients may have received aggressive management at a later date. Unfortunately, our chart reviews did not reveal why men in this series chose conservative management as opposed to more aggressive alternatives. Finally, as with any analysis of data from case series, there may be other unknown factors that have biased the construct of this analysis.

Summary

Based on our analysis of a series of men residing in Connecticut, diagnosed as having localized prostate cancer between 1971 and 1984, aged 55 to 74 years at diagnosis, and managed conservatively, we conclude that men with well-differentiated disease (Gleason scores, 2-4) identified by prostate biopsy face a minimal risk of death from prostate cancer within 15 years of diagnosis. Conversely, men with poorly differentiated disease (Gleason scores, 7-10) face a high risk of death from prostate cancer when treated conservatively even when diagnosed as late as age 74 years. Men with moderately differentiated disease (Gleason scores, 5-6) face a modest risk of death from prostate cancer that increases slowly over at least 15 years of follow-up. These men face a risk of dying from prostate cancer, but it is unclear from a population perspective what percentage of these men will actually benefit from treatment. Only through ran-

domized trials designed to measure treatment efficacy and additional research on issues surrounding health-related quality of life can we answer questions concerning which patients benefit from aggressive screening and treatment of prostate cancer.

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