INTRODUCTION

Prostate cancer encompasses a wide spectrum of clinical outcomes. Some patients suffer a rapid progression of their disease: others live with their disease for many years, ultimately succumbing to competing medical hazards. Only about 30% of the patients in the Veterans Administration Cooperative Urological Research Group (VACURG) studies of prostate cancer actually died from prostate cancer (1). In 1999, an estimated 179,300 American men will be diagnosed with prostate cancer and 37,000 will die from this disease (2). These statistics suggest that variable outcomes are as prevalent today as they were approximately half a century ago.

The wide spectrum of clinical outcomes poses a special burden to the physician treating patients with prostate cancer. Physicians cannot easily determine whether the interventions they propose are likely to alter the natural outcome of this disease. Unlike some cancers where death is a virtual certainty in the absence of treatment, the natural history of prostate cancer is much more varied. When counseling patients with this
disease, clinicians often follow the safest approach and recommend aggressive therapy. If the disease progresses, the physician takes solace in that he or she has done everything possible. If the disease does not progress, the physician assumes that he or she has “cured” the patient. Unfortunately, the efficacy of different treatment strategies remains uncertain for many patients. Neither surgery nor radiation therapy has been shown to be an effective method of controlling disease among a substantial number of patients who are at the highest risk of dying from prostate cancer. The advent of testing for prostate-specific antigen (PSA) has dramatically increased our ability to detect early-stage prostate cancer and monitor the progression of this disease, but it has also increased the uncertainty concerning how best to manage men with less aggressive forms of this disease. To understand the true benefit of treatment, clinicians must have a good understanding of the natural history of prostate cancer.

The purpose of this chapter is to review the critical studies that have led to our current understanding of the natural progression of prostate cancer. Both tumor histology and tumor volume should be assessed when advising patients concerning the likely clinical outcome of this disease. Using standardized assessments of tumor histology and volume, clinicians can better estimate the relative risk posed by different prostate cancers and the relative value provided by different treatment strategies. By refining our understanding of the risks and benefits of different therapeutic approaches, patients can select a strategy appropriate to their disease that hopefully optimizes their life expectancy with a minimal compromise to their quality of life.

THE SIGNIFICANCE OF HISTOLOGY

*The VACURG Studies and the Gleason Grading System*

Many physicians have recognized the important relationship between histology and the clinical outcome of prostate cancer (3–4). This information, however, has only recently been incorporated into treatment decision analysis. Prior to the publication of the Gleason grading system, many pathologists found it difficult to classify prostate cancers consistently according to their malignant potential. Gleason’s accumulated experience with almost 3000 tumors from the VACURG studies confirmed that prostate cancer histology was strongly correlated with the clinical behavior of this cancer and that prostate cancer histology provided information concerning outcome that was independent of clinical stage. Because of its relative simplicity, pathologists have adopted
Gleason’s scoring system as the standard for assessing prostate cancer histology.

The VACURG studies were begun in 1960 as controlled, randomized, prospective comparisons of the different treatments available for prostate cancer (5). Three different protocols enrolled a total of 2911 men. Study 1 (1960–1967) compared placebo vs 5 mg of diethylstilbestrol (DES)/d following radical prostatectomy for patients with clinically localized disease. Men with regional and metastatic disease were randomized to one of four treatment groups: placebo; 5 mg of DES/d; orchiectomy alone; orchiectomy plus 5 mg DES/d. Study 2 (1967–1969) compared radical prostatectomy with no surgery for men with localized disease. Men with regional and advanced disease were randomized to one of four arms: placebo; 0.2 mg DES/d; 1 mg DES/d; 5 mg DES/d. Study 3 opened for accrual in 1969 and randomized men with localized disease to radical prostatectomy vs no surgery, while men with regional or advanced disease were randomized into four groups: 1 mg DES/d; 2.5 mg of conjugated equine estrogens (Premarin)/d; 30 mg of medroxyprogesterone acetate (Provera)/day; 30 mg of medroxyprogesterone acetate plus 1 mg DES/d.

By 1974, 2911 cases were available for follow-up clinical correlation. For each case the cause of death was determined by an evaluation committee that consisted of three participating clinicians. Original histology slides were re-evaluated by Dr. Donald Gleason and assigned a score according to his classification system. The system developed by Gleason involved an assessment of the degree of glandular differentiation viewed under low-power magnification. Originally nine independent patterns were identified, but these were combined into the classic patterns that constitute the Gleason grading system.

The VACURG assessed clinical outcomes by calculating the number of deaths per patient-year of follow-up. This statistic is calculated by dividing the number of deaths in the group under consideration by the sum of the follow-up times for all the patients (both living and dead) in that group. The follow-up time was measured from the date of admission to the study to the date of death or to the date of last known follow-up. Time was recorded in months and ranged from 0 to 14 yr/patient.

The observed incidence of the primary and secondary histology patterns was strongly correlated. Low-grade primary patterns were usually associated with low-grade secondary patterns and high-grade primary patterns were usually associated with high-grade secondary patterns. Mortality rates were strongly correlated with both the primary and secondary histology patterns, but the average histology pattern provided
Albertsen

the strongest correlation. Accordingly, Gleason proposed summing the pattern scores to provide the best predictor of clinical outcome. This sum is now frequently called a Gleason score.

A review of the clinical outcomes of the patients involved in the VACURG study shows that grading prostate cancers by histology can separate patients into groups that experience markedly different mortality rates (Fig. 1). Patients with Gleason score 2–5 tumors had a cancer death rate of only 0.012 or 1.2 deaths/100 patient-yr. The remaining 2187 patients with Gleason scores from 6 to 10 had a cancer death rate of 0.124 deaths/patient-yr; a rate that is 10 times higher than the rate for men with low-grade disease.

**The Johansson Studies**

Between 1989 and 1997, Johansson and colleagues published a series of three articles that documented the natural history of untreated prostate cancer in a population-based cohort of patients diagnosed with prostate cancer in Orebro Medical Center in Sweden, a hospital with a strictly defined catchment area (6–8). No screening for prostate cancer took place during the period when this study population of 648 consecutive cases was assembled. They found relatively low 5- and 10-year mortality rates among men with clinically localized disease and challenged the use of aggressive initial treatment for all patients with early-stage prostate cancer. Their studies were criticized primarily because of issues surrounding the selection of the study cohort.

Johansson et al. utilized a prospective, population-based study design to assemble their study cohort. Between March 1977 and February 1984, all consecutive cases of clinically diagnosed prostate cancer were enrolled in the study. Diagnoses were confirmed by fine-needle aspiration biopsy of palpable prostate tumors in 542 (84%) of the 648 cases. In another 106 cases (16%), the diagnosis was made during surgery for benign prostate hyperplasia. Staging examinations included chest radiography, intravenous pyelography, bone scan, and skeletal radiography of suspicious lesions on bone scan. Digital rectal examination was also performed to determine the clinical stage of the disease. Medical information on six patients could not be located.

Of the 642 patients evaluated, 300 had disease localized to the prostate (T0–T2) and 183 patients had locally advanced disease (T3–T4) without detectable metastases (M0). Metastatic disease was found in 159 patients (25%). Of the 300 patients with localized disease, 223 received no initial treatment. Of the remaining 77 patients, 2 underwent a radical prostatectomy and 75 received some combination of external beam radiation, estrogen, estramustine, or an orchiectomy. Of the 342
patients with locally advanced disease or with metastatic disease, most were treated with hormonal therapy, predominantly with estrogen or estramustine.

All patients were followed until death or until the end of the observation period on September 1, 1994. The observation period ranged from 126 to 210 mo, the average being 168 mo (14 yr). Patients were followed at least every year and some much more frequently. Prostate cancer was recorded as the underlying cause of death, a contributory cause of death, or unrelated to the cause of death for each patient who died during the follow-up period. An autopsy was performed if the cause of death was unclear. If the treatment of the prostate cancer was related to the patient’s death, (e.g., cardiovascular complications following estrogen therapy), prostate cancer was recorded as a contributory cause of death. Cause of death determinations were reviewed and compared with the classification assigned by the county tumor registrar. There was agreement in 90% of cases, and no evidence of systematic overascertainment or underascertainment of prostate cancer cause of death. The authors performed several survival analyses, including an analysis of all-cause survival and diseasespecific survival. The effect of different variables on survival was determined using the Cox proportional hazards model.

At the end of the observation period, 541 (84%) of all 642 patients in the study cohort had died. Prostate cancer was considered the underlying cause of death in 201 patients (31%), whereas in 35 patients (5%), prostate cancer contributed to the cause of death. Prostate cancer accounted for more deaths among younger patients compared with older patients at the time of diagnosis. More patients with poorly differentiated tumors and/or advanced local tumors died of prostate cancer. For
the 300 men with localized disease at the time of diagnosis, 37 (12%) developed metastases and 33 (11%) died of their disease. Of these 300 patients, 223 received no initial therapy. Among these 223 patients, 29 (13%) developed metastases, 25 (11%) died of prostate cancer, and 4 died of prostate cancer as a contributing cause of death (Fig. 2).

A careful review of the 223 patients receiving no initial therapy reveals that 148 had well differentiated disease and 66 had moderately differentiated disease. Presumably, these cases would be classified as Gleason 2–6 tumors. Of the 148 patients with well-differentiated disease, only 9 (6%) died from prostate cancer and only 2 developed distant metastases. Results were not quite as good for men with moderately differentiated disease. Of these 66 men, 11 (17%) died from prostate cancer and 2 (1.8%) developed metastatic disease. The nine men with poorly differentiated disease fared poorly. Three patients developed local progression and six developed metastases. Five of these patients had died from prostate cancer at the time of last follow-up.

Based on their findings, Johannson et al. stated that men with well-differentiated or moderately differentiated disease have an excellent prognosis in the absence of any aggressive treatment. These findings are in agreement with those published by Gleason. Unfortunately, men with poorly differentiated prostate cancer had a high incidence of progression and death from their disease. This finding is also similar to that of Gleason. Of the 201 men who died from prostate cancer in the entire cohort of 642 men, 28 (13%) of these patients had well-differentiated prostate cancers, 101 (33%) had moderately differentiated cancers and 72 (58%) had poorly differentiated cancers. When contributory causes are considered, a total of 68% of men presenting with poorly differentiated disease and 38% of men with moderately differentiated disease
died from prostate cancer. Johannson et al. concluded their study by noting that because of the favorable survival rate among the untreated patients with early-stage disease, at least 80% of these patients would be treated without survival benefit. Although this may be true for older men with well-differentiated and moderately differentiated disease, these results cannot be generalized to younger men and men with poorly differentiated cancers. The distribution of Gleason scores in contemporary series of incident cases is more heavily weighted toward moderate and poorly differentiated disease compared with the sample reported by Johannson et al.

The Chodak study

In 1994, Chodak et al. published a report concerning the results of conservative management of clinically localized prostate cancer (9). Unlike the Johannson report, this study consisted of a pooled analysis of 828 case records from 6 nonrandomized studies published during the decade preceding the report. None of the patients included in the report underwent a radical prostatectomy or received radiation therapy. Patients who had symptomatic progression or who developed metastases received hormonal therapy. The final report contained information derived from six previously reported studies (6, 7, 10–14). Two were conducted in the United States, two in Sweden and one each in Scotland and Israel. The final series consisted of 828 patients ranging in age from 37 to 93 yr at the time of diagnosis. The median follow-up of the study group was approx 6.5 yr.

A Cox proportional hazards regression model was initially used to determine the combined effects of the patient’s age at diagnosis, tumor grade, disease stage, and the origin of the patient cohort on disease-specific survival. The risk ratio for disease progression was substantially higher for patients with poorly differentiated histology when compared with all the other risk ratios. As a result, the authors stratified patients into three categories by biopsy tumor histology for subsequent analysis. The goal of the study was to calculate conservative estimates of the effect of nonaggressive treatment on disease-specific survival, overall survival, survival among patients who did not die of prostate cancer (noncancer survival), and metastasis-free survival among men with clinically localized prostate cancer.

Disease-specific survival and metastasis-free survival for men with well-, moderately, and poorly differentiated disease were reported. Patients with poorly differentiated (grade 3) cancers had a significantly lower cancer-specific survival rate (34%) when compared with men who had well-differentiated (grade 1) or moderately (grade 2) differen-
tiated cancers (87%). Men with moderately differentiated cancer (grade 2) had a lower disease-specific survival rate when compared with men who had well differentiated disease (grade 1), but the difference was not statistically significant (Fig. 2). The rate of progression to metastasis differed significantly among men with the three tumor grades. Men with poorly differentiated tumors were much more likely to progress to metastatic disease compared with men who were diagnosed with well-differentiated disease. These results are similar to those reported by Gleason and Johannson et al.

The authors tested for several potential biases that could have compromised their findings. They concluded that the relatively favorable outcome associated with conservative management could not be explained by the inclusion of men with shorter than average life expectancies. They also investigated the potential impact of including patients with small, focal tumors because these patients are thought to have a more favorable outcome when compared with patients with other stages of localized disease. They found that the inclusion of these cases did not affect the overall rates of disease-specific survival reported for the entire population of patients.

Based on these findings, the authors concluded that prostate cancer is a progressive disease when managed conservatively. Furthermore, the prognosis of men with poorly differentiated disease is considerably worse when compared with men with well-differentiated or moderately differentiated disease. The authors also commented that aggressive treatment of prostate cancer may result in a lower mortality from prostate cancer at 10 yr among men with well-differentiated and moderately differentiated disease, but the differences appear to be small. The relative benefit of aggressive treatment for poorly differentiated disease is less clear. These patients face a significant risk of disease progression in the absence of treatment, therefore the potential benefit of more aggressive treatment is substantially larger.

The Lu-Yao Study

In 1997, Lu-Yao and Yao published an analysis of 59,876 prostate cancer registry patients at age 50–79 years at diagnosis to ascertain overall and prostate cancer-specific survival rates among men treated with surgery, radiation, or a more conservative approach (15). Their study relied on the population-based records compiled by the Surveillance, Epidemiology and End Results (SEER) of the National Cancer Institute. Their study utilized the SEER histology classification system: grade 1 (Gleason scores 2–4), grade 2 (scores 5–7), grade 3 (scores 8–10) and
grade unknown. The patients included in the study were diagnosed between January 1, 1983 and December 31, 1992. Men with other cancers were excluded from the analysis.

Using an intention to treat analysis, they found that cancer grade had a significant effect on overall survival. All patients with well-differentiated disease had similar or even better overall survival when compared with an age-matched control regardless of treatment. In contrast, patients with poorly differentiated disease had much lower overall survival than their age-matched controls in all treatment groups. The risk of dying of prostate cancer within 10 yr of diagnosis was ten times greater for men with poorly differentiated disease compared with men with well-differentiated disease. Poorly differentiated cancers had a uniformly poor outcome for men with localized disease as well as regional disease. Furthermore, the authors found that the effect of poorly differentiated disease on survival was rapid. Five years after diagnosis, patients with poorly differentiated disease managed conservatively had a relative survival of only 0.61 compared with age-matched controls and a disease-specific survival of only 63–69%.

Ten-year disease-specific survival rates for the entire cohort ranged from 45% to 94% (Fig. 2). For men with well-differentiated disease, survival rates were 94%, 90%, and 93%, respectively, for men undergoing prostatectomy, radiation therapy, and conservative management. For men with moderately differentiated disease (Gleason score 5–7), 10-yr disease-specific survival rates were 87%, 76%, and 77%, respectively. Men undergoing prostatectomy appeared to have a significant survival advantage in this group compared with men treated with radiation or managed conservatively. Men with poorly differentiated disease had the worst 10-yr disease-specific survival rates. They were 67%, 53%, and 45%, respectively, for men undergoing prostatectomy, radiation therapy, and conservative management. Patients undergoing prostatectomy and radiotherapy had a higher relative and prostate-cancer-specific survival with poorly differentiated disease.

The Albertsen Study

We recently reported long-term outcomes of a competing risk analysis of 767 men diagnosed between 1971 and 1984 who were managed expectantly for clinically localized prostate cancer (16). Our study design consisted of a case series analysis of patients identified through the Connecticut tumor registry who satisfied several criteria. First, we searched for men with long-term follow-up extending 10–20 yr after diagnosis to capture the impact of prostate cancer and competing medical hazards. Second, we looked for men aged 55–74 yr at diagnosis to identify a group of men who
had an average life expectancy of more than 10 yr. Third, we recovered the 
original histology slides of these patients to permit reanalysis using contem-
porary Gleason grading standards. Finally, we assembled a patient cohort 
sufficiently large to permit stratification by the biopsy Gleason score and 
age at diagnosis, factors known to be important determinants of outcome.

Long-term outcome information was obtained from the Connecticut 
tumor registry and the vital statistics bureau of the Department of Public 
Health. The mean follow-up of the patient cohort from diagnosis until 
death was 8.6 yr. 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 yr. Only 2 of 
these men were lost to follow-up before 10 yr, 76 of these men were 
followed for 10–14 yr and the remaining 79 were followed for 15 yr or 
more. Cause of death was determined by reviewing death certificates 
for each of the men who had died. Connecticut death certificates follow 
the format recommended by the World Health Assembly and contain 
two parts. Part I contains three lines for physicians to record the train of 
medical events leading directly to the patient’s death. Part II contains 
one line for physicians to record any “other significant conditions: 
conditions contributing to death, but not related to cause.” For this 
study, men were classified as dying from prostate cancer if any of the 
lines on Part I of the death certificate mentioned prostate cancer.

The results of our study are presented in Fig. 3. Few men (4–7%) 
with Gleason 2–4 tumors identified by prostate biopsy had progres-
sion leading to death from prostate cancer within 15 yr of diagnosis. 
A majority of the younger men are still alive, but they face the 
possibility of death from prostate cancer in the future. In contrast, 
most of the older men with Gleason 2–4 tumors identified by biopsy 
at diagnosis have died from competing medical hazards rather than 
prostate cancer.

Compared with men with well-differentiated tumors, men with 
Gleason 5 and 6 tumors identified by prostate biopsy experienced 
a somewhat higher risk of death from prostate cancer when man-
aged expectantly (6–11% and 18–30%, respectively). Of the 
younger men with Gleason 5 and 6 tumors, more than half are still 
alive after 15 yr, whereas a majority of the older men have died from 
competing medical hazards.

Men with Gleason scores 7 and 8–10 tumors identified by prostate 
biochemistry experienced a very high rate of death from prostate cancer regardless of their age at diagnosis (42–70% and 60–87%, respectively). 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.
Fig. 3. Survival (white lower band) and cumulative mortality from prostate cancer (dark gray upper band) and other causes (light gray middle band) up to 15 yr after diagnosis stratified by age at diagnosis and Gleason score. The percentage of men alive can be read from the left-hand scale, and the percentage of men who have died from prostate cancer or from other causes during this interval can be read from the right-hand scale. [From Albertsen PC, Hanley JA, Gleason DF, Barry MJ (1998) Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. JAMA 280:975–980, with permission. Copyrighted 1998, American Medical Association.]
Our data are remarkably consistent with those reported by Gleason, Johansson et al., Chodak et al. and Lu-Yao et al. After 15 yr, men diagnosed with low-grade disease (Gleason score 2–4) have a small risk of dying from prostate cancer. Men with moderate-grade disease (Gleason score 5–6) have a slightly higher risk of dying from prostate cancer, whereas men with high-grade disease (Gleason score 7–10) have a substantial risk of dying from their disease when managed expectantly.

The Aus Study

In 1995, Aus et al. published an article that appeared to contradict these findings (17). These investigators assembled a group of 514 Swedish men who died during the period 1988–1990. All of these men were alive at the time of diagnosis and received only noncurative therapy. Prostate cancer was diagnosed by fine-needle aspiration in 359 cases, by examination of surgical specimens in 128, by needle biopsy in 19, and by clinical findings in 14. The stage of disease was assigned retrospectively. Patients received either primary endocrine therapy (324) or deferred treatment (185). Cause of death was determined by consensus by two urologists after reviewing the medical records and the death certificates. The main outcome of the study was the cause of death among patients with disease who died during a 3 yr interval. Of the 514 patients studied, 108 (21%) had no evidence of metastatic disease, 296 (58%) had metastatic disease, and 110 (21%) had inadequate staging to determine their clinical status. Of the 301 patients without evidence of metastatic disease, 50% died of prostate cancer.

Unlike traditional population-based studies that accrue patients based on the date of their diagnosis, Aus et al. accrued patients on their date of death. By sampling only men who had died, the authors assembled a study cohort that was enriched by men who had moderately or poorly differentiated disease. The distribution of men by histology was 24%, 38%, and 35%, respectively, for men with well-differentiated, moderately and poorly differentiated cancers. In Johansson’s study, this distribution was approx 33%, 48%, and 19%, respectively; in Lu-Yao’s study, this distribution was 32%, 50%, and 18%, respectively; and in our study, this distribution was 33%, 56% and 10%, respectively. The 10% of patients with Gleason 8–10 tumors in our series accounted for 25% of the cancer deaths, and the 19% of men with poorly differentiated cancers in Johansson’s series accounted for 36% of the cancer deaths. Because their accrual methodology yielded a significantly higher percentage of men with poorly differentiated disease, the estimates by Aus et al. of 15-yr mortality from prostate cancer are much higher than those
reported by Gleason, Johansson, Chodak, Lu-Yao, and us. All five of these studies are in agreement that men with poorly differentiated prostate cancers have a high probability of dying from their disease when managed conservatively.

**THE SIGNIFICANCE OF VOLUME AS ASSESSED BY SERUM PROSTATE SPECIFIC ANTIGEN**

The volume of prostate cancer at the time of diagnosis is the other key variable that consistently predicts long-term clinical outcomes. Prior to the advent of testing for prostate specific antigen, clinicians relied on the digital rectal examination (DRE) and imaging studies such as the bone scan and computerized tomography (CT) to assess the extent of disease. The advent of testing for PSA has enabled clinicians to identify disease much earlier than previously imagined.

McNeal and colleagues have demonstrated that tumors less than 0.5 cc frequently occur in older men, but rarely extend beyond the confines of the prostate. Tumors greater than 3.0 cc often demonstrate seminal vesicle invasion and loss of normal histology features. Tumors that are 6.0 cc or larger are rarely curable even with aggressive management. In a large autopsy series, McNeal and colleagues showed that only tumors containing poorly differentiated histology features, specifically patterns 4 and/or 5, grow to sufficient size to metastasize (18).

Stamey et al. have shown that many prostate cancers grow at a very slow rate (19). Half of all prostate cancers take more than 5 yr to double in size, as compared with breast cancers, which can double in size every 3 mo. Most men over age 50 yr with prostate cancers smaller than 0.5 cc at the time of diagnosis will not live long enough for their cancers to achieve sufficient size to metastasize. Most clinicians now utilize a standard sextant biopsy technique to evaluate men who are suspected of having prostate cancer. Stamey has determined that patients with one or more cores containing more than 3 mm of tumor are likely to have a prostate volume greater than 0.5 cc (20).

Although serum PSA levels are not sufficiently reliable to predict tumor burden for individual patients, serum PSA levels do correlate with tumor volume when evaluating large groups of men. In a classic analysis of over 10,000 men aged 50 yr and older participating in a screening program for prostate cancer, Catalona et al. reported that only 45% of men with a PSA score greater than 10 ng/mL had disease localized to the prostate (21). Recently, Partin et al. combined information provided by serum PSA level, Gleason score, and clinical stage to gen-
erate a series of nomograms to predict local tumor extension and capsule penetration (22).

The Carter Study

One of the early studies that contributed to our understanding of the natural progression of prostate cancer as measured by a rising PSA is the report by Carter et al. that evaluated longitudinal changes of PSA in men with and without prostate cancer (23). They performed a case-control study utilizing men participating in the Baltimore Longitudinal Study of Aging (BLSA). Although the sample size was small, consisting of only 18 men with prostate cancer, 20 men with benign prostate hyperplasia and 16 controls, the authors suggested that the rate of change of PSA was an early clinical marker of the development of prostate cancer.

Thirty-seven men with the diagnosis of prostate cancer were identified from 1459 male participants in the BLSA. Of these patients, 18 were older than age 60 yr and had participated in the study for at least 7 yr prior to the diagnosis of cancer. Patients were classified as having local, regional or metastatic disease based on the clinical examination, prostatic acid phosphatase determination, bone scan results, and pathology reports from the treating physician’s records. Sixteen subjects had no prior history of prostate disease and were selected as controls. Patients identified as controls were recruited between January 1990 and October 1990 when approximately 200 men returned for their routine visits. Serum samples available in the BLSA serum bank were tested for serum PSA. Unfortunately, serum samples were not available for all subjects for each visit.

A mixed-effects regression model was used to test the hypothesis that, after controlling for the effect of age at diagnosis, PSA values increase faster in subjects with prostate cancer compared with controls. Observed PSA levels are shown for each patient as a function of years prior to diagnosis for subjects with prostate cancer (Fig. 4). The patients with prostate cancer had significantly greater rates of change in PSA levels when compared with those patients without prostate cancer up to 10 yr before diagnosis. The graphs also demonstrate the variable progression of disease. Some patients with local or regional disease at diagnosis had an elevated serum PSA as much as 8 yr prior to diagnosis. Among patients presenting with metastatic disease, one patient had an elevated serum PSA level 16 yr prior to diagnosis. Unfortunately no information was provided concerning the Gleason score of the patients with prostate cancer who were included in the study.
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The Gann Study

In 1995, Gann and colleagues published a nested case-control study of men participating in the Physician’s Health Study (PHS), an ongoing randomized trial of β-carotene that enrolled 22,071 men aged 40–84 yr in 1982 (24). Their purpose was to evaluate the validity of using PSA to screen for prostate cancer. A total of 366 men diagnosed with prostate cancer were matched to three controls by age. Controls were randomly selected from the entire cohort at risk at the time of case diagnosis. Gann reviewed the medical records of each case to determine the stage at diagnosis, tumor grade, Gleason score, type of presentation (screening vs symptoms), and the PSA level just prior to treatment. If multiple tissue samples were available for evaluation, the highest Gleason score was recorded. Patients with regional or distant extension of their disease and all patients with Gleason scores of 7 or higher were classified as having aggressive cancers. Patients with pathologically determined localized disease and Gleason score 6 or less were classified as having nonaggressive cancers. The remaining patients who could not be staged pathologically and who had Gleason score 6 tumors or less were classified as having indeterminate aggressiveness. The mean age at baseline for both case patients and control patients was 62.9 yr and the mean age at prostate cancer diagnosis was 68.7 yr.

Fig. 5 presents the distributions of lead times for fatal cancers and all cancers that were detectable by the baseline PSA level at a cutoff of 4 ng/mL. On average, the diagnosis of prostate cancer was advanced 5.5 yr compared with the time of diagnosis in the pre-PSA era. This potential gain in lead-time was based on a single-screening PSA mea-
measurement and most likely underestimates the potential gain achieved by periodic screening. Lead-time distributions for aggressive cancers (those with regional or distant extension of Gleason scores of 7–10) were similar to those of nonaggressive cancers (those with local extension only and a Gleason score of 6 or less).

THE HISTORY OF PROSTATE CANCER FOLLOWING DIAGNOSIS AND TREATMENT WITH RADICAL SURGERY

Determining the efficacy of therapeutic interventions for prostate cancer is notoriously difficult. Utilizing data from two case-series analyses and two population-based studies, an attempt has been made to estimate the 10-yr disease-specific survival of men diagnosed with prostate cancer in the PSA era. Because PSA testing has introduced a lead time of at least 5 yr and possibly longer, the estimates provided in Figs. 2 and 3 are likely to be conservative. Unfortunately, these estimates do not account for several known and unknown selection biases that can impact the construct of any case series. Despite these concerns, some cautious comparisons are possible if attempts are made to match patients by known risk factors such as clinical stage and Gleason score.

Gerber et al. published a multi-institutional pooled analysis of men with clinically localized prostate cancer treated by radical prostatectomy between 1970 and 1993 (25). They reported excellent 10-yr disease-specific survival estimates of 94%, 80%, and 77% for men with well-differentiated (Gleason 2–4), moderately differentiated (Gleason

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**Fig. 5.** Percent of tumors that theoretically could have been detected at earlier time than the actual diagnosis by prostate cancer screening using prostate specific antigen. (Data derived from ref. 24.)
5–7) and poorly differentiated (Gleason 8–10) disease. Lu-Yao and Yao estimated 10-yr disease specific survival rates for men undergoing radical prostatectomy to be 94%, 87%, and 67% for men with well-differentiated, moderately differentiated and poorly differentiated disease, respectively (14). A review of these data initially suggests that radical prostatectomy is most efficacious among men with well differentiated disease and least efficacious among men with poorly differentiated disease (Fig. 2).

When compared to the retrospective, population-based sample of 767 men diagnosed with localized disease in Connecticut during the same time period, we found that the 10-yr disease-specific survival for men treated expectantly was 94%, 71%, and 30% for men with well-differentiated, moderately differentiated and poorly differentiated disease (15). Lu-Yao and Yao estimated the 10-yr disease specific survival for expectant management to be 94%, 77%, and 45%. These results are identical to those reported by Gerber et al. for men with well-differentiated disease, suggesting that expectant management achieves comparable results when compared with radical prostatectomy for this subset of men. Conversely, results were much worse for men with poorly differentiated disease receiving expectant management, suggesting a potentially significant advantage following surgery among men with poorly differentiated disease. These findings may be the result of selection biases, but the data suggest that expectant management is clearly not the optimal strategy for men with poorly differentiated cancers.

For men with Gleason 5–7 tumors, the group of men most frequently targeted for aggressive intervention, disease-specific survival outcomes do not appear to be dramatically different. Gerber reported a 10-yr disease-specific survival of 80% (95% confidence interval of 74–85%) following radical prostatectomy. Data from Lu-Yao and Yao estimates a 10-yr disease-specific survival of 77% (95% confidence interval of 74–80%) and our analysis suggests a 10-yr disease-specific survival of 72% (95% confidence interval of 67–76%) for men managed expectantly. Because of the significant selection biases inherent to all three study groups and the inadequate staging of many patients managed expectantly, it is difficult to determine the relative efficacy of surgery over expectant management for this group of patients.

Lu-Yao and colleagues also addressed this question from a different perspective (26). Using Medicare claims, they estimated the need for secondary cancer therapy among a group of Medicare patients diagnosed with prostate cancer during the period January 1, 1985 through December 31, 1991 and undergoing radical prostatectomy before December 31,
Patients were considered to have had additional cancer therapy if they had radiation therapy, orchiectomy, and/or androgen-deprivation therapy by injection after radical prostatectomy. The interval between the initial treatment and any follow-up treatment was calculated from the date of radical prostatectomy to the first day of the follow-up cancer therapy. The study population consisted of 3494 Medicare patients, 3173 of whom underwent radical prostatectomy within 3 mo of cancer diagnosis.

A review of the surgical pathology reports suggested that less than 60% of patients whose records were included in the study had organ-confined disease. Overall, the 5-yr cumulative incidence of having any additional cancer treatment after a radical prostatectomy was 35%. For patients with organ-confined disease, the group most likely to benefit from surgery, the 5-yr cumulative incidence of the need for additional cancer therapy was 24% and ranged from 16% for men with well-differentiated disease to 42% for men with poorly differentiated disease. Men with disease extending beyond the prostate capsule at the time of surgery had a much higher probability of needing additional treatment. Approximately 68% of men with poorly differentiated disease and extracapsular extension required additional cancer treatment within 5 yr of prostatectomy. For men at the greatest risk of disease progression, more than half required additional cancer therapy within 5 yr of undergoing a radical prostatectomy. These patients clearly need more effective therapies.

**SUMMARY**

Prostate cancer is a complex disease with an extraordinarily variable clinical outcome. The natural history of this disease is best predicted by its histology as measured by the Gleason scoring system. Based on information provided by randomized trials, population-based studies, and case-series analyses, it appears that prostate cancer will inevitably progress to systemic disease and death if given sufficient amount of time. The competing risk analysis presented in Fig. 3 provides patients and clinicians with estimates of disease progression given a patient’s age and tumor histology at the time of diagnosis. These estimates are conservative and do not incorporate the lead time introduced by PSA testing. The advent of screening for prostate cancer using serum PSA has advanced the date of diagnosis for most patients diagnosed in the contemporary era. The leadtime provided by PSA testing appears to be at least 5 yr and is similar for men with well-differentiated disease and poorly differentiated disease.

The impact of treatment on the natural history of prostate cancer is uncertain and is best assessed through randomized clinical trials.
Although case-series and population-based analyses suggest excellent outcomes for men with well-differentiated disease regardless of treatment, it is unclear how much aggressive intervention alters the natural history of this disease for men with moderately differentiated disease. Men at high risk of dying from prostate cancer are those men diagnosed with Gleason score 7–10 tumors. These men have a 10-fold increased risk of dying from prostate cancer in the absence of treatment. How much aggressive intervention alters outcomes for these men remains to be determined.

By carefully documenting clinical outcomes and precisely stratifying patients by Gleason score and tumor volume assessed using PSA measurements, clinicians and patients can obtain greater insights concerning how best to manage this complex disease. Ideally, such studies will lead to more carefully designed clinical trials. Until then, we are haunted by the words of the late Willet Whitmore who ended his manuscript on the natural history of prostate cancer with the following comment:

_Only with better methods for defining the natural history of the particular tumor, more sophisticated means for anticipating life expectancy of the individual host, and good data on the effects of various treatments on the quality and quantity of survival in patients with appropriately stratified tumors will it be possible to inject more science into the extant art of treatment of the prostatic cancer patient and substitute an era of cold fact for the present era of heated opinion._ (27)

Although written over 25 yr ago, these words summarize the continued debate concerning the appropriate management of clinically localized prostate cancer.

**REFERENCES**


Prostate Cancer Screening
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