Chapter 2

THE NATURAL HISTORY OF PROSTATE CANCER

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Abstract: Although prostate cancer is the most common solid tumor among American men, it is not a leading cause of cancer death. In fact, the majority of men diagnosed with this malignancy do not ultimately die of their disease. While this may be due in part to effective therapies, it is also likely due to the fact that many prostate cancers are indolent in nature, taking many years to present with clinical manifestations, if at all. The goal of this chapter is to review the literature on the natural history of untreated prostate cancer and to identify factors predictive of clinical significant disease. We begin by reviewing the influence of pathologic differentiation, clinical stage and tumor volume on the natural history of prostate cancer. We then discuss how underlying patients characteristics, such as age and co-morbidity influence outcomes in this disease. By reviewing the effect of these factors on the natural history of prostate cancer, the reader will obtain a better understanding of this malignancy and will be able to improve outcomes in men affected by this common condition.

Key words: prostate cancer, natural history, epidemiology

In 2004, 230,000 new cases of prostate cancer were identified in the United States making this disease the most common solid tumor of men. Despite the high incidence of disease in the U.S., only 30,000 men will die of prostate cancer this year (1). While this may be due, at least in part, to effective management of early prostate cancer, there is little doubt that many newly diagnosed cases are indolent in nature and require no treatment. Many patients are likely to die with, rather than of, prostate cancer. This is particularly true of older men who present with localized disease that can often take decades to metastasize (2).

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Once prostate cancer metastasizes, the natural history of the disease is ominous. Patients presenting with symptomatic metastases to bone respond to hormone ablation therapy for an average of only 2 years (3). The disease then progresses to its hormone-insensitive stage with most patients surviving only a matter of months (4). Clearly, one of the great challenges facing both clinicians and researchers is to identify which patients with prostate cancer have aggressive, clinically significant prostate cancer with metastatic potential and which patients have indolent tumors which are unlikely to become problematic during the patient's lifetime.

In contemporary practice, a majority of patients with prostate cancer present with localized disease (5). Understanding which of these malignancies will ultimately become "clinically significant" permits more selective application of aggressive therapy, with a subsequent reduction in morbidity experienced by prostate cancer patients and an improved quality of life. To appreciate which tumors will impact clinical outcomes, known biologic characteristics of the tumor, including tumor volume (as evidenced by baseline prostate-specific antigen (PSA) levels), pathologic differentiation (as measured by Gleason score) and stage at presentation, must be balanced against underlying host factors (such as age and co-morbid conditions.) The goal of this chapter is to review the existing literature on the natural history of untreated prostate cancer and to identify which factors are predictive of clinically significant disease. By providing the reader with a better understanding of the relationship between tumor characteristics, underlying host factors and clinical outcomes, clinicians and researchers alike will understand better the natural history of prostate cancer, which hopefully will lead to improved clinical care and properly constructed, risk-adjusted research.

1. TUMOR CHARACTERISTICS THAT AFFECT THE NATURAL HISTORY OF PROSTATE CANCER

1.1 Influence of Histologic Differentiation on Natural History

Clearly, not all prostate cancers are "equal". Some tumors have considerably greater biologic potential for local and/or distant progression than others. The degree of histologic differentiation, or pathologic grade, is an important variable that is clearly associated with the malignant potential of the tumor. Prior to the publication of the Gleason grading system as part of the Veterans Administration Cooperative Urological Research Group's

(VACURG) clinical trials of the 1960's and 70's, many pathologists found it difficult to classify pathologic differentiation in adenocarcinoma of the prostate. As part of the VACURG trials, Dr. Gleason classified prostate cancer specimens from 270 men enrolled in VA cooperative trials. After reviewing the pathology of each of these tumors, he developed a relatively simple scoring system for grading pathologic differentiation (6). Not surprisingly, patients with higher grade prostate cancer were more likely to present with advanced disease (7). However, patients with higher primary Gleason score (more poorly differentiated prostate cancers) were also more likely to die of prostate cancer at both 6 and 30 months following diagnosis (see Table 1). This finding underscores the fact that histological differentiation of the tumor impacts natural history in men with prostate cancer.

Gleason updated his grading system in 1974 using the 1032 cases enrolled in the VACURG trials nationally that had prostate tissue available for review (8). When considering the results of this study, readers should remember that the trials included men who were randomized to various treatments for prostate cancer according to one of four protocols. They included: 1) radical prostatectomy vs. radical prostatectomy and 5 mg of diethylstilbesterol (DES) per day for localized disease; 2) radical prostatectomy versus no therapy for men with localized disease; 3) placebo vs. 5 mg DES/day vs. orchiectomy alone vs. orchiectomy and 5 mg of DES/day for regional or

Table 1. The relationship of Gleason pathologic score and survival in 270 men diagnosed with prostate cancer in the pre-PSA era. Results from Bailer et al. (7)

	6 month outcome			30 month outcome		
Pathologic pattern	**N**	**Total deaths (%)**	**Prostate-cancer specific deaths (%)**	**N**	**Total deaths (%)**	**Prostate-cancer specific deaths (%)**
Primary						
1	30	1 (3)	0 (0)	16	1 (6)	0 (0)
2	89	4 (4)	0 (0)	57	10 (18)	2 (4)
3	121	8 (7)	4 (3)	71	17 (24)	9 (13)
4	10	1 (10)	1 (10)	6	2 (33)	2 (33)
5	20	5 (25)	2 (10)	12	9 (75)	6 (50)
Secondary						
1	9	0 (0)	0 (0)	4	0 (0)	0 (0)
2	57	1 (2)	0 (0)	36	3 (8)	1 (3)
3	152	11 (7)	3 (2)	89	24 (27)	10 (11)
4	20	3 (15)	0 (0)	12	3 (25)	1 (8)
5	32	4 (13)	4 (13)	21	9 (43)	7 (33)

metastatic disease or; 4) 1 mg DES/day vs. 2.5 mg of estrogen/day vs. 30 mg of progesterone/day alone vs. 30 mg progesterone and 5 mg DES/day for regional or metastatic disease. Despite the differing treatments, one can draw reasonable conclusions regarding the impact of histological differentiation on the natural history of prostate cancer in these patients. The VACURG investigators did this by calculating number of deaths per patient-year of follow-up. This variable was derived by taking the number of deaths and dividing by the sum of follow-up times for all patients for whom tissue was available. The results are presented in Figure 1. Unlike Gleason's prior work, where he had identified both primary and secondary pathologic patterns within a tumor, in this report he combined two scores into a single sum on a scale from 2 to 10, with higher scores being more poorly differentiated disease. As the data indicate, men with more poorly differentiated prostate cancer (Gleason sum 8–10) are more likely to die of their disease than men with well-differentiated disease (Gleason sum 2–5).

Others have also noted the strong influence of histology on the natural history of prostate cancer. In particular, Johansson et al. (9–11) have studied both 10 and 15 year survival rates in a population-based cohort of men with early, untreated localized prostate cancer. From a group of 648 consecutive men who were diagnosed with prostate cancer at Orebro Medical Center from March 1977 through February 1984, they identified 223 with localized disease who did not receive any initial treatment. Overall ten and fifteen year survival was 41% and 21%, respectively. Importantly, 10 and 15 year prostate cancer-specific survival (corrected for causes of death other than prostate cancer) was much higher, 86 and 81% respectively. When

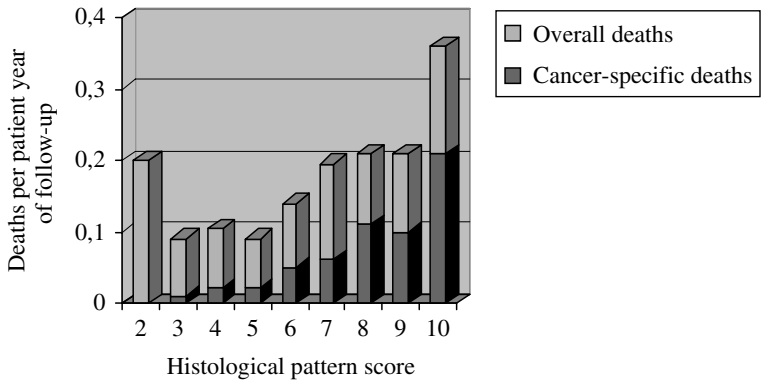

Figure 1. Deaths per patient year follow-up in the VACURG trials stratified by Gleason pathologic sum. Data from Gleason et al. (8).

stratified by histologic grade, men with poorly differentiated prostate cancer were more likely to develop metastases and to die from prostate cancer, as demonstrated in Table 2.

While the results from this study illustrated the relationship between histology and the natural history of localized prostate cancer, the authors' final conclusion that "patients with localized prostate cancer have a favorable outlook following watchful waiting, and that the number of deaths potentially avoidable by radical initial treatment is limited"(11) generated considerable controversy. In particular, critics noted that the study cohort was primarily comprised of men with well-differentiated prostate cancer (148 out of 223, presumably with Gleason grade 2–5/6 disease). This does not reflect current diagnostic trends in the United States, where most men present with moderately differentiated (Gleason 5–7) prostate cancer(12). Furthermore, critics of the Johansson studies note that the advanced age of patients at diagnosis (62% were over the age of 70) limits the number of years they are at risk for disease progression or prostate cancer-specific death. In other words, the patients never had a chance to experience problems from their prostate cancer because they had such a short life expectancy at entry into the cohort. In support of this, Aus et al. (13) from Goteborg, Sweden, used the Swedish Cancer Registry to identify all men with prostate cancer who died in Goteborg of any cause between 1988 and 1990. A cohort of 536 men, selected for younger, healthier men with higher grade disease, was initially identified, from which 14 cases were excluded because they were diagnosed at autopsy, 6 because they were treated with curative intent and 2 because they were lost to follow-up. Of the remaining 514 patients, 301 (59%) had non-metastatic disease at the time of presentation. In this group of patients, the longer a subject survived after diagnosis, the more likely he was to die of prostate cancer. For men who survived 0–5 years

Table 2. Fifteen year local and metastatic progression rates and prostate-cancer specific deaths in 223 men with localized prostate cancer treated expectantly in Orebro, Sweden. Data from Johansson et al. (11)

Pathologic differentiation	**Total number of patients**	**Number with local progression (%)**	**Number with metastatic progression (%)**	**Number who died from prostate cancer (%)**
Highly (grade I)	148	37 (25)	2 (8)	9 (6)
Moderately (grade II)	66	33 (50)	2 (18)	11 (17)
Poorly (grade III)	9	3 (33)	6 (67)	5 (56)

after diagnosis, the risk of prostate cancer death was 39%. This increased to 54% for men who survived 5–10 years after diagnosis, 57% for those who survived 10–15 years, 71% for those who survived 15–20 years and 71% for those who survived more than 20 years. The Aus study calls into question the generalizability of the Johansson data to younger and healthier men diagnosed with localized prostate cancer. In addition, it supports the observation that histology impacts natural history, as men with poorly differentiated prostate cancer were still more likely to die of their disease (risk of prostate cancer-related death was 43% for men with well-differentiated disease, 48% with moderately differentiated disease and 60% for men with poorly differentiated disease.)

More recently, Lu-Yao and Yao (14) studied a group of 59,876 American men aged 50–79 years diagnosed with localized prostate cancer from 1983 through 1992. This population-based cohort was identified using the Surveillance, Epidemiology and End Results (SEER) dataset maintained by the National Cancer Institute (NCI). In this cohort, 19,898 (33.2%) initially received conservative management. Within the group of watchful waiting patients, 9804 (49%) had histologically well-differentiated disease, 6198 (31%) had moderately differentiated disease, 2236 (11%) had poorly differentiated disease, and 9% had cancer of unknown pathologic grade. Patients initially managed with watchful waiting tended to be older than men receiving radical prostatectomy (mean age at diagnosis: 70.7 vs. 65.8 years respectively). Mean follow-up was 44.5 months with 10% of patients followed for 92 months or longer. An intention-to-treat analysis was performed and 10-year overall and disease-specific survival rates were calculated utilizing annual mortality rates. Ten-year prostate cancer-specific survival in all 19,898 men with localized prostate cancer electing conservative management was 82%. However, stratifying the results by pathologic grade illustrates the importance of this variable in predicting the natural history of this disease. In men with well-differentiated disease, 10 year prostate cancer-specific survival was 93%; in moderately differentiated disease, it was 77%; and in poorly differentiated disease, it dropped to 45%. Lu-Yao and Yao (14) clearly demonstrate that pathologic grade is an important predictor of the natural history of localized prostate cancer.

1.2 Influence of Stage on Natural History

While there is little debate that men who present with metastatic disease have a worse prognosis than those who present with localized disease, the impact of tumor volume in localized prostate cancer patients is less clear. In a controversial meta-analysis of 6 non-randomized studies examining

survival in men with localized prostate cancer who elected conservative management, Chodak et al. (15) used proportional hazards analysis to examine the independent effect of grade, stage and age on disease-specific survival. Like the prior studies (one of which (10) was included in the meta-analysis), higher pathologic grade was a strong predictor of worse survival in the multivariable analysis. Ten-year disease specific survival was 87% for both men with well-differentiated (Grade 1) and moderately differentiated (Grade 2) prostate cancer, while men with poorly differentiated (Grade 3) disease had a ten-year survival of only 34%. In the Cox regression, which controlled for age, study cohort and stage at presentation, men with Grade 2 disease were 1.64 times more likely to die of prostate cancer than men with grade 1 disease, although this did not quite reach statistical significance ($p = 0.08$). However, men with Grade 3 disease were 10 times more likely to die of prostate cancer than men with Grade 1 disease and this relationship was highly statistically significant ($p < 0.001$).

While the results from the Chodak meta-analysis concerning pathologic grade are fairly conclusive, the data regarding stage at presentation are considerably less clear. The cohorts included in the study were all accrued prior to the introduction and use of prostate-specific antigen as a screening test. Therefore, most of the patients were detected either at the time of transurethral resection of the prostate (TURP) or by palpable disease on digital rectal exam. Stage at presentation was categorized using a combination of the 1992 AJCC TNM Staging System,(16) the Jewitt-Whitmore system(17) and the Chisholm system.(18) Of the 828 subjects in the meta-analysis, 19% had Stage A1 disease, 26% had A2 disease, 12% had B1 disease, 42% had B2 or B3 disease, while stage was unknown in the remaining 1%. In the Cox regression analysis, Stage A1 was chosen as the referent category. When controlling for age, grade and study cohort, there was a trend towards higher stage cancer being associated with increased prostate cancer-specific mortality, but this did not reach statistical significance (risk ratios: $A2 = 1.38$, $B1 = 1.77$, and $B2/3 = 2.38$ when compared to men with A1 disease). The unreliability of digital rectal examination or transurethral resection of the prostate as staging tests that adequately quantify overall tumor volume may explain why tumor stage is not a more powerful predictor of overall mortality.

1.3 Influence of Tumor Volume, as Evidenced by Serum PSA Levels, on Natural History

Prior studies have shown that serum PSA levels can serve as reasonable proxies for tumor volume, at least in the aggregate. Catalona et al. (19)

collected data on 10,251 men aged 50 years or older who participated in a community screening program for prostate cancer. In patients with PSA levels above 10 ng/ml, only 45% had disease localized to the prostate, indicating that PSA may be a proxy marker for tumor volume. If tumor volume reflects the natural history of prostate cancer, it follows that PSA at the time of diagnosis may also reflect the natural history of this disease. Although there are no studies looking specifically at this issue in men treated with expectant management, there are a number of reports that document this relationship in men treated with aggressive therapy. For example, Kupelian et al. (20) studied a cohort of 423 patients treated with radical prostatectomy for presumably localized prostate cancer at a single institution. Five year biochemical recurrence-free survival was 88% in men with a preoperative PSA of less than or equal to 4 ng/ml, 62% in men who presented with a PSA from 4–10 ng/ml, 48% for men who presented with a PSA between 10–20 ng/ml and 31% for those who presented with a PSA greater than 20 ng/ml. In fact, in the multivariable analysis of the same dataset, baseline PSA was the strongest predictor of 5-year recurrence-free survival, although baseline Gleason score and surgical margin status were also found to be significant predictors of outcomes. D'Amico and colleagues (21) also found baseline PSA to be an important predictor of biochemical recurrence in a proportional hazards analysis of 688 men undergoing radical prostatectomy at a single institution. They later confirmed these findings in a larger group of patients that included 468 men undergoing radiotherapy for localized disease, demonstrating that baseline PSA is a predictor of outcomes in localized prostate cancer (22).

Researchers have also suggested that longitudinal changes in PSA may be useful in identifying men who have occult prostate cancer. Carter et al. (23) performed a case-control study using serum from men participating in the Baltimore Longitudinal Study of Aging. The study consisted of 16 men with no prostate cancer (controls), 20 men with a histological diagnosis of benign prostatic hyperplasia (BPH) and 18 men over age 60 with pathologically confirmed prostate cancer who had participated in the study for at least 7 years prior to diagnosis. Patients were classified as having local, regional or distant disease on the basis of clinical examination, prostatic acid phosphatase levels, bone scan results and information from the treating physician's medical records. While there was serum available from subjects on several occasions, this was not collected at each visit and, therefore, the number and interval of PSA measurements was not standardized. 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. Mean PSA levels

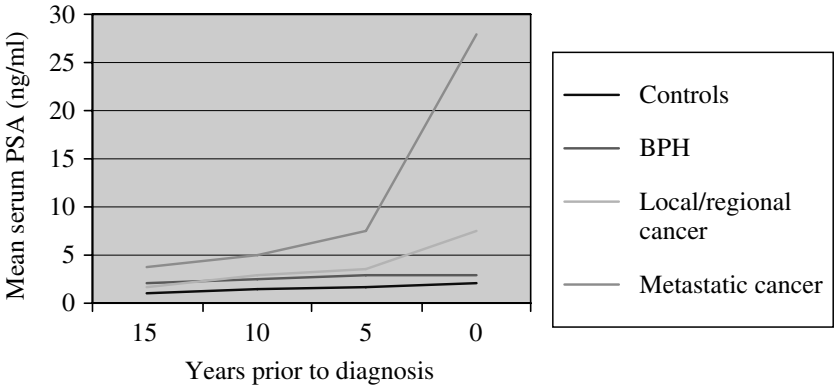

Figure 2. Mean prostate-specific antigen levels of 44 men from the Baltimore Longitudinal Study of Aging with either no prostate cancer, benign prostatic hyperplasia or prostate cancer at 5 year interval prior to diagnosis. (Data from Carter et al. (23)).

for the various groups of patients in the study are presented graphically in Figure 2. Patients with prostate cancer had significantly higher rates of change of PSA than those without prostate cancer up to 10 years prior to diagnosis. Rates of change in serum PSA also helped distinguish between men with localized and metastatic prostate cancer, as shown in Figure 2. Although the study did not provide information regarding Gleason score, it does demonstrate that patients with prostate cancer have elevated serum PSA levels well before the diagnosis of prostate cancer and that the rate of change of PSA may be helpful in identifying men with more advanced disease.

The studies described above summarize the available evidence on the influence of various tumor characteristics, such as pathologic differentiation, clinical stage at presentation and tumor volume on the natural history of localized prostate cancer. There is little doubt that as our comprehension of the genetic mechanisms involved in prostate cancer development and growth improves, we will identify additional markers of more aggressive disease that will be useful in understanding the natural history of prostate cancer. Any advances in our understanding of prostate cancer tumor biology, however, must be framed against the underlying host characteristics of the patient. As life expectancies of men with the most aggressive prostate cancers are often still measured in years, as opposed to months, other factors, such as age at diagnosis and co-morbid conditions must be considered when counseling patients on the natural history of their disease.

2. HOST CHARACTERISTICS THAT AFFECT THE NATURAL HISTORY OF PROSTATE CANCER

2.1 Influence of Age on Natural History

There is some debate regarding the independent impact of age on outcomes in prostate cancer. Some authors feel that younger age is associated with more aggressive disease (24), while others do not (25). When assessing non-randomized cohort studies of men with localized prostate cancer who elect conservative management, age is often an important predictor of survival, due at least in part to the selected nature of observational cohorts of men choosing watchful waiting. In particular, selection bias may be present in two forms: first, elderly men (>75 years) with short life expectancies (less then 10 years) are often counseled by their providers to choose conservative management, as many providers feel aggressive therapy should be reserved for men with longer life expectancies. Alternatively, younger men (<60 years) who elect watchful waiting tend to have significant co-morbid disease which makes them more likely to die of other conditions and impacts any analysis of the natural history of localized disease in this population. This observation underscores the importance of controlling for both age and co-morbid conditions when assessing the impact of treatment on outcomes in prostate cancer.

To address this issue, Albertsen et al. (2) studied 767 men diagnosed with clinically localized prostate cancer between 1971 and 1984 who were managed expectantly. Using the Connecticut Tumor Registry to identify patients eligible for inclusion in this population-base study, the authors limited their analysis to men aged 55 to 74 years at the time of diagnosis. They obtained original histology specimens and reanalyzed these slides using contemporary Gleason grading criteria. They then stratified their cohort by both age at diagnosis and Gleason grade. Using both the Connecticut tumor registry and the vital statistics bureau of the Department of Public Health, long-term disease-specific and overall survival information was collected. The mean follow-up of the cohort from diagnosis to death was 8.6 years. 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. Cause of death was determined using death certificate data according to accepted algorithms for assessing this outcome from these data.

The results of the stratified survival analysis are shown in Figure 3. These data underscore the importance of considering both tumor factors

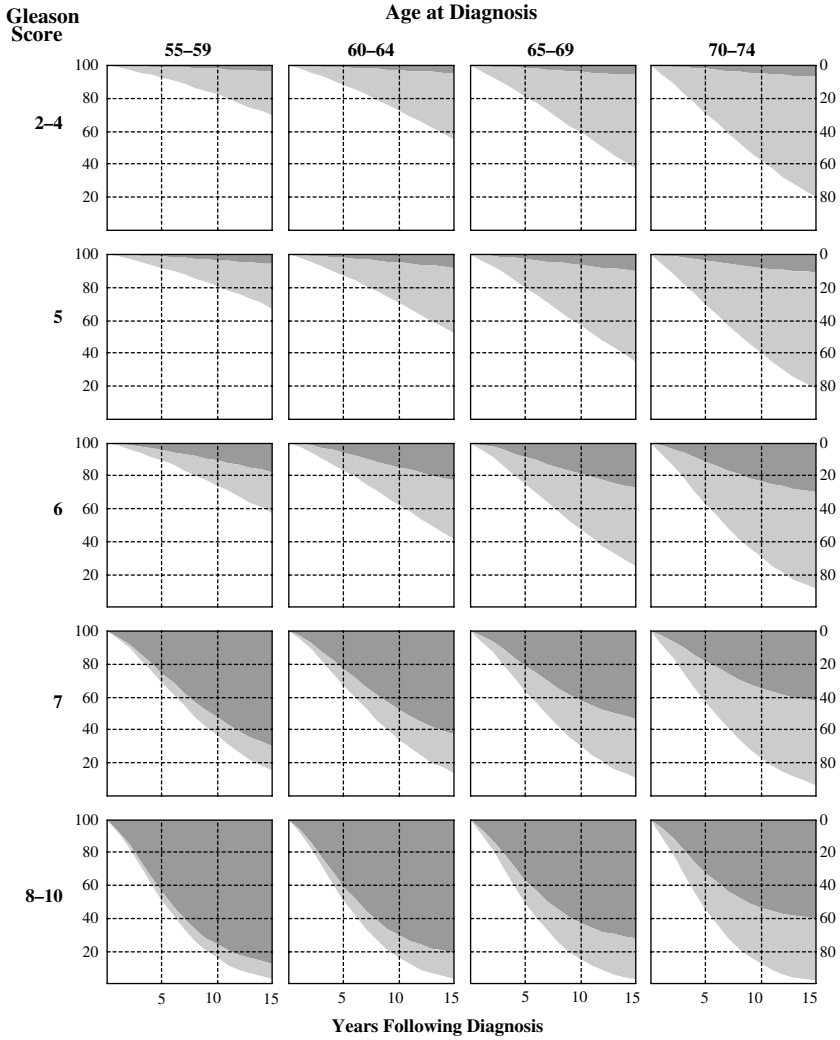

Figure 3. Survival (white lower band) and cumulative mortality from prostate cancer (dark gray upper band) and all other causes (light gray middle band) up to 15 years following diagnosis stratified by age at diagnosis and Gleason score. The percentage of men alive can be read from y-axis on the left, and the percentage of men who have died of prostate cancer or other causes can be read from the y-axis on the right. (From Albertsen et al. (2) with permission. Copyrighted 1998, American Medical Association).

(histological grade) and host characteristics (age at diagnosis) when studying the natural history of localized prostate cancer.

Patients with low-grade disease (Gleason 2–4) were unlikely to die of prostate cancer within 15 years of diagnosis. Older men (age 70–75) with low-grade disease had an approximately 20% overall survival at 15 years due to deaths from competing causes. If one is to counsel a patient regarding his probability of dying from localized prostate cancer, these data underscore that both the Gleason score of the tumor and the age of the patient must be considered. Men with high grade disease (Gleason 8–10) experienced high prostate-cancer specific mortality within 15 years of diagnosis, regardless of their age at diagnosis, underscoring the very aggressive nature of poorly differentiated prostate cancer.

The results from Albertsen and colleagues' research are remarkably consistent with the studies mentioned earlier (10, 14, 15). After 15 years, men diagnosed with low-grade disease (Gleason 2–4) have a small risk of dying from prostate cancer. Men with moderate-grade disease (Gleason 5–6) have a slightly higher risk of dying from their disease, while those with high-grade disease (Gleason 7–10) have a substantial risk of dying from prostate cancer if managed conservatively.

2.2 Influence of Co-Morbid Conditions on Outcomes

The number of co-morbid conditions a patient has at the time of diagnosis also affects outcomes in prostate cancer. Patients may be more likely to die of a competing condition than die of prostate cancer. It follows that, if a patient has another illness that significantly limits his life expectancy, he may be a better candidate for expectant management. The natural history of indolent prostate cancer will be clinically irrelevant. To this end, a number of researchers have examined the impact of co-morbidity on outcomes in prostate cancer.

Albertsen et al. (26) studied the impact of co-morbidity on life expectancy in men with prostate cancer using three well-known, validated co-morbidity indexes. They used the Connecticut tumor registry to identify men aged 65 to 75 years old diagnosed with prostate cancer between 1971 and 1976 at one of the 39 hospitals in the state. Four hundred and fifty-one men were included in the cohort with a mean age of 70.9 years and mean follow-up of 15.5 years. Information on Gleason score, clinical stage at presentation, current vital status and cause of death was obtained from hospital medical records and from the Connecticut Tumor Registry. In the univariate analysis, Gleason score was still the best single independent predictor of age-adjusted survival. However, all three co-morbidity indexes were also predictive of

survival in this cohort. In a multivariate analysis, the combination of Gleason score and co-morbidity index score was more predictive than Gleason score, age or clinical stage alone, demonstrating the importance of assessing co-morbid conditions when considering the natural history of prostate cancer.

Given the fact that host factors, such as age and co-morbid condition, can affect outcomes in prostate cancer as much as tumor characteristics, researchers must develop methods of incorporating this information into prognostic systems to help clinicians understand the clinical significance of newly diagnosed disease. Although there are many nomograms available that predict proxy outcomes, such as biochemical-free survival (27, 28) or pathological outcomes following surgery (29), there are few that prognosticate overall or disease-specific survival. Clemens et al. (30) developed such a system in 1986, prior to the introduction of PSA. Using a cohort of 230 men diagnosed with prostate cancer at a single institution in the late 1970's, they employed a statistical method called conjunctive consolidation to develop a staging system that stratified patients using conventional anatomic staging (Jewitt/VACURG score), age, urinary and systemic symptoms and co-morbidity. Although the system did not incorporate Gleason score, it was still able to identify patients who were more likely to survive at least 5 years following diagnosis of prostate cancer. The staging system calculated a score from 0-10 with worse scores predicting poorer prognosis. Men with scores from 0–2, 3–5, 6, and 7–10, had a five-year survival of 91%, 61%, 31% and 9% respectively. Although this "clinical-anatomic" staging system is now somewhat outdated, given the introduction of PSA testing and the importance of Gleason score as a predictor of outcomes, it still demonstrates the importance of using information regarding both the tumor and the host to improve our understanding of the natural history of prostate cancer.

3. SUMMARY

Prostate cancer is a heterogeneous disease that is influenced by a number of variables. Clearly, the best predictor of its natural history is histological differentiation, commonly measured using the Gleason scoring system. However, this is not sufficient when counseling patients with newly diagnosed disease. Stage at presentation and serum PSA must also be considered when assessing the metastatic potential of any prostate tumor. Given the fact that all prostate cancers will eventually progress to systemic disease and death if given sufficient time, it is important to consider host factors when treating men with newly diagnosed prostate cancer or conducting epidemiological studies. The impact of age at diagnosis and

concurrent illnesses should not be underestimated. Only by incorporating information on all of these variables will we obtain a better understanding of the natural history of prostate cancer and improve outcomes in men affected by this common disease.

REFERENCES

1. Jemal A, Tiwari RC, Murray T, Ghafoor A, Samuels A, Ward E *et al*. Cancer statistics, 2004. Cancer J Clin 2004, 54:8–29.
2. Albertsen PC, Hanley JA, Gleason DF, Barry MJ. Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. J Am Med Assoc 1998, 280:975–80.
3. Jacobi GH. LH-RH agonist monotherapy in patients with carcinoma of the prostate and reflections on the so-called total androgen blockade. Recent results. Cancer Res 1990, 118:174–85.
4. Beynon LL, Chisholm GD. The stable state is not an objective response in hormone-escaped carcinoma of prostate. Br J Urol 1984, 56:702–5.
5. Stephenson RF. Population-based prostate cancer trends in the PSA era: Data from the SEER program. Monogr Urol 1998, 91:1–19.
6. Gleason DF. Classification of prostatic carcinomas. Cancer Chemother Rep 1966, 50:125–8.
7. Bailar JC, 3rd, Mellinger GT, Gleason DF. Survival rates of patients with prostatic cancer, tumor stage, and differentiation–preliminary report. Cancer Chemother Rep 1966, 50:129–36.
8. Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. J Urol 1974, 111:58–64.
9. Johansson JE, Adami HO, Andersson SO, Bergstrom R, Krusemo UB, Kraaz W. Natural history of localised prostatic cancer. A population-based study in 223 untreated patients. Lancet 1989, 1:799–803.
10. Johansson JE, Adami HO, Andersson SO, Bergstrom R, Holmberg L, Krusemo UB. High 10-year survival rate in patients with early, untreated prostatic cancer. J Am Med Assoc 1992, 267:2191–6.
11. Johansson JE, Holmberg L, Johansson S, Bergstrom R, Adami HO. Fifteen-year survival in prostate cancer. A prospective, population-based study in sweden. J Am Med Assoc 1997, 277:467–71.
12. Stephenson RA, Stanford JL. Population-based prostate cancer trends in the united states: Patterns of change in the era of prostate-specific antigen. World J Urol 1997, 15:331–5.
13. Aus G, Hugosson J, Norlen L. Long-term survival and mortality in prostate cancer treated with noncurative intent. J Urol 1995, 154:460–5.
14. Lu-Yao GL, Yao SL. Population-based study of long-term survival in patients with clinically localised prostate cancer [see comments]. Lancet 1997, 349:906–10.
15. Chodak GW, Thisted RA, Gerber GS, Johansson JE, Adolfsson J, Jones GW *et al*. Results of conservative management of clinically localized prostate cancer. N Engl J Med 1994, 330:242–8.
16. Schroder FH, Hermanek P, Denis L, Fair WR, Gospodarowicz MK, Pavone-Macaluso M. The TNM classification of prostate cancer. Prostate Suppl 1992, 4:129–38.

17. Whitmore WF Jr. Natural history and staging of prostate cancer. Urol Clin North Am 1984, 11:205–20.
18. Chisholm GD. Treatment of advanced cancer of the prostate. Semin Surg Oncol 1985, 1:38–55.
19. Catalona WJ, Smith DS, Ratliff TL, Basler JW. Detection of organ-confined prostate cancer is increased through prostate-specific antigen-based screening. J Am Med Assoc 1993, 270:948–54.
20. Kupelian PA, Katcher J, Levin HS, Klein EA. Stage T1-2 prostate cancer: A multivariate analysis of factors affecting biochemical and clinical failures after radical prostatectomy. Int J Radiat Oncol Biol Phys 1997, 37:1043–52.
21. AV DA, Whittington R, Schultz D, Malkowicz SB, Tomaszewski JE, Wein A. Outcome based staging for clinically localized adenocarcinoma of the prostate. J Urol 1997, 158:1422–6.
22. AV DA, Desjardin A, Chung A, Chen MH, Schultz D, Whittington R *et al*. Assessment of outcome prediction models for patients with localized prostate carcinoma managed with radical prostatectomy or external beam radiation therapy. Cancer 1998, 82:1887–96.
23. Carter HB, Pearson JD, Metter EJ, Brant LJ, Chan DW, Andres R *et al*. Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease [see comments]. J Am Med Assoc 1992, 267:2215–0.
24. Gronberg H, Damber JE, Jonsson H, Lenner P. Patient age as a prognostic factor in prostate cancer. J Urol 1994, 152:892–5.
25. Neulander EZ, Duncan RC, Tiguert R, Posey JT, Soloway MS. Deferred treatment of localized prostate cancer in the elderly: The impact of the age and stage at the time of diagnosis on the treatment decision. BJU Int 2000, 85:699–704.
26. Albertsen PC, Fryback DG, Storer BE, Kolon TF, Fine J. The impact of co-morbidity on life expectancy among men with localized prostate cancer [see comments]. J Urol 1996, 156:127–32.
27. Kattan MW, Eastham JA, Stapleton AM, Wheeler TM, Scardino PT. A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. J Natl Cancer Inst 1998, 90:766–71.
28. Kattan MW, Wheeler TM, Scardino PT. Postoperative nomogram for disease recurrence after radical prostatectomy for prostate cancer. J Clin Oncol 1999, 17:1499–507.
29. Partin AW, Kattan MW, Subong EN, Walsh PC, Wojno KJ, Oesterling JE *et al*. Combination of prostate-specific antigen, clinical stage, and gleason score to predict pathological stage of localized prostate cancer. A multi-institutional update [see comments] [published erratum appears in J Am Med Assoc 1997 9;278:118]. J Am Med Assoc 1997, 277:1445–51.
30. Clemens JD, Feinstein AR, Holabird N, Cartwright S. A new clinical-anatomic staging system for evaluating prognosis and treatment of prostatic cancer. J Chronic Dis 1986, 39:913–28.