Journal of Cellular Biochemistry, Supplement 16H:20-25 (1992)

The Natural History of Adenocarcinoma of the Prostate

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Abstract All analyses of the efficacy of therapy for prostate cancer must control for the natural history of the disease. Over the past years, several long-term series involving several hundred patients have helped to describe the results of untreated disease. In general, most patients will not die of their disease, although approximately half of the patients will develop disease progression within 10 years. Predictors of progression include tumor stage, grade, and ploidy status.

Key Words: *expectant management, natural history, prostate cancer*

To properly understand the many facets of carcinoma of the prostate, the clinician must understand one of the most confusing aspects of the disease: its natural history. In this discussion, the natural history of prostate cancer will be presented through a published series of untreated patients. Additionally, predictors of biologic activity will be discussed.

The necessity of understanding the natural history of carcinoma of the prostate is clear to the student of this disease and the clinician who treats many patients with prostate cancer. In Figures 1 and 2, several different behaviors of prostate cancer have been postulated. Figure 1 hypothesizes various growth rates of the disease for disease onset or for disease inception at various times prior to the patient's "natural" death. Curves "A" and "B" hypothesize a slow growth rate of the tumor; "A" patients may spend their lives in ignorance of the tumor's existence. Curve "B" patients may or may not develop symptoms of their disease but die of other causes prior to the development of metastatic disease. Figure 2 demonstrates that the expected survival of these two groups of patients would be identical to the normal population, since survival is not affected by the presence of disease. Group "C" patients, on the other hand, have tumors that increase in volume and in extent over time as illustrated in Figure 1. As these patients will expire due to their disease before an otherwise "natural" death, the surviv-

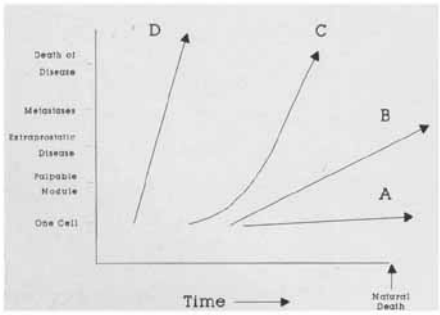

Fig. 1. Various possible behaviors of carcinoma of the prostate.

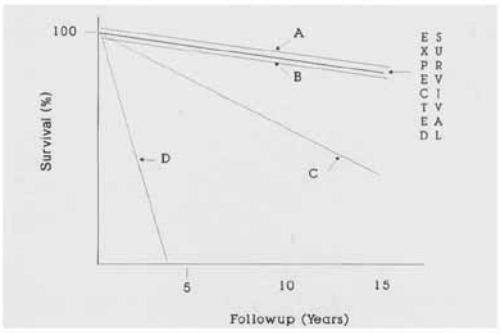

Fig. 2. Survival curves of patients with tumors with growth characteristics from Fig. 1.

al curve would be affected as shown in Figure 2. Finally, Group "D" patients would experience an even more rapid demise due to the existence of the tumor.

These four types reflect the natural history of prostate cancer in the U.S. population and have a tremendous impact upon clinical decision-making and public health policies. The first impact is upon selection of treatment options: if prostate cancer always behaves as curve "C" in Figure 1, then the conclusion can be made that treatment is universally necessary. However, if the disease behaves more like curve "A" or "B," treatment is unnecessary. The variable mix of patients with these types of tumors would change treatment decisions accordingly.

Another area of importance affected by natural history is the issue of early tumor detection. If it can be concluded that prostate cancer generally follows curve "C" as illustrated in Figure 1, the relatively long period of time between a palpable tumor and the development of extraprostatic disease would support early detection efforts in preventing death from the disease. However, if most patients followed curves "A" or "B," early detection would be unnecessary. Similarly, if most patients who die of their disease follow curve "D," the extremely short period between the time when the tumor is detectable and the development of extraprostatic disease may make early detection impossible.

These hypothetical examples illustrate the critical importance of the natural history of prostate cancer in all aspects of disease management. The natural history can be determined by a number of methods. One such method, advocated by some, has been to analyze a series of patients treated for the disease. Unfortunately, this method has two significant biases: (1) it is impossible in patients treated for prostate cancer to determine the degree to which survival was affected by the treatment and to what extent it was affected by the disease's natural history; and (2) patients selected for treatment are rarely a representative sampling of all patients with the disease.

A second method of analyzing the "normal" behavior of prostate cancer is to deduce this behavior through epidemiologic data. Although there are serious biases to this method, some valid conclusions can be reached. A final method to determine the natural history of this disease is to analyze patients with prostate cancer who were not treated for their disease. In this treatise, the last of these methods of analysis will be employed in an attempt to best characterize how this enigmatic disease "behaves."

EXPERIENCES WITH UNTREATED DISEASE

Perhaps the best evidence available for the "behavior" of prostate cancer comes from a series of patients who received no treatment for their disease. Data from the first half of the 20th century are probably not representative of results obtained today. As examples, Nesbit and Plumb in 1946 [1], reporting on 795 patients treated prior to the endocrine era, found the median time from diagnosis to death to be 12.8 months in patients without evidence of metastatic disease. Similarly, Hanash *et al.* [2] found that five-, 10-, and 15-year survivals for patients with clinical stage B disease were 19%, 4%, and 1%, respectively, while the expected survivals were 71%, 45%, and 25%.

More recent series have found considerable improvement in survival compared to earlier series. The explanation for this improved survival is almost certainly not due to an improvement in treatment (as no treatment is given) but due to improved staging—the so-called "Stage Migration Phenomenon." With better methods to detect metastatic disease, primarily radionuclide bone scanning, patients who were previously thought to have localized disease have been removed from analysis. Thus the current series of patients followed conservatively for localized prostate cancer better reflect the natural history of this disease.

Eight series of patients with localized prostate cancer who were treated conservatively (*i.e.*, not treated for "cure") are worthy of analysis. The first of these series was reported in 1968 by Cook and Watson [3]. The authors followed 20 men with presumed B1 nodules for periods of one to 11 years, with a mean followup of 5 years. Although five patients (25%) died of prostate cancer, 14 additional patients (70%) died of other causes including heart disease, cerebrovascular accidents, accidents, and infections. Although the 10-year survival was only 20%, the cancer-specific survival at 10 years was 52%.

Barnes *et al.* [4] published a series of reports on a group of patients with untreated carcinoma of the prostate, culminating with his 1976 report. In this series of 115 patients with stage B disease, none received treatment for cure of the disease (*e.g.*, radical prostatectomy or external beam radiotherapy) although a proportion of patients underwent hormonal therapy for disease progression or transurethral resection of the prostate for obstructive symptoms. Although a significant number of patients developed disease progression during followup (up to 85% by 15 years), the five-, 10-, and 15-year survivals of 71%, 58%, and 28%, respectively, were dramatically better than those from the series of Nesbit and Plumb [1] or Hanash [2].

In 1987, Moskovitz [5] presented his series of 101 untreated patients from Haifa, Israel. The stages of these patients ranged from $T0_b$ to T3, and 21.8% had high-grade disease. Five-year survivals for stages $T0_b$, T1+T2, and T3 were 91.3%, 60.61%, and 41.67%, respectively. High-grade and high-stage tumors generally had the poorest prognosis.

In 1988, Madsen *et al.* [6] reported on the 15-year followup of 142 patients with stages A and B carcinoma of the prostate who were randomized to receive either radical prostatectomy and placebo, or placebo only. A serious problem with the comparison was the lack of prerandomization bone scans, but the results relative to the disease's natural history are illuminating. For patients with stage B disease, those receiving radical prostatectomy actually had a reduced survival compared to placebo, although there was not a statistically significant difference detected. Overall, five-, 10-, and 15-year survivals were 85%, 59%, and 39%, respectively.

George in 1988 [7] reported a series of 120 patients who had histologic evidence of prostate cancer with negative bone scans, and were followed while receiving no treatment for cure. Tumor progression was noted in 84% of patients but symptoms of progression occurred in only a small proportion of patients. Local progression in these 100 patients led to disease treatment in 23, and only one of these 23 developed metastases. Bony metastases developed in 11% of patients at a mean followup time of 36 months. A total of 5 patients (4%) died due to prostate cancer while 48 (40%) died of other causes (other malignancies, cardiovascular disease, etc.).

Probably the only population-based study of the natural history of untreated, localized prostate cancer is that of Johansson *et al.* from 1989 [8]. From a referral area of about 195,000 patients, 223 patients with localized prostate cancer (negative bone scan) were followed for a mean period of 78 months. Sixty-five patients (29%) developed disease progression and two-thirds of these developed extraprostatic disease. The five- and 10-year overall survivals of 68% and 51% are quite impressive but most interesting are the authors' calculations of five-year "corrected survival," *i.e.*, the percent of patients who died due to prostate cancer at five years. For stages T1 and T2, the corrected survival was 92.4%. Most of the deaths due to prostate cancer occurred in patients with high-grade disease.

A similar series from Stockholm and Linkoping, Sweden was published in 1991 [9]. Adolfsson and Carstensen summarized their experience with 61 patients, all of whom were less than 70 years old and had stage T1-T2NXMO prostate cancer. No patient with high-grade disease was included in their analysis. Over a mean observation period of 96 months, local progression occurred in 69% of patients; five- and 10-year progression rates were 49% and 72%, respectively. Only nine patients developed metastatic disease during the observation period and eight patients died: four due to prostate cancer and four of other diseases. The five- and 10-year cancer-specific survivals were 98% and 92%, respectively.

The most recent series of patients with prostate cancer who were followed conservatively is also the series with the longest followup. Of 4000 patients treated for prostate cancer at Memorial Sloan-Kettering Cancer Center, Whitmore *et al.* [10] identified 75 who were followed conservatively. Patients were classified as stage B1 (palpable nodule less than 2 cm in diameter confined to one lobe), B2 (palpable nodule greater than 2 cm in diameter confined to one lobe), or B3 (nodule involving both prostatic lobes). The median followup for these three groups of patients was 124, 120, and 96 months, respectively. During followup, five patients were treated definitively with iodine-125 implantation. Although the 15-year progres-

sion-free survivals for these three groups were 26%, 0%, and 0%, respectively, it is remarkable that 15-year actual survivals of 61%, 35%, and 65%, respectively, were realized.

Although it is statistically unsound to group patients from these varied series to definitively establish the behavior of untreated prostate cancer, such an analysis does provide a very general glimpse into the natural history of the disease. In Figure 3, such an analysis has been performed, weighing each series' results by the total number of patients at risk in each year of followup. Several very important conclusions can be reached, most of which are apparent in a number of the individual series. First, the risk of disease progression increases inexorably with time, with a median time to progression of approximately 10 years in the above series. It is obvious that the rate of progression may be dependent upon the definition of terms in each individual series. Overall survival is not significantly different from progression and, in the series above, most deaths were caused by disease processes other than carcinoma of the prostate. The median time to development of metastatic disease may be well beyond the 10-year mark, but the certainty of this value is questionable due to the small number of patients who developed metastatic disease in any series. Finally, the cancer-specific survival rate, dependent upon only three series encompassing only 201 patients, may be in the 80% range at 10 years of followup.

Any conclusions reached from the above data must be understood to be subject to question. Patient selection bias in most series make the extrapolation of data to the general population fraught with potentially large errors. However, to date, these represent the most valuable data available which characterize the natural history of untreated carcinoma of the prostate.

PREDICTORS OF BIOLOGIC ACTIVITY

Future studies of various interventions for carcinoma of the prostate will suffer from the uncertainty of the disease's natural history unless appropriate control groups are included for analysis. It is possible, however, to stratify risks of progression and death due to disease based upon several predictors of the disease's natural history. These predictors include tumor grade, tumor stage, and ploidy.

Grade of carcinoma of the prostate has long been acknowledged as a powerful predictor of ultimate outcome of treatment. Ritchie and associates [11] found that Gleason's Sum Score was very highly correlated with disease recur-

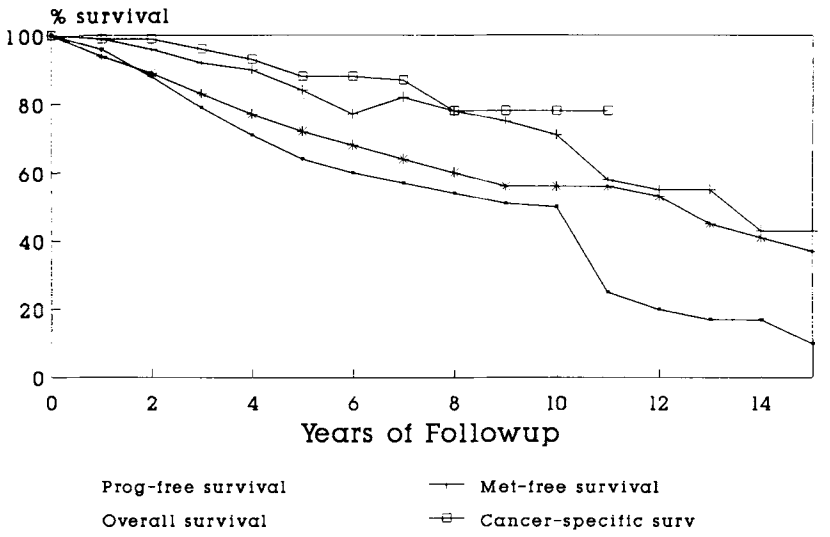

Fig. 3. Combined series of patients who received no therapy for cure of carcinoma of the prostate [3–10].

rence following radical prostatectomy. At 96 months followup, the risks of recurrence for Gleason scores <5, scores of 5, 6, and 7, and for scores >7 were 0%, 30%, and 55%, respectively. Similar results were found in several of the series of untreated patients. Moskovitz [5] found five-year survivals of 90%, 60%, and 42% for patients with $T0_b$, T1+T2, and T3 disease, respectively. Adolfsson [9] found five-year progression-free survivals of 55% and 25% for well- and moderately well-differentiated tumors, respectively [9]. Johansson's [8] experience was similar with five-year corrected survivals for Grade I, II, and III tumors of 98.8%, 90.9%, and 24.5%, respectively. Finally, Barnes [4] found five-, 10-, and 15-year survivals of 81%, 70%, and 42% for Grades I and II disease compared with 56%, 43%, and 19% for Grades III and IV disease [4].

Tumor stage is a well-established predictor of behavior of prostate cancer. However, in general, the series of patients who are untreated for prostate cancer demonstrate that it is less of a significant predictor than tumor grade. Although Johansson's series [8] found that the risk of prostate cancer death increased 216-fold with high-grade disease, no significant increase in risk of death due to disease was detected among stages T0, T1, and T2. Similarly, Adolfsson and Carstensen [9] found no difference in behavior between T1 and T2 tumors. Finally, Whitmore [10] found that risk of progression was virtually identical in stages B1 and B3 disease, both of which had a lower rate of distant progression than stage B2 disease. In general, however, the best survival was noted in patients with stage B1 disease.

A final, more recent predictor of the biologic activity of prostate cancer is ploidy status. The value of tumor ploidy has been well-established in patients treated for their disease; in general, diploid and tetraploid patients have the lowest risk of disease progression, with a marked increase in progression in patients with aneuploid disease [12]. The only series of patients with prostate cancer in whom ploidy analysis was established prior to entry into a program of conservative followup was that of Adolfsson *et al.* [13]. The authors found a significant divergence of progression curves with five-year progression-free survivals of 45% in diploid tumors and only 20% in non-diploid tumors.

SUMMARY

Prior to the 1980's, the natural history of adenocarcinoma of the prostate was, in general, poorly documented. Studies from the first half of the 20th century were not translatable into current thought due to significant differences in tumor staging. With the 1980's came the presentation of six significant series of patients with untreated disease. The analysis of these data suggests several conclusions. First, disease progression occurs in almost all patients who are left untreated. However, this equates only occasionally with metastatic disease and death due to prostate cancer since the majority of patients will expire of other causes. Patients with high-grade disease and those with aneuploid tumors seem to fare the worst with local tumor stage playing less of a role in prognosis.

A thorough understanding of the behavior of untreated prostate cancer is essential to the interpretation of studies employing varying treatments for this disease. In addition, as most patients will not die due to prostate cancer, future studies assessing prevention strategies for early-stage disease must reckon with the natural history confound. Only by proper study design, employing appropriately selected control populations, will conclusions regarding the efficacy of these prevention strategies be translatable to the general population.

REFERENCES

1. Nesbit RM, Plumb RT: Prostatic carcinoma. Surgery 20:263–272, 1946.
2. Hanash KA, Utz DC, Cook EN, Taylor WF, Titus JL: Carcinoma of the prostate: A fifteen year followup. J Urol 107:450–453, 1972.
3. Cook GB, Watson FR: Twenty single nodules of prostate cancer not treated by total prostatectomy. J Urol 100:672–674, 1968.
4. Barnes R, Hirst A, Rosenquist R: Early carcinoma of the prostate: Comparison of stages A and B. J Urol 115:404–405, 1976.
5. Moskovitz B, Nitecki S, Levin DR: Cancer of the prostate: Is there a need for aggressive treatment? Urology Int 42:49–52, 1987.
6. Madsen PO, Graversen PH, Gasser TC, Corle DK: Treatment of localized prostatic cancer. Radical prostatectomy versus placebo. A 15-year follow-up. Scand J Urol Nephrol (suppl.) 110:95–100, 1988.
7. George NJR: Natural history of localized prostatic cancer managed by conservative therapy alone. Lancet 1:494–497, 1988.

8. Johansson JE, Adami HO, Andersson SO, Bergstrom R, Krusemo UB, Kraaz W: Natural history of localized prostatic cancer. A population-based study in 223 untreated patients. Lancet 1:799–803, 1989.
9. Adolfsson J, Carstensen J: Natural course of clinically localized prostate adenocarcinoma in men less than 70 years old. J Urol 146:96–98, 1991.
10. Whitmore WF, Warner JA, Thompson IM: Expectant management of localized prostatic cancer. Cancer 67:1091–1096, 1991.
11. Ritchie AWS, Dorey F, Layfield LJ, Hannah J, Lovrekovich H, deKernion JB: Relationship of DNA content to conventional prognostic factors in clinically localized carcinoma of the prostate. Br J Urol 62:254–260, 1988.
12. Montgomery BT, Nativ O, Blute ML, Farrow GM, Myers RP, Zincke H, Thernedo TM, Lieber MM: Stage B prostate adenocarcinoma. Flow cytometric nuclear DNA ploidy analysis. Arch Surg 125:327–331, 1990.
13. Adolfsson J, Ronstrom L, Hedlund PO, Lowhagen T, Carstensen J, Triburait B: The prognostic value of modal deoxyribonucleic acid in low grade, low stage untreated prostate cancer. J Urol 14:1404–1407, 1990.