Natural History of Progression After PSA Elevation Following Radical Prostatectomy

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Context In men who develop an elevated serum prostate-specific antigen level (PSA) after having undergone a radical prostatectomy, the natural history of progression to distant metastases and death due to prostate cancer is unknown.

Objective To characterize the time course of disease progression in men with biochemical recurrence after radical prostatectomy.

Design A retrospective review of a large surgical series with median (SD) follow-up of 5.3 (3.7) years (range, 0.5-15 years) between April 1982 and April 1997.

Setting An urban academic tertiary referral institution.

Patients A total of 1997 men undergoing radical prostatectomy, by a single surgeon, for clinically localized prostate cancer. None received neoadjuvant therapy, and none had received adjuvant hormonal therapy prior to documented distant metastases.

Main Outcome Measures After surgery, men were followed up with PSA assays and digital rectal examinations every 3 months for the first year, semiannually for the second year, and annually thereafter. A detectable serum PSA level of at least 0.2 ng/mL was evidence of biochemical recurrence. Distant metastases were diagnosed by radionuclide bone scan, chest radiograph, or other body imaging, which was performed at the time of biochemical recurrence and annually thereafter.

Results The actuarial metastasis-free survival for all 1997 men was 82% (95% confidence interval, 76%-88%) at 15 years after surgery. Of the 1997 men, 315 (15%) developed biochemical PSA level elevation. Eleven of these underwent early hormone therapy after the recurrence and are not included in the study. Of the remaining 304 men, 103 (34%) developed metastatic disease within the study period. The median actuarial time to metastases was 8 years from the time of PSA level elevation. In survival analysis, time to biochemical progression ($P<.001$), Gleason score ($P<.001$), and PSA doubling time ($P<.001$) were predictive of the probability and time to the development of metastatic disease. An algorithm combining these parameters was constructed to stratify men into risk groups. Once men developed metastatic disease, the median actuarial time to death was 5 years. The time interval from surgery to the appearance of metastatic disease was predictive of time until death ($P<.02$).

Conclusions Several clinical parameters help predict the outcomes of men with PSA elevation after radical prostatectomy. These data may be useful in the design of clinical trials, the identification of men for enrollment into experimental protocols, and counseling men regarding the timing of administration of adjuvant therapies.

JAMA. 1999;281:1591-1597 www.jama.com

RADICAL PROSTATECTOMY provides excellent cancer control in most men with clinically localized disease. However, approximately 35% of men will experience a detectable serum prostate-specific antigen (PSA) elevation within 10 years following surgery.[1-5] At this early sign of biochemical recurrence, patients want to know what this means, whether they will survive, and if not, how long they will have to live. Cancer-specific and metastasis-free survival rates following radical prostatectomy have been reported.[2,6-10] However, until now, the time course of progression to distant metastases or death due to prostate cancer in men with biochemical failure following radical prostatectomy has not been documented. This report characterizes the natural history of the disease in these men. This analysis provides information to men and their physicians considering systemic therapy, even in the setting of minimal elevation of PSA levels. It provides additional background data that are lacking in the proper design of some clinical trials.

METHODS

A total of 1997 men had undergone radical prostatectomy for clinically localized prostate cancer by a single surgeon at The Johns Hopkins Hospital, Baltimore, Md, between April 1982 and April 1997. The Hybritech-Tandem R and E, San Diego, Calif, and the TOSOH PSA assays, (Hybritech/Beckman, San Francisco, Calif) were used at The Johns Hopkins Hospital. These assays have been demonstrated to be comparable in

See also pp 1598 and 1642.

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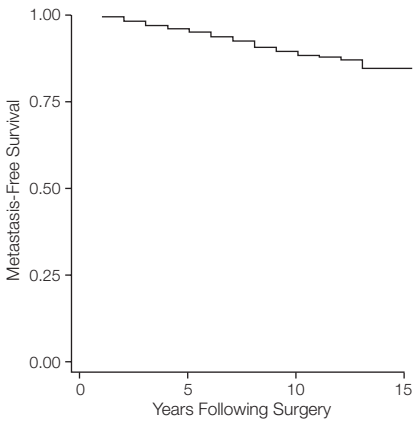
Table 1. Disease Characteristics in 1997 Men Before Undergoing Anatomical Radical Prostatectomy

Characteristic	No. (%) of Patients
TNM staging classification	
T1a	55 (2.8)
T1b	110 (5.5)
T1c	586 (29.3)
T2a	731 (36.6)
T2b	364 (18.2)
T2c	103 (5.2)
T3a	48 (2.4)
Total	**1997 (100)**
Serum prostate-specific antigen level, ng/mL	
0-4	487 (28.1)
4.1-10	824 (47.6)
10.1-20	326 (18.8)
≥20	96 (5.5)
Total	**1733 (100)**
Pathologic Gleason score	
2-4	59 (2.9)
5	380 (16.5)
6	728 (40.0)
7	655 (32.8)
8-10	155 (7.8)
Total	**1997 (100)**
Pathologic stage	
Organ confined	911 (45.6)
Capsular penetration with Gleason score <7	434 (21.7)
Capsular penetration with Gleason score ≥7	427 (21.4)
Involvement of seminal vesicles, negative lymph nodes	105 (5.3)
Involvement of pelvic lymph nodes	120 (6.0)
Total	**1997 (100)**

Figure 1. Actuarial Likelihood of Metastasis-Free Survival in 1997 Men Treated With Radical Prostatectomy



No man received early hormonal therapy prior to diagnosis of metastatic disease or symptomatic local recurrence.

intralaboratory testing. Other comparable PSA assays may have been used at referring institutions. Pathologic diagnosis of prostate cancer was based on examination of prostate tissue. Histologic grading was performed using the Gleason system for the prostatectomy specimen. No man received neoadjuvant radiation or hormonal therapy. The method of pathologic analysis at our institution has been described.[11] Tumors were determined to be organ-confined, to penetrate the prostatic capsule without extension to the seminal vesicles, to involve the seminal vesicles without nodal disease, or to involve the pelvic lymph nodes.

After the operation, men were followed up, either at our institution or by referring physicians, with serum PSA levels and digital rectal examinations performed every 3 months for the first year, semiannually for the second year, and yearly thereafter. Isolated biochemical PSA elevation was defined as a serum PSA level of at least 0.2 ng/mL, which represents a measurable value above the level of detection for this assay. Radionuclide bone scans were performed either at our institution or by the referring physicians at the time of biochemical recurrence and on a yearly basis thereafter unless performed earlier for symptoms suggestive of distant metastasis. A positive bone scan result or other radiographic or histologic (lymph node biopsy) evidence of distant failure was used for the diagnosis of distant metastases.

Thirteen men who had received immediate adjuvant radiation therapy based on pathologic features and 11 men who had received adjuvant hormonal therapy prior to the development of metastatic disease were not included in the analysis of progression after PSA elevation. Therefore, adjuvant hormonal therapy had no impact on either the time to biochemical progression or the time to distant metastasis in this analysis. Men with a PSA elevation following surgery who received postoperative radiation to the prostatic bed and demonstrated a biochemical response for longer than 24 months were considered to have local recurrences only and cured by the combination of surgery and radiation, and thus were not included in this analysis. Conversely, 83 (27%) of 304 men who had a PSA level elevation and had received adjuvant radiation without a sustained biochemical response (not cured by adjuvant radiation) were considered to harbor distant metastatic disease and were included in this analysis.

Some men with documented metastatic disease had received a variety of experimental therapies for androgen-insensitive disease. No form of systemic therapy substantially prolonged survival in men with hormone-resistant prostate cancer. These therapies were not considered to have had a significant effect on the length of survival after the development of metastatic disease.[12]

Serum PSA level increases above 0.2 ng/mL demonstrated an exponential growth curve similar to that originally reported by Patel et al.[13] By this manner, a correlation between the log of PSA levels and time was linear. Prostate-specific antigen doubling time (PSADT) was calculated by natural log of 2 (0.693) divided by the slope of the relationship between the log of PSA and time of PSA measurement for each patient. To determine the optimal PSADT cutoff for predicting metastatic disease progression for this cohort, several doubling-time calculation models were analyzed. Models that used all postoperative PSA values, only the first 2 values regardless of level,[13] only the first 2 values after a level of 0.2 ng/mL was reached, and all PSA values within a 2-, 3-, and 5-year period following a documented PSA elevation were analyzed by recursive partitioning to determine the optimal PSADT cutoff level. The method of recursive partitioning involved calculating PSADT based on the PSA values in all of the above models and using sequential values of PSADT provided by each model as a trial cutoff level to determine the optimal separation of men based on their risk of developing metastatic disease. The PSADT values that were less than 0 (stable, nonincreasing, or decreasing PSA levels) were assigned a value equal to 0. The PSADT values that were exceptionally long (eg, >100 months)

were assigned a value of 100 months for ease of calculations.

Patients who died were placed into 1 of 3 categories: dead with no evidence of disease (no previous history of a detectable PSA), dead with cancer (history of a detectable PSA, and elevated PSA with documented death due to another cause), and death due to cancer. Death due to prostate cancer was defined as death in any man with metastatic disease that showed any progression following treatment with hormonal therapy. No patient with metastatic disease died due to any cause other than prostate cancer and thus cancer-specific survival was the same as overall survival in men with metastatic disease for this series.

Statistical analyses were performed using the STATA 5.0 software package (Stata Corporation, College Station, Tex). Cox proportional hazards regression analysis was used to compare the models for calculating the PSADT. The PSADT method used was optimized to provide the best χ^2 P value with the most number of men with PSA data. Analyses of actuarial survival were performed as described by Kaplan and Meier.[14] Statistical significance of Kaplan-Meier actuarial survival curves was calculated using the Wilcoxon-Gehan statistic.

RESULTS

The clinical TNM stages, the range of preoperative PSA levels, prostatectomy Gleason scores, and the pathologic stages of all 1997 men are detailed in TABLE 1. These men have been followed up for a mean (SD) of 5.3 (3.7) years (range, 0.5-15 years). Seventeen percent (344/1997) have been followed up for 10 or more years. FIGURE 1 depicts the actuarial metastasis-free likelihood following surgery for all 1997 men with a 15-year metastasis-free likelihood of 82% (95% confidence interval [CI], 76%-88%). Actuarial cancer-specific survival at 10 and 15 years following surgery was 94% (95% CI, 92%-96%) and 91% (95% CI, 87%-94%), respectively.

Three hundred fifteen men (15%) have demonstrated biochemical recurrence. No man has experienced a distant or local recurrence with an undetectable serum PSA level. Eleven of these 315 men with biochemical recurrence underwent early hormonal therapy after PSA elevation and are not included in the analysis of progression to metastatic disease. TABLE 2 depicts the pathologic stage, Gleason score, follow-up, and year of PSA recurrence for the remaining 304 men.

Various models for determining PSADT were compared using a Cox proportional hazards regression model (TABLE 3). Use of all PSA values within 2 years of initial documented PSA level elevation provided the optimal combination of statistical significance and number of evaluable men for this group. The median PSADT for this group of men (n = 131) was 10 months. When used as a cutoff level for further comparison, a PSADT of greater than or less than 10 months provided the most statistically significant prediction ($P<.001$) of time to distant disease progression after PSA elevation.

The time from PSA elevation to the development of clinically evident metastasis is depicted by actuarial analysis in FIGURE 2. The significance of Gleason score on the risk of developing metastatic disease after PSA elevation is illustrated in FIGURE 3, A ($P<.001$). At the time of this report, of the 304 men with biochemical recurrence, 103 (34%) have developed distant metastases. The median actuarial time to development of metastases following PSA elevation was 8 years, and the 5-year metastasis-free rate was 63%. Figure 3, B demonstrates that the time to development of distant metastases was dependent on the time of the PSA elevation (≤2 or >2 years following surgery; $P<.001$). Figure 3, C demonstrates that a PSADT cutoff of 10 months predicted the likelihood of subsequent development of metastatic disease as well ($P<.001$). In men with Gleason score 6 or 7 tumors, substratification according to the presence of organ-confined disease or surgical margin status did not identify a subset of men with a significantly different time course to

Table 2. Pathologic Gleason Score, Pathologic Stage, and Follow-up in the 304 Men Who Had Demonstrated Prostate-Specific Antigen (PSA) Recurrence After Anatomical Radical Prostatectomy

Variable	No. (%) of Patients
Pathologic Gleason score	
5	15 (4.9)
6	41 (13.5)
7	151 (49.7)
8-10	97 (31.9)
Total	**304 (100)**
Pathologic stage	
Organ-confined	31 (10.2)
Capsular penetration with Gleason score ≤7	30 (9.9)
Capsular penetration with Gleason score ≥7	108 (35.5)
Involvement of seminal vesicles, negative lymph nodes	52 (17.1)
Involvement of pelvic lymph nodes	83 (27.3)
Total	**304 (100)**
Years of follow-up after surgery	
0-2	304 (100)
3-5	280 (92.1)
6-9	228 (75.0)
≥10	109 (35.9)
Year of PSA recurrence	
1-2	136 (44.7)
3-5	97 (31.9)
6-9	59 (19.4)
≥10	12 (4.0)
Total	**304 (100)**

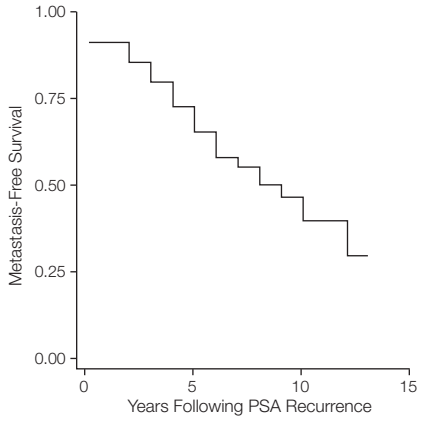
Table 3. Prostate-Specific Antigen Doubling Times and Calculation Methods*

Doubling Time Calculation	No. of Patients	Cox Regression Coefficient	95% Confidence Intervals	z	χ^2 P Value
All PSA values	228	−0.09	−0.11 to −0.05	−5.3	<.001
First 2 PSA values	212	−0.04	−0.06 to −0.02	−3.2	<.001
First 2 PSA values after 0.2 mg/mL	201	−0.03	−0.06 to −0.01	−2.6	.002
All PSA values within 2 y after recurrence	131	−0.06	−0.09 to −0.03	−3.3	<.001
All PSA values within 3 y after recurrence	91	−0.12	−0.17 to −0.07	−4.4	<.001
All PSA values within 5 y after recurrence	64	−0.04	−0.08 to −0.005	−1.7	.05

*PSA indicates prostate-specific antigen; z, the z statistic value from the Cox model; and 0.2 mg/mL, the PSA recurrence value. The Cox proportional hazards regression was used to test the predictive power of each doubling time calculation method. Time interval for the Cox regression was time from PSA recurrence to development of distant progression.

metastatic disease. When all 304 men were considered, pathologic stage stratified as organ-confined disease, capsular penetration with negative seminal vesicles and lymph nodes, or involvement of the seminal vesicles and/or pelvic lymph nodes was statistically significant in predicting time to metastatic disease (data not shown, $P = .01$).

Figure 2. Actuarial Likelihood of Metastasis-Free Survival in 304 Men With Prostate-Specific Antigen (PSA) Elevation After Radical Prostectomy



Times indicated are years from biochemical recurrence. None of the men received endocrine therapy prior to development of metastatic disease. None of the men received hormonal therapy prior to development of metastatic disease. Estimates are calculated at 3, 5, or 7 years from the time of the initial PSA elevation (metastatic disease free period), based on Gleason score in the surgical specimen, the time of initial biochemical recurrence (≤2 vs >2 years), and PSA doubling time (<10 vs ≥10 months).

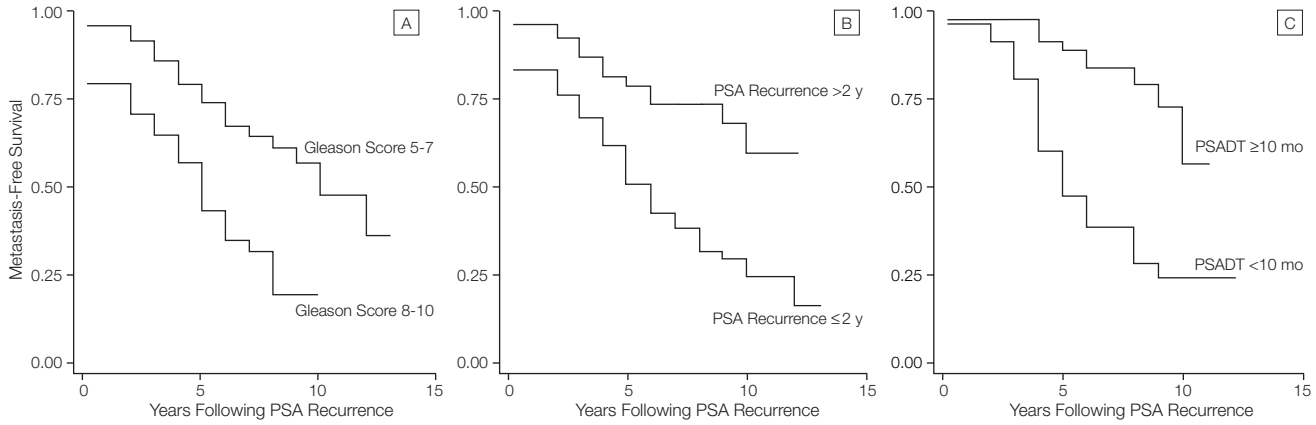
We constructed an algorithm (FIGURE 4) to predict a man's likelihood of developing metastatic disease within various periods following initial biochemical recurrence. Unfortunately, when pathologic stage was used to further subcategorize the algorithm in Figure 4, the number of men within each category was not sufficient to obtain reasonable 95% CIs, and pathologic stage was not included in the algorithm for this reason. Using the prostatectomy Gleason score, the time of initial biochemical recurrence (≤2 vs >2 years), and PSADT (<10 vs ≥10 months) for men with Gleason score of less than 8, we estimated a man's likelihood of remaining free of clinically evident metastatic disease over various times (3, 5, and 7 years) without additional therapeutic intervention. The PSADT was not a statistically significant predictor for men with a Gleason score of greater than 7 when time to PSA elevation was known. This may be due to small numbers of men within each subset and requires further investigation. The periods indicate years from biochemical recurrence as opposed to years from surgery.

Forty-four (43%) of the 103 men with metastatic disease died due to prostate cancer. Again, no man with metastatic disease died due to any cause other than prostate cancer. The actuarial median time to death after development of metastatic disease was slightly less than 5 years (FIGURE 5). The only variable that reliably separated men based on time to death was the length of time from surgery until diagnosis of metastatic disease. FIGURE 6 demonstrates a significant difference in the time to death after development of distant disease between those men who developed metastatic disease within 1 to 3, 4 to 7, and 8 to 15 years following surgery ($P = .02$). Median survival for men developing metastases within the first 3 years after surgery was approximately 4 years from the diagnosis of metastatic disease. For men developing metastases between 4 and 7 years following surgery, median survival was approximately 5 years, and the median survival has not been reached in men developing metastases at 8 or more years following surgery. Gleason score, time to biochemical recurrence, PSADT, and serum PSA levels at diagnosis of metastases did not significantly influence time until death.

COMMENT

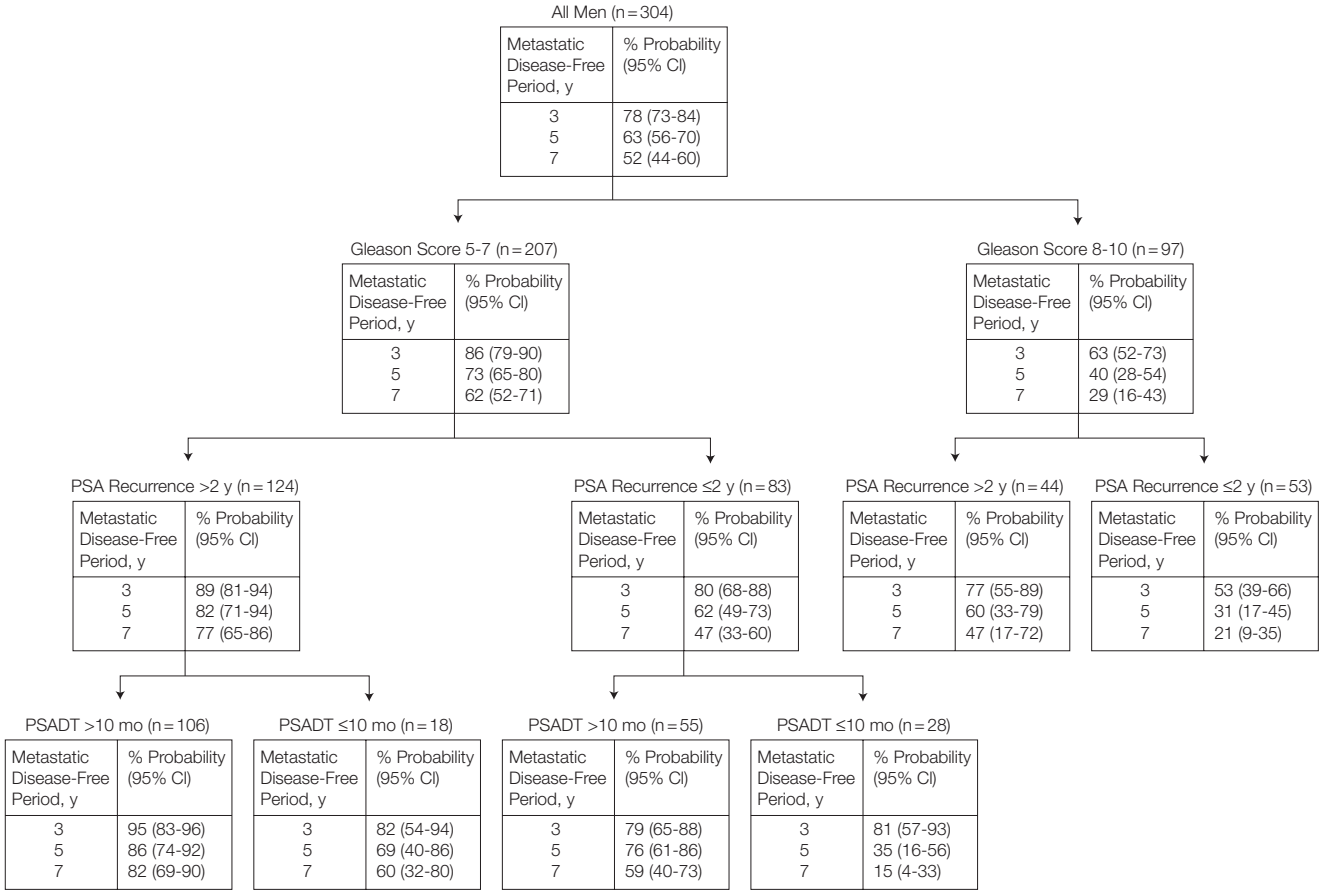
We are able to estimate a patient's probability of long-term cure after radical prostatectomy using pathologic stage as

Figure 3. Actuarial Likelihood of Metastasis-Free Survival in 304 Men With Prostate-Specific (PSA) Antigen Elevation After Radical Prostatectomy



A, Based on Gleason scores in the radical prostatectomy specimen ($P<.001$). B, Based on years until initial biochemical recurrence ($P<.001$). C, Based on prostate-specific antigen doubling time (PSADT) ($P<.001$).

Figure 4. Algorithm for Estimating a Man's Likelihood of Remaining Free of Metastatic Disease



Estimates are calculated at 3, 5, or 7 years from the time of the initial prostate-specific antigen (PSA) elevation (metastatic-disease free period, based on Gleason score in the surgical specimen, the time of initial biochemical recurrence (≤2 vs >2 years), and prostrate-specific antigen doubling time (PSADT) (<10 vs ≥10 months). CI indicates confidence interval.

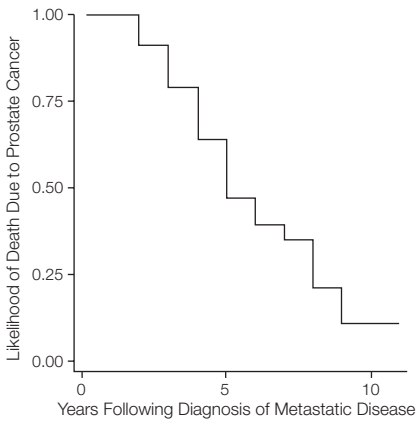
a surrogate end point. Both clinical and pathologic factors play a role in determining a patient's likelihood of having an undetectable serum PSA level at 10 to 15 years following surgery.[1-5] The most predictive of these factors include pretreatment PSA level, pathologic stage, and Gleason score; however, other microscopic features and biomarkers have also been suggested to identify patients at risk for failure following surgery.[1-5,15-17]

Between 27% and 53% of men undergoing radical prostatectomy will have a detectable serum PSA elevation within 10 years following surgery.[1-5] Until now, there have been no reliable data concerning the timing and natural history of disease progression for men with an isolated PSA level elevation after radical prostatectomy. These findings should allow physicians and patients to make educated decisions about the progression of disease and need for treatment and to facilitate the design of clinical trials.

Twenty-three percent of the men who demonstrated biochemical recurrence in our series had an undetectable serum PSA level for at least 5 years, and a small percentage (4%) had an undetectable level for 10 years prior to biochemical recurrence (Table 2). In other series, PSA progression has been rare in men with an undetectable PSA level for 5 to 6 years after surgery.[18] Our series demonstrates that with a larger number of patients and with yearly extended follow-up, men do continue to experience recurrence even 10 years and longer after surgery.

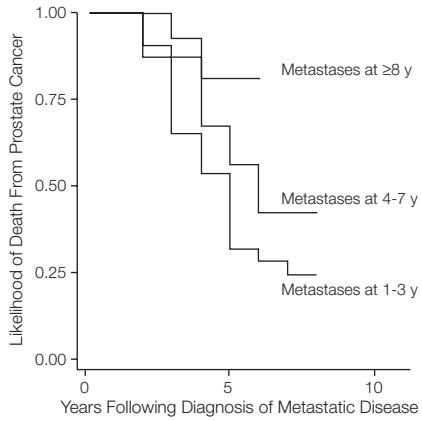
This analysis demonstrates that some men remain free of metastasis for an extended length of time after biochemi-

Figure 5. Actuarial Likelihood of Death Due to Prostate Cancer in 104 Men Diagnosed as Having Metastases After Radical Prostatectomy



The survival times indicated are years from the diagnosis of metastatic disease.

Figure 6. Actuarial Likelihood of Death Due to Prostate Cancer in 104 Men Diagnosed as Having Metastases After Radical Prostatectomy



Men are categorized according to the period after surgery in which the diagnosis of metastatic disease was made at 1 to 3 years, 4 to 7 years, or more than 8 years. The time of survival is indicated as years from diagnosis of metastatic disease.

cal recurrence. The median actuarial time from biochemical recurrence until progression to metastases was 5 years (mean, 8 years). The metastasis-free rate of 63% for all men at 5 years after biochemical progression is similar to the 60% to 75% progression-free rates at 5 years after surgery in men with lymph node–positive disease treated solely by radical prostatectomy.[19-21]

The risk of developing metastatic disease after biochemical recurrence was shown to correlate with pathologic Gleason scores. Men with tumors of Gleason scores less than 8 had a 73% chance of remaining free of progression at 5 years after biochemical recurrence compared with a 40% probability in men with higher grade tumors (Gleason score, 8-10). A similar correlation between risk of progression and tumor grade was also seen in men with lymph node–positive disease treated solely with radical prostatectomy.[20]

The length of time after surgery prior to biochemical recurrence was important in determining the risk of eventual distant failure for men with lower (5, 6, and 7) and men with high (8, 9, and 10) Gleason scores (Figure 4). A similar observation was made previously by Partin et al[22] in a report demonstrating that a high Gleason score and advanced pathologic stage were important in determining the likelihood of local or distant failure. Using a cutoff of 10 months, PSADT provided further substratification for men with a Gleason score of less than 8. Men with rapid PSA level elevation (<2 years), a Gleason score of 5 to 7, and a PSADT (>10 months) demonstrated a 76% probability of remaining free of metastatic disease for 5 years following initial PSA level elevation compared with men with a shorter PSADT (<10 months) who had only 35% chance of remaining free of metastatic disease for 5 years after biochemical recurrence. Although not as strong as Gleason score, time of biochemical recurrence, and PSADT, the pathologic stage did contribute to the likelihood of distant metastasis ($P = .01$). The PSADT has been suggested by Patel et al[13] as a useful predictor of the type of eventual recurrence after radical prostatectomy. They measured the PSADT for a group of 77 men with biochemical recurrence following radical retropubic prostatectomy and found that shorter PSADTs (<6 months) were more indicative of distant disease when compared with local recurrence.

The overall 10- and 15-year metastasis-free survival rates in the present report were 87% and 82%, respectively. Zincke et al[2] previously reported 10- and 15-year metastasis-free rates of 82% and 76% in more than 3000 men undergoing radical prostatectomy. In a multiinstitutional study, Gerber et al[6] reported 10-year metastasis-free rates that varied directly with tumor grade (low, 87%; intermediate, 68%; and high, 52%). When patients in our series were divided into these same categories, the metastasis-free rates at 10 years were better than those reported for those who had the low-grade tumors (100%) and intermediate-grade tumors (91%) but were somewhat lower in the higher-grade tumors (43%). This lower rate for the high-grade tumors may be due to the lack of early hormonal therapy in our patients with high-grade disease. Although this issue was not specifically addressed by Gerber et al,[6] more than one quarter of the men in the report from the Mayo Clinic received either early hormonal or radiation therapy.[2]

After the development of metastatic disease, the actuarial median time until death due to prostate cancer was slightly less than 5 years and dependent on the timing of progression to distant disease. Men who progressed to distant disease within 1 to 3 years following surgery died due to cancer at a higher rate than those men who developed metastases at 4 to 7 years or more than 8 years after surgery. Seventy-eight percent of the men who developed distant disease 8 years or more after surgery survived an additional 5 years. Time to original biochemical recurrence, serum PSA level at the time of diagnosis of metastatic disease, and Gleason score did not prove useful in stratifying risk of cancer-specific death. Data relating to the extent of disease on radionuclide bone scan, serum testosterone level, and performance status was not available in these men. These factors have also been shown to be important in determining overall survival in men with metastatic disease.[23,24]

The 10- and 15-year cancer-specific survival rates of 94% and 91% for all 1997 men were similar to those reported in 2 recent analyses.[7-10] As was the case for metastasis-free survival, our rates of cancer-specific survival are higher than those reported by Gerber et al[6] and Zincke et al[2]; this may due to patient selection.

None of the men in our study with metastatic disease died due to causes other than prostate cancer. This means that our cancer-specific death rate in men with metastatic disease is the same as the overall survival rate. The overall survival rate of 43% at 5 years was almost identical to that reported in men with minimal metastatic disease and good performance status in the National Cancer Institute Intergroup Study Number 0036 and other studies.[24-32]

For men who experience an isolated biochemical recurrence, the algorithm in Figure 4 should provide a reasonable estimate of their probability of developing metastatic disease over the next 3, 5, or 7 years. This information should

allow physicians and patients to make educated treatment decisions based on their risk of recurrence.[25-32]

We anticipate that this algorithm should provide valuable information for the stratification of patients into different risk groups when designing and enrolling patients in investigational protocols. This analysis demonstrates that the duration of survival in these men is quite long and must be taken into account when determining the feasibility of proposed clinical trials.

CONCLUSION

This report characterizes the natural history of disease progression to distant metastasis and death due to prostate cancer in men with a PSA elevation following radical prostatectomy. Radical prostatectomy was shown to provide excellent long-term cure rates with 82% metastasis-free survival at 15 years following surgery for all men in this study group. Of the men who did develop a PSA elevation, many remained free of metastatic disease for an extended period after initial biochemical recurrence without other forms of therapy. This has important implications in the selection of systemic therapies that are not curative and have no demonstrated impact on eventual outcome. The extended interval between biochemical recurrence and clinical metastatic disease emphasizes the need to design clinical trials to examine new treatment modalities in these men.

Factors that predicted the time course to the development of metastatic disease included the timing of initial PSA elevation, Gleason score, and PSADT. These factors were used to construct an algorithm that should be useful to the clinician in counseling patients about the time course and likelihood of eventual development of metastatic disease after initial biochemical recurrence.

Funding/Support: This study was supported by the Fund for Research and Progress in Prostate Cancer of the James Buchanan Brady Urological Institute, The Johns Hopkins Medical Institutions, Baltimore, Md, and the National Cancer Institute, Bethesda, Md, SPORE Grant, CA 58326.

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