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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