Evidence to Support a Continued Stage Migration and Decrease in Prostate Cancer Specific Mortality

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Purpose: We evaluated whether the proportion of patients with a postoperative PSA-DT less than 3 months, a surrogate for PCSM, decreased significantly during the PSA era.

Materials and Methods: Between July 1988 and July 2002, 3,719 men with clinically localized prostate cancer treated with RP comprised the study cohort. A chi-square metric was used to compare the preoperative and postoperative characteristics, 5-year actual PSA failure rates, and PSA-DTs for patients treated during the 2 equally divided eras of the early PSA era, July 1988 to July 1995 and the late PSA era, August 1995 to July 2002.

Results: Patients presenting in the more recent PSA era were of younger age ($p < 0.0001$), with earlier stage ($p < 0.0001$) and lower grade disease ($p = 0.01$). Similarly, patients had lower grade ($p < 0.001$), stage ($p < 0.0001$), and positive margin ($p < 0.0001$) and lymph node rates ($p = 0.0002$) at RP. The 5-year actual PSA failure rates decreased from 14.3% in the early PSA era to 2.5% in the later PSA era ($p < 0.0001$). There was a 37% reduction in the proportion of patients with a PSA-DT less than 3 months, corresponding to a decrease in absolute magnitude from 9% to 5.7% between the 2 eras. Absolute reductions of 3.1% and 9% were also noted for the proportion of PSA-DTs of 3 to 5.99 months and 6 to 11.99 months, respectively, whereas PSA-DTs of 12 months or greater increased by 15.3%.

Conclusions: During the recent PSA era, postoperative PSA failure has significantly decreased and PSA-DTs have increased, suggesting that PCSM will continue to decrease.

Key Words: prostatic neoplasms, prostate-specific antigen, prostatectomy, mass screening, treatment failure

Prostate cancer is the most commonly diagnosed noncutaneous cancer and is the second leading cause of cancer death in men in the United States. It is estimated that approximately 230,000 new cases of prostate cancer were diagnosed in 2004 compared with about 99,000 cases diagnosed in 1988.[1] The increased incidence of prostate cancer has been attributed to the increased use of PSA testing. Since the advent of the PSA era, investigators have shown a migration toward diagnosis at a younger age with earlier stage, lower PSA and less aggressive cancer compared with the results of digital rectal examination detection of prostate cancer.[2–5]

PSA testing has also been used to detect prostate cancer recurrence after definitive treatment with RP or radiation therapy for patients with clinically localized prostate cancer. Since the institution of PSA testing, studies have shown a decrease in biochemical or PSA failure after therapy.[6,7] However, today up to 30% of patients who undergo RP or radiation therapy for clinically localized disease will still sustain a biochemical recurrence within 10 years following treatment.[8]

To identify patients for whom a PSA defined recurrence will likely translate into death from prostate cancer, investigators have tried to determine factors associated with the development of metastases and PCSM following biochemical recurrence. Repeatedly, one of these factors, the PSA-DT has been found to be associated with the time to appearance of metastatic disease on bone scan following PSA failure.[8–11] Recently evidence to support a PSA-DT of less than 3 months as a surrogate end point for PCSM has become available.[12]

Despite the shift toward smaller volume and less aggressive disease as well as lower PSA failure rates, the question remains whether PCSM will be impacted. Specifically whether the PCSM rate will decrease with the use of PSA based screening is the subject of 2 large randomized control trials.[13,14] However, given the significant association between a PSA-DT of less than 3 months and PCSM, an assessment of how the distribution of PSA-DTs has changed

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TABLE 1. *Pretreatment clinical characteristics*

	No. (%)
Time interval:	
Before 8/1/95	2,249 (60.5)
On or after 8/1/95	1,470 (39.5)
PSA (ng/ml):	
4 or Less	1,021 (27.5)
4–10	2,099 (56.4)
10–20	439 (11.8)
Greater than 20	160 (4.3)
Biopsy Gleason score:	
6 or Less	2,892 (77.8)
7	644 (17.3)
8–10	183 (4.9)
2002 AJCC category:[16]	
T1c	2,339 (62.9)
T2a	1,026 (27.6)
T2b	283 (7.6)
T2c	65 (1.8)
T3a	6 (0.2)
Age:	
Younger than 50	128 (3.4)
50–59	1,042 (28.0)
60–69	1,926 (51.8)
70 or Older	623 (16.6)
Risk group:[18]	
Low	2,468 (66.4)
Intermediate	892 (24.0)
High	359 (9.7)

Percentages may not sum to 100% due to rounding.

during the PSA era may provide information regarding the impact that PSA screening may have on PCSM rates, and was the purpose of this study.

MATERIALS AND METHODS

Patient selection and treatment. We gathered pretreatment and followup data on 3,719 men treated with RP at the Brigham and Women's Hospital and the Barnes-Jewish Hospital for clinical stage T1c-T3aNX or N0M0 (ie localized or locally advanced, nonmetastatic) prostate cancer between July 14, 1988 and July 11, 2002. An approved and signed Internal Review Board approved consent form was obtained on each patient before study entry. To be eligible for this study, patients treated surgically were permitted to have received up to 3 months of neoadjuvant androgen suppression therapy, given that the 5-year results of a randomized trial have shown no statistically significant impact on PSA outcome when 3 months of neoadjuvant androgen suppression therapy was added to radical prostatectomy.[15] Median patient age was 63.7 years (range 30.3 to 85.1). The pretreatment clinical characteristics are shown in table 1.

Staging. In all patients a history and physical examination including digital rectal examination, determination of serum PSA and a transrectal ultrasound guided needle biopsy of the prostate were performed. The Gleason score was determined by histological examination. The prostate biopsy was generally performed transrectally with an 18 gauge Tru-Cut® needle. All specimens were step sectioned at 3 and 5 mm, and a single genitourinary pathologist at each institution assigned the Gleason score for all biopsy and prostatectomy specimens. Before 1996 patients generally had a computerized tomographic scan of the pelvis and a bone scan. After 1996 patients with a pretreatment Gleason score of 6 or less did not generally undergo radiological staging because of the less than 1% chance that these studies would reveal metastatic disease. The clinical T category was obtained from the results of the digital rectal examination and the 2002 AJCC staging system.[16] Radiological and biopsy information was not used to determine clinical T category.

Followup. Median followup for the entire study cohort of 3,719 patients was 5.3 years (range 0.0 to 19.4). Seven patients had a PSA that never became undetectable postoperatively and, therefore, had a score of PSA failure at time 0. All patients were followed with serial serum PSA determinations after RP every 3 months for the first 2 years, every 6 months for up to 5 years and annually thereafter. Biochemical failure was defined with the occurrence of 2 consecutive detectable serum PSA values (greater than 0.2 ng/ml) following an undetectable serum PSA measurement postoperatively. The time of PSA failure was defined as the date of the first increase greater than 0.2 ng/ml or the date of last followup if PSA failure was not observed.

Statistical analysis. Clinical Presentation and Prostatectomy Findings: We divided our patient cohort into 2 subsets according to the date of RP, namely the early PSA era of July 1988 to July 1995 and the late PSA era of August 1995 to July 2002. These 2 eras were chosen based on dichotomization about the median point from the start of PSA screening in the United States to our study end point. The distributions of pretreatment clinical and postoperative prostatectomy characteristics were determined for the patients during these 2 intervals, and compared using a Mantel-Haenszel chi-square metric.[17]

The pretreatment clinical characteristics included age on the day of RP, serum PSA at diagnosis, biopsy Gleason score, clinical T category and a previously defined pretreatment risk group stratification[18] for PCSM. The low risk group comprised patients with 2002 AJCC clinical T category T1c or T2a, and a serum PSA of 10 ng/ml or less and biopsy Gleason score of 6 or less. The high risk group comprised patients with 2002 AJCC clinical stage T2c-T3a disease, or PSA greater than 20 ng/ml or biopsy Gleason score of 8 or higher. The remaining patients comprised the intermediate risk group. The postoperative prostatectomy characteristics included prostatectomy T category, Gleason score, and margin and lymph node status. Of the 3,719 patients there was missing documentation of prostatectomy T category for 28 patients, prostatectomy Gleason scores for 6 patients, margin status for 45 patients and lymph node status for 40 patients.

Time Dependent PSA Outcomes: PSA-DTs were calculated by assuming first order kinetics and by using a minimum of 3 PSA measurements, each separated by a minimum of 3 months and each with a PSA increase of more than 0.2 ng/ml. Therefore, the minimum PSA that was used to calculate the PSA-DT needed to be more than 0.2 ng/ml for all study patients. If a patient had 1 or 2 consecutive increases in PSA from an undetectable PSA (less than 0.2 ng/ml) after surgery, PSA-DT could not be calculated and such patients were excluded from the analysis. Of the 3,719 patients 1,283 sustained PSA failure and 1,030 had sufficient information to calculate PSA-DT. For the purpose of ensuring that the comparison of PSA-DT distributions was not influenced by the potential for longer followup in the earlier PSA era, 89 patients whose PSA failure time in the