Standardizing the Definition of Biochemical Recurrence after Radical Prostatectomy—What Prostate Specific Antigen Cut Point Best Predicts a Durable Increase and Subsequent Systemic Progression?

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Purpose: Multiple definitions of biochemical recurrence for prostate cancer exist after radical prostatectomy, and variation continues in prostate cancer outcome reporting and secondary treatment initiation. We reviewed long-term prostatectomy outcomes to assess the most appropriate prostate specific antigen cut point that predicts future disease progression.

Materials and Methods: We identified 13,512 patients with cT1-2N0M0 prostate cancer who underwent radical prostatectomy between 1987 and 2010. Single prostate specific antigen cut points of 0.2, 0.3, 0.4 and 0.5 ng/ml or greater, as well as confirmatory prostate specific antigen value definitions of 0.2 ng/ml or greater followed by prostate specific antigen greater than 0.2 ng/ml and 0.4 ng/ml or greater followed by prostate specific antigen greater than 0.4 ng/ml were tested. Continued prostate specific antigen increase after a designated cut point definition was estimated using cumulative incidence. The strength of association between biochemical recurrence definitions and subsequent systemic progression were analyzed using Cox proportional hazard models and the O'Quigley event based R^2 test.

Results: At a median postoperative followup of 9.1 years (IQR 4.9–14.3) a detectable prostate specific antigen developed in 5,041 patients and systemic progression developed in 512. After reaching the prostate specific antigen cut point of 0.2, 0.3 and 0.4 ng/ml, the percentage of patients experiencing a continued prostate specific antigen increase over 5 years was 61%, 67% and 74%, respectively, plateauing at 0.4 ng/ml. The strongest association between biochemical recurrence and systemic progression occurred using a single prostate specific antigen cut point of 0.4 ng/ml or greater (HR 36, R^2 0.92).

Conclusions: A prostate specific antigen cut point of 0.4 ng/ml or greater reflects the threshold at which a prostate specific antigen increase becomes durable and shows the strongest correlation with subsequent systemic progression. Consideration should be given to using a prostate specific antigen of 0.4 ng/ml or greater as the standard biochemical recurrence definition after radical prostatectomy.

Key Words: recurrence, prostate-specific antigen, prostatectomy

Abbreviations and Acronyms

BCR = biochemical recurrence
CaP = prostate cancer
PSA = prostate specific antigen
RP = radical prostatectomy
SP = systemic progression

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CANCER recurrence after radical prostatectomy is a concern for men undergoing definitive surgical treatment for prostate cancer. Approximately 20% to 35% of patients experience an increasing PSA after radical prostatectomy for clinically localized prostate cancer,[1–3] and the median time to biochemical recurrence typically varies between 2 and 3 years.[4,5] However, a standard PSA cut point to indicate BCR has yet to be established. Without a universally accepted definition for post-prostatectomy recurrence, heterogeneity has developed in outcome reporting and initiation of secondary treatments for prostate cancer.

There are currently several recommended definitions for BCR set by the American Urological Association,[6] European Association of Urology[7] and the National Comprehensive Cancer Network®.[8] However, these recommended definitions are disparate. There have also been a number of independent series from high volume centers analyzing PSA cut point definitions.[9,10] With the multiplicity of available post-prostatectomy BCR definitions, it is crucial to standardize a cut point for patient counseling and overall risk stratification.

To help standardize the definition of BCR we evaluated 6 PSA cut point definitions using a large cohort of patients with clinically localized prostate cancer who had undergone RP. Through identifying which PSA cut point results in the most durable PSA increase and which has the strongest correlation to systemic progression, we propose a threshold that should be considered the most optimal BCR definition after RP.

MATERIALS AND METHODS

Patient Sample

After obtaining institutional review board approval we reviewed our prostatectomy registry to identify 16,719 patients who underwent RP for clinical stage cT1-2N0 disease between 1987 and 2010. A total of 3,207 patients were excluded from analysis due to neoadjuvant or prior treatment (1,361), receipt of adjuvant treatment within 90 days of RP (1,429), lack of followup (130) and refusal to consent for research inclusion (287). Given the retrospective nature of the study, PSA monitoring after RP was not standardized. However, the majority of the patients underwent PSA monitoring and a digital rectal examination quarterly for the first 2 years and semiannually for the next 3 years, followed by annual surveillance. Imaging of the abdomen/pelvis and bone scan were performed as indicated based on clinical discretion. For patients followed elsewhere the registry coordinators captured the results of PSA monitoring and overall CaP specific outcomes annually through patient or treating physician correspondence.

Definitions of PSA Cut Point and Systemic Progression

A detectable PSA after RP was defined as a value greater than 0.15 ng/ml. Six definitions of BCR were analyzed, including PSA 0.2 ng/ml or greater, PSA 0.3 ng/ml or greater, PSA 0.4 ng/ml or greater, PSA 0.5 ng/ml or greater, 2 confirmatory PSA values 0.2 ng/ml or greater, and 2 confirmatory PSA values 0.4 ng/ml or greater. Individual patients were not limited to only 1 of the 6 analyzed definitions. Patients who commenced treatment for biochemical recurrence before reaching a designated PSA cut point were also included in the analysis. For example, a patient in whom a PSA of 0.2 ng/ml developed at 6 months after prostatectomy and then who started secondary treatment at a PSA of 0.3 ng/ml was analyzed according to the PSA cut point definitions of 0.2 ng/ml or greater or treatment, PSA 0.3 ng/ml or greater or treatment, and PSA 0.2 ng/ml or greater followed by a confirmatory PSA greater than 0.2 ng/ml or treatment. Systemic progression was defined as demonstrable local or distant metastasis on imaging studies or via biopsies after a detectable PSA.

Statistical Analysis

To understand the influence of adding patients who had started treatment to the PSA cut point definitions, we estimated the number of BCR and SP events 5 and 10 years for each PSA cut point definition with and without such patients using cumulative incidence models. Overall the rate of BCR and SP events did not greatly differ when including patients who had commenced treatment in the PSA cut point definitions. Thus, to be more inclusive we chose to use the PSA cut point definitions that included patients who had commenced treatment for BCR in our analyses going forward.

Cumulative incidence analyses were also used to estimate the probability of 5 and 10-year SP rates after each PSA cut point definition. The 3 and 5-year estimates of the durability in PSA increase after initial PSA values were estimated using cumulative incidence models. Patients were censored at the time of last followup or death from other causes. The strength of association between PSA cut point definitions and subsequent SP was analyzed using time dependent Cox proportional hazard models with a 90-day lag. Hazard models were adjusted for GPSM score, a previously established and validated nomogram which formulates the risk of BCR using a sum of pathological Gleason score, PSA, seminal vesicle involvement and margin status.[11,12]

The O'Quigley event based R^2 test was calculated based on the number of events and estimated how well each model predicted the outcome. This statistical model measures the predictive ability of the Cox proportional hazard ratio for time dependent variables. The R^2 value represents the goodness of fit and is stronger as it approaches 1. All tests were 2-sided with $p < 0.05$ considered statistically significant. Statistical analysis was done using SAS® version 9.4.

RESULTS

Patient clinicopathological features are summarized in table 1. Median age was 63 years (IQR 57–68). [T1] Median postoperative followup for the entire cohort was 9.1 years (IQR 4.9–14.3). The median number