Low Detectable Prostate Specific Antigen after Radical Prostatectomy—Treat or Watch?

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Abbreviations and Acronyms

ADT = androgen deprivation therapy
BCR = biochemical recurrence
LD = low detectable
NCCN® = National Comprehensive Cancer Network®
ORP = open retropubic RP
PSA = prostate specific antigen
PSAV = PSA velocity
RARP = robot-assisted RP
RP = radical prostatectomy
UD = undetectable
XRT = radiation therapy

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Editor's Note: This article is the third of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 1584 and 1585.

Purpose: We determined whether the pattern of low detectable prostate specific antigen during the first 3 years of followup after radical prostatectomy would predict subsequent biochemical recurrence.

Materials and Methods: An institutional database was queried to identify 1,136 patients who underwent open retropubic or robot-assisted radical prostatectomy between January 5, 1993 and December 29, 2008. After applying exclusion criteria we used serum prostate specific antigen and the prostate specific antigen pattern during the first 3 years of followup to divide 566 men into 3 groups, including 1) undetectable prostate specific antigen (0.03 ng/ml or less), 2) low detectable-stable prostate specific antigen (greater than 0.03 and less than 0.2 ng/ml, no 2 subsequent increases and/or prostate specific antigen velocity less than 0.05 ng per year) and 3) low detectable-unstable prostate specific antigen (greater than 0.03 and less than 0.2 ng/ml, 2 subsequent increases according to NCCN criteria and/or prostate specific antigen velocity 0.05 ng per year or greater). The primary end point was biochemical recurrence, defined as prostate specific antigen 0.2 ng/ml or greater, or receipt of radiation therapy beyond 3 years of followup.

Results: Seven-year biochemical recurrence-free survival was 95%, 94% and 37% in the undetectable, low detectable-stable and low detectable-unstable groups, respectively (log rank test $p < 0.0001$). On multivariate analysis the prostate specific antigen pattern during 3 years postoperatively (undetectable vs low detectable-unstable HR 15.9 and vs low detectable-stable HR 1.6), pathological T stage (pT2 vs greater than pT2 HR 1.8), pathological Gleason score (less than 7 vs 7 HR 2.3 and less than 7 vs 8–10 HR 3.3) and surgical margins (negative vs positive HR 1.8) significantly predicted biochemical recurrence.

Conclusions: The combination of prostate specific antigen velocity and NCCN criteria for biochemical recurrence separated well men with low detectable prostate specific antigen after radical prostatectomy into those who required treatment and those who could be safely watched.

Key Words: prostate; neoplasm recurrence, local; prostatectomy; prostate-specific antigen; prognosis

RADICAL prostatectomy provides excellent long-term cure rates in most men with clinically localized disease.[1] PSA is the most sensitive and widely used method to detect recurrence after RP. Increasing PSA after curative therapy without clinical or radiological evidence of disease is termed BCR. The incidence and behavior of BCR depend on its

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definitions.[2] The NCCN divides men with BCR into 3 groups, including 1) those whose PSA fails to decrease to undetectable levels after RP (persistent disease), 2) those who achieve undetectable PSA after RP with a subsequent detectable PSA level that increases on 2 or more subsequent laboratory determinations (recurrent disease) and 3) those with low detectable, persistent PSA.[3] However, exact definitions were not provided for the third group. PSA greater than 0.4 or greater than 0.2 ng/ml has been used in most studies as a BCR cutoff point.[1,2] There is no consensus regarding treatment in men with detectable PSA less than 0.2 ng/ml.

As many as 40% of patients experience BCR after RP[4] but the significance of BCR remains unclear. A reported 13% to 36% of patients with BCR experience clinical progression and 1.1% to 14% die of the disease.[5] BCR precedes clinical recurrence in almost all patients.[6] Those with BCR are at increased risk for subsequent metastasis and mortality.[7] However, others reported that BCR correlated poorly with overall survival and expressed doubt about its clinical significance.[8] About a third of patients with BCR receive secondary treatment[9] but the best treatment in an individual with BCR remains controversial. Options for men with BCR include ADT, adjuvant or salvage XRT with or without ADT, or observation. Recent meta-analyses suggested that the treatment response rate for salvage XRT depends on pretreatment PSA and recommended initiating salvage XRT at the lowest possible PSA.[10,11] On the other hand, early initiation of secondary treatment could lead to overtreatment since the natural history of BCR is prolonged and difficult to predict in an individual.

Shinghal at al described a subset of patients with detectable nonprogressive PSA recurrence after RP who did not show a progressive increase in serum PSA or clinical progression after 10 years of followup.[12] Most of these men were characterized by late BCR (longer than 36 months after RP) and low PSA at BCR but no clinical or pathological characteristics were identified that predicted stable disease.

We hypothesized that men with low detectable and stable PSA should show the characteristics of men with undetectable PSA. To test this hypothesis we determined whether the pattern of low detectable PSA during the first 3 years of followup and/or clinicopathological characteristics were predictors of subsequent BCR.

MATERIALS AND METHODS

Patients

Institutional review board approval was obtained to query an institutional RP database to identify 1,136 patients who underwent ORP or RARP, performed by different surgeons between January 5, 1993 and December 29, 2008. Clinicopathological variables were populated retrospectively into a database until 2004, when data were collected and entered prospectively. Study exclusion criteria were fewer than 4 years of followup, preoperative ADT or XRT, lymph node metastasis, XRT or ADT, or PSA greater than 0.2 ng/ml within the first 3 years after RP, loss to followup and followup elsewhere due to the variable quality of PSA measurement. Serum PSA and the PSA pattern during the first 3 years of followup were used to divide the remaining 566 men into 3 groups, including 1) UD PSA (0.03 ng/ml or less), 2) LD-stable PSA (greater than 0.03 and less than 0.2 ng/ml, no 2 subsequent increases and/or PSAV less than 0.05 ng per year) and 3) LD-unstable PSA (greater than 0.03 and less than 0.2 ng/ml, 2 subsequent increases and/or PSAV 0.05 ng per year or greater). PSAV was calculated for 2 or more PSA values during 1 year or greater. PSAV thresholds less or greater than 0.05 ng per year did not improve the separation between the unstable and stable groups.

PSA Measurement and Followup

Serum PSA was measured using the Hybritech® PSA assay and the PHOTON™ Era™ Immunoanalyzer with 0.03 ng/ml sensitivity since 1993, the Immuno 1™ Immunoanalyzer with 0.03 ng/ml sensitivity since 1999 and the Centaur Immunoassay analyzer (Siemens Healthcare, Erlangen, Germany) with 0.01 ng/ml sensitivity since 2004. Serum PSA was measured routinely 6 weeks after RP, every 6 months for 5 years and annually thereafter unless prostate cancer was organ confined and PSA was undetectable, in which case PSA was measured annually from years 1 to 5. Additional PSA levels were measured as clinically indicated. Digital rectal examination was performed at each annual or semiannual visit and additional tests were done according to NCCN guidelines. Indications for initiating secondary treatment varied during the years. However, all recommendations for care have been NCCN guideline compliant since 2003. BCR was defined as PSA 0.2 ng/ml or greater, or receipt of XRT after 3 years of followup. Systemic progression was defined as demonstrable metastasis on computerized tomography, magnetic resonance imaging or radionuclide bone scan and/or positive tissue biopsies outside the prostatic bed.

Statistical Analysis

Patient baseline characteristics are reported by PSA group using the mean, median and SD for continuous variables and frequencies, and relative frequencies for categorical variables. Comparisons were made between groups using the Kruskal-Wallis and Fisher exact (Freeman-Halton extension) tests for continuous and categorical variables, respectively. Postoperative BCR-free survival was summarized using standard Kaplan-Meier methods with between group comparisons made using the log rank test. Univariate Cox regression models were used to determine HRs. Patients were censored at last followup or death if BCR had not been attained. A multivariate Cox regression model was used to evaluate