Ultrasensitive Prostate Specific Antigen after Prostatectomy Reliably Identifies Patients Requiring Postoperative Radiotherapy

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Abbreviations and Acronyms

ART = adjuvant RT
BCR = biochemical relapse
cBCR = conventional BCR
iPSA = initial PSA
PSA = prostate specific antigen
RP = radical prostatectomy
RT = radiation therapy
SRT = salvage RT
uPSA = ultrasensitive PSA

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Purpose: Integrating ultrasensitive prostate specific antigen with surveillance in patients at high risk after radical prostatectomy potentially optimizes treatment by correctly identifying recurrence, promoting an early salvage strategy and minimizing overtreatment. We tested the power of postoperative ultrasensitive prostate specific antigen to identify eventual biochemical failure.

Materials and Methods: We identified 247 patients at high risk with a median followup of 44 months who underwent radical prostatectomy from 1991 to 2013. Each patient had extraprostatic extension and/or a positive margin. Surgical technique, initial prostate specific antigen, pathology findings and postoperative prostate specific antigen were analyzed. The ultrasensitive prostate specific antigen assay threshold was 0.01 ng/ml. Conventional biochemical relapse was defined as prostate specific antigen 0.2 ng/ml or greater. Kaplan-Meier and Cox multivariate analyses were done to compare the rates of ultrasensitive prostate specific antigen recurrence and conventional biochemical relapse.

Results: Sensitivity analysis revealed that ultrasensitive prostate specific antigen 0.03 ng/ml or greater was the optimal threshold to identify recurrence. A first postoperative ultrasensitive value of 0.03 ng/ml or greater, Gleason grade, T stage, initial prostate specific antigen and margin status predicted conventional biochemical relapse. On multivariate analysis only a first postoperative ultrasensitive value of 0.03 ng/ml or greater, Gleason grade and T stage independently predicted conventional biochemical relapse. First postoperative ultrasensitive prostate specific antigen 0.03 ng/ml or greater conferred the highest risk (HR 8.5, $p < 0.0001$) and identified conventional biochemical relapse with greater sensitivity than undetectable first conventional prostate specific antigen (70% vs 46%). Any postoperative prostate specific antigen 0.03 ng/ml or greater captured all failures missed by the first postoperative value (100% sensitivity) with accuracy (96% specificity). Defining failure at an ultrasensitive value of 0.03 ng/ml or greater yielded a median lead time advantage of 18 months (mean 24) over the conventional definition of prostate specific antigen 0.2 ng/ml or greater.

Conclusions: Ultrasensitive prostate specific antigen 0.03 ng/ml or greater is an independent factor that identifies biochemical relapse more accurately than any traditional risk factors and confers a significant lead time advantage. This factor enables critical decisions on the timing of and indication for postoperative radiotherapy in patients at high risk after radical prostatectomy.

Key Words: prostatic neoplasms; prostatectomy; prostate-specific antigen; neoplasm recurrence, local; diagnosis

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FOR a perspective on the scope of the problem one should consider that each year in the United States alone approximately 100,000 men undergo RP and relapse will develop in about a fourth of them.[1] At recurrence RT remains the only potentially curative treatment available. Postoperatively some individuals are at such high risk for recurrence that a strategy of adjuvant RT is used to prevent this. Accordingly randomized clinical trials show that compared to observation adjuvant RT after RP decreases the risk of biochemical relapse and provides an overall survival benefit in patients at high risk (those with extraprostatic disease or positive margins). However, treatment would not have failed in up to half of the patients who receive adjuvant RT and, thus, they would have been unnecessarily irradiated. To maximize benefit and minimize overtreatment RT should optimally be reserved for confirmed recurrences within the earliest time frame.

PSA assays, which were discovered in 1979, were incorporated into clinical use in the late 1980s at a detection threshold of 0.2 to 0.6 ng/ml.[2] Detectable postoperative PSA identifies prostate cancer but at such a low disease burden that imaging cannot reliably locate the source. Technological advances have lowered detection limits to an ultrasensitive range as low as less than 0.003 ng/ml.[3] As biochemical detection limits of modern uPSA assays have decreased, questions have arisen about its appropriate use.

The AUA (American Urological Association) consensus panel evaluated 145 articles encompassing 53 definitions of post-prostatectomy BCR and concluded that it is best defined as serum PSA 0.2 ng/ml or greater with a second confirmatory PSA of greater than 0.2 ng/ml.[4] While this is most widely used clinically, it is tenfold above the lower limit of detection of current assays. With improved detection thresholds the definition of BCR warrants study.

The success of postoperative RT depends on whether relapse is due to local or distant disease. Biochemical failure precedes distant metastasis by about 8 years.[5] Thus, it follows that earlier detection of biochemical relapse should confer a therapeutic advantage by selecting cases with more probable localized failure. Large multi-institutional trials show that presalvage RT PSA profoundly impacts the likelihood of the success of salvage RT.[6,7] A meta-analysis quantified that the success of salvage RT decreased by 2.5% with each 0.1 ng/ml PSA increment.[8] Thus, detecting failure at the lowest possible PSA would be valuable to establish a greater lead time to identify recurrence early while it is most likely to be confined to the prostate bed.

Despite several studies evaluating uPSA kinetics to diagnose failure a clear threshold and clinical usefulness are still undefined. It is uncertain at which value patients would truly eventually experience BCR or which values reflect clinically insignificant but anxiety provoking uPSA fluctuations. We evaluated a cohort of patients with RP who had high risk disease and were otherwise eligible for adjuvant RT. We compared uPSA to conventional risk factors for predicting recurrence and evaluated the usefulness of uPSA for diagnosing BCR.

MATERIALS AND METHODS

Patient Selection

After receiving institutional review board approval we retrospectively reviewed the records of patients who were treated with RP from 1991 to 2013 or referred for postoperative RT. We identified 247 patients with pathologically node negative and high risk disease, defined as pT3/4 and/or positive margins. No patient received preoperative or postoperative androgen deprivation therapy, or immediate adjuvant RT. We assessed the surgical approach (open or laparoscopic), preoperative iPSA, complete surgical pathology according to AJCC (American Joint Committee on Cancer) 2002 TNM staging guidelines and postoperative PSA.

PSA Followup

In all patients uPSA was measured postoperatively. The Access® Hybritech PSA assay was used before 2006 and the electrochemiluminescence Elecsys® immunoassay run on a Modular E170 device (Hoffman-La Roche, Basel, Switzerland) was used thereafter. The reported lower limit of detection (analytical sensitivity) of the Access and Elecsys assays is 0.005 and 0.014 ng/ml with 0.007 and 0.030 ng/ml functional (biological) sensitivity, respectively. In all patients the laboratory reported a uPSA threshold of 0.01 ng/ml. For the purpose of labeling and analysis so-called cBCR was defined as PSA 0.2 ng/ml or greater. Patients were censored at last followup or at the time of adjuvant therapy (salvage RT or androgen deprivation).

Analysis

Statistical. BCR rates were calculated by the Kaplan-Meier method with differences between groups determined by the log rank test. Multivariate Cox proportional hazards regression modeling was used to determine whether uPSA above a certain threshold predicted cBCR, adjusting for clinicopathological factors (iPSA, pathological T stage, Gleason sum, surgical approach and surgical margin status). Statistical significance was considered at $p < 0.05$.

Sensitivity and specificity. Sensitivity and specificity analysis was done to compare BCR definitions. A positive result was defined as detectable PSA that progressed to 0.2 ng/ml or greater. A negative result was defined as undetectable PSA that never reached 0.2 ng/ml. A total of 139 patients in whom PSA increased above nadir but did not reach 0.2 ng/ml during followup were excluded from this subset analysis due to a clinical course suggesting relapse but with insufficient followup to be classified as