Do Ultrasensitive Prostate Specific Antigen Measurements Have a Role in Predicting Long-Term Biochemical Recurrence-Free Survival in Men after Radical Prostatectomy?

Lori J. Sokoll,* Zhen Zhang, Daniel W. Chan, Adam C. Reese, Trinity J. Bivalacqua, Alan W. Partin and Patrick C. Walsh

From the Department of Pathology (LJS, ZZ, DWC, AWP) and James Buchanan Brady Urological Institute (LJS, DWC, ACR, TJB, AWP, PCW), The Johns Hopkins Medical Institutions, Baltimore, Maryland

Abbreviations and Acronyms

BCR = biochemical recurrence
LOQ = limit of quantitation
PSA = prostate specific antigen
RP = radical prostatectomy

Accepted for publication August 17, 2015.

Supported by the Johns Hopkins Brady Urological Institute Prostate Cancer Awareness Week Fund and NCI P50CA58236 (SPORE in Prostate Cancer).

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

* Correspondence: Department of Pathology, Johns Hopkins Medical Institutions, 1800 Orleans St., Zayed B1-1020K, Baltimore, Maryland 21287 (telephone: 410-955-2673; FAX: 410-955-0767; e-mail: lsokoll@jhmi.edu).

See Editorial on page 243.

Purpose: In this study we evaluate an ultrasensitive prostate specific antigen assay in patients with prostate cancer after radical prostatectomy to predict long-term biochemical recurrence-free survival.

Materials and Methods: A total of 754 men who underwent radical prostatectomy and had an undetectable prostate specific antigen after surgery (less than 0.1 ng/ml) were studied. Prostate specific antigen was measured in banked serum specimens with an ultrasensitive assay (Hybritech® PSA, Beckman Coulter Access® 2) using a cutoff of 0.01 ng/ml. Prostate specific antigen was also measured in 44 men after cystoprostatectomy who had no pathological evidence of prostate cancer with the Hybritech assay and with the Quanterix AccuPSA™ assay.

Results: Of the 754 men 17% (131) experienced biochemical recurrence (median 4.0 years). Those men without biochemical recurrence (83%, 623) had a minimum of 5 years of followup (median 11). Prostate specific antigen was less than 0.01 ng/ml in 93.4% of men with no biochemical recurrence, whereas 30.5% of men with biochemical recurrence had a prostate specific antigen of 0.01 ng/ml or greater. On multivariate analysis postoperative prostate specific antigen at a 0.01 ng/ml cutoff, pathological stage and Gleason score, and surgical margins were significant independent predictors of biochemical recurrence risk. Kaplan-Meier estimates for mean biochemical recurrence-free survival were 15.2 years (95% CI 14.9–15.6) for prostate specific antigen less than 0.01 ng/ml and 10.0 years (95% CI 8.4–11.5) for prostate specific antigen 0.01 ng/ml or greater ($p < 0.0001$). Biochemical recurrence-free rates 11 years after surgery were 86.1% (95% CI 83.2–89.0) for prostate specific antigen less than 0.01 ng/ml and 48.9% (95% CI 37.5–60.3) for prostate specific antigen 0.01 ng/ml or greater ($p < 0.0001$). Prostate specific antigen concentrations in 44 men after cystoprostatectomy were all less than 0.03 ng/ml, with 95.4% less than 0.01 ng/ml.

Conclusions: In men with a serum prostate specific antigen less than 0.1 ng/ml after radical prostatectomy a tenfold lower cutoff (0.01 ng/ml) stratified biochemical recurrence-free survival and was a significant independent predictor of biochemical recurrence, as were pathological features. Prostate specific antigen concentrations in men without pathological evidence of prostate cancer suggest that a higher prostate specific antigen concentration (0.03 ng/ml) in the ultrasensitive range may be needed to define the detection threshold.

Key Words: prostate-specific antigen, prostatic neoplasms, recurrence, prostatectomy

0022-5347/16/1952-0330/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2015.08.080
Vol. 195, 330-336, February 2016
Printed in U.S.A.

TOTAL PSA assays are FDA (Food and Drug Administration) approved for the 2 prostate cancer clinical indications of aiding in detection in conjunction with digital rectal examination in men older than age 50, and in prognosis and management with serial measurements. PSA is particularly valuable for the detection of recurrence in patients undergoing definitive treatment for prostate cancer such as radical prostatectomy.[1] The natural history of progression after PSA increase after RP was described by Pound et al with median time to metastasis at 8 years.[2] In this and a 2012 followup study,[3] biochemical recurrence was defined as a PSA concentration of at least 0.2 ng/ml. The AUA (American Urological Association) and the American Society for Radiation Oncology recently defined BCR after surgery as initial and confirmatory PSA concentrations of 0.2 ng/ml or greater.[4] A BCR definition of 0.4 ng/ml PSA has also been proposed.[5] The National Comprehensive Cancer Network® clinical practice guidelines define PSA recurrence as an undetectable PSA after RP with a subsequent detectable PSA that increases on 2 or more determinations.[6] However, detectable is not specifically defined.

PSA results that are sensitive, accurate and precise are essential for monitoring the treatment of men with prostate cancer and calculating PSA related metrics such as doubling times. Ultrasensitive or third-generation PSA assays have limits of quantitation of 0.01 ng/ml or less, where LOQ is the concentration meeting a coefficient of variation of 20% or less. The Immulite® Third Generation PSA assay is so named but has no additional clinical claims for recurrence. Initial studies with this and other assays suggested that ultrasensitive PSA assays could lead to the earlier detection of biochemical relapse,[7–10] although treatment guidelines for BCR after RP such as salvage radiotherapy are based on traditional limits.[4] Most PSA assays in clinical use meet the definition of third-generation. The AUA has stated that although the usefulness of ultrasensitive assays has not been established, their use may distinguish men less likely or more likely to have recurrence after RP.[11]

Recently, fourth and fifth-generation PSA assays using novel technologies with detection limits tenfold to a hundredfold below ultrasensitive have been reported. Thaxton et al developed a nanotechnology based bio-barcode assay with a detection limit of 0.33 pg/ml (0.00033 ng/ml), which allowed a measurable value in 18 men after surgery.[12] The FDA cleared NADiA® ProsVue™ immuno-polymerase chain reaction based assay, calculated as the slope of 3 PSA values, has a LOQ of 0.65 pg/ml (0.00065 ng/ml) and an indicated use to identify patients at reduced risk for recurrence after RP.[13,14] Finally, the Quanterix AccuPSA test is a fifth-generation assay using SiMoA (single molecule array) technology with a LOQ of 0.035 pg/ml (0.000035 ng/ml).[15,16]

However, at present, none of these fourth or fifth-generation PSA assays is available for clinical use. In addition, the role of ultrasensitive PSA assays for BCR after RP has primarily been assessed in studies with small sample sizes and short to intermediate term monitoring intervals.[17] Therefore, in this investigation we reexamined ultrasensitive PSA assays for predicting long-term BCR-free survival in 754 men subsequent to RP. In addition, we determined the distribution of PSA values in men after cystoprostatectomy with no pathological evidence of prostate cancer to assess the potential for false-positive results due to background or nonprostatic sources of PSA.

MATERIALS AND METHODS

The 754 men in this study underwent RP at The Johns Hopkins Hospital between 1993 and 2008, had initial post-RP PSA results of less than 0.1 ng/ml (Hybritech Tandem-R or Tandem-E, or Tosoh Bioscience assays) and had a banked serum specimen for analysis. Men with positive lymph nodes or with distant metastasis at surgery or those who had undergone adjuvant or neoadjuvant therapy were excluded from analysis. The first available specimen after RP with a PSA less than 0.1 ng/ml was analyzed with an ultrasensitive PSA assay. BCR was defined as a postoperative PSA of 0.2 ng/ml or greater. Of the 754 men 131 subsequently experienced BCR while 623 did not. Men without recurrence had a minimum of 5 years of followup. An additional group of 44 men was studied who had undergone cystoprostatectomy for bladder cancer during 1993 to 2009 with no pathological evidence of prostate cancer and a serum specimen collected after surgery. This study was approved by the Johns Hopkins Medicine institutional review board.

All specimens were frozen at −80C before analysis with the Hybritech PSA assay on the Access 2 immunoassay analyzer (Beckman Coulter, Inc., Brea, California). Specimens from the patients who underwent cystoprostatectomy were additionally analyzed at Quanterix Corporation (Lexington, Massachusetts) with the AccuPSA assay.

Continuous and categorical variables were compared using t-tests, Mann-Whitney tests or chi-squared tests. Preoperative PSA was log-transformed to correct for left skewness distribution. Cox proportional hazards models were constructed for individual variables and multivariate analysis was performed with a final model selected by backwards elimination. Kaplan-Meier curves were used to examine BCR-free survival by PSA cutoff with comparison using the log rank test. Cases without BCR were censored at the last followup visit. Statistical analysis was performed using MedCalc® Version 15.2.2.