Ultrasensitive Prostate Specific Antigen and its Role after Radical Prostatectomy: A Systematic Review

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Purpose: Prostate specific antigen is an important tool to monitor patients with prostate cancer after radical prostatectomy. Ultrasensitive prostate specific antigen assays are increasingly used with a lower limit of detection as low as 0.001 ng/ml. We systematically reviewed currently available ultrasensitive prostate specific antigen technologies and the role of this method in monitoring patients after radical prostatectomy.

Materials and Methods: We searched the relevant literature using the MEDLINE® database. For various study objectives the series eligible for review provided serial ultrasensitive prostate specific antigen (lower detection limit less than 0.1 ng/ml) data on men after radical prostatectomy as well as comparative data on standard prostate specific antigen (lower detection limit 0.1 ng/ml or greater).

Results: Ultrasensitive prostate specific antigen could potentially detect prostate cancer recurrence years earlier than standard prostate specific antigen assays. The specificity of detectable ultrasensitive prostate specific antigen is low. Ultrasensitive prostate specific antigen kinetics may improve the positive predictive value for detecting cancer recurrence. However, the usefulness of prostate specific antigen doubling time at the ultrasensitive level remains controversial. Undetectable nadir ultrasensitive prostate specific antigen after radical prostatectomy confers a low risk of disease recurrence while a detectable nadir above 0.01 ng/ml requires additional measurement and consideration of other risk factors to determine management and avoid overtreatment. This monitoring method may spare patients with high risk disease adjuvant radiation therapy and enable more selective early salvage radiation. Currently no data demonstrate improved survival after early salvage therapy prompted by ultrasensitive prostate specific antigen surveillance.

Conclusions: Ultrasensitive prostate specific antigen is useful in the early diagnosis of cancer recurrence after radical prostatectomy but specificity is poor. To date there is a lack of evidence that earlier detection of recurrence translates into prolonged time to metastasis. Integrating ultrasensitive prostate specific antigen with other clinicopathological factors can help determine optimal adjuvant and salvage therapy.

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

Abbreviations and Acronyms

BCR = biochemical recurrence
ePSADT = early PSADT
LLD = lower detection limit
PCa = prostate cancer
PPV = positive predictive value
PSA = prostate specific antigen
PSADT = PSA doubling time
RP = radical prostatectomy
TRIFA = time resolved immunofluorometric assay
uPSA = ultrasensitive PSA
uPSADT = ultrasensitive PSADT
XRT = external radiation therapy

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Supplementary references 31 to 58 for this article can be obtained at http://jurology.com/.

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Since PSA was approved by the United States FDA (Food and Drug Administration), it has become the most widely used tool to monitor and detect PCa. Annual screening in the prostate portion of the PLCO (Prostate, Lung, Colorectal and Ovarian) Cancer Screening Trial was not associated with decreased PCa specific mortality.[1,2] A significant portion of men would be over diagnosed and overtreated as a result of PSA screening.[3] On the other hand, PSA derivatives such as PSAD appear to identify patients at low risk with PCa who would not need active treatment.[4] In the context of monitoring patients after therapy PSA kinetics better predicted the outcome than a single PSA measurement.[5,6] Low PSA predicted a lower long-term risk of PCa and all-cause mortality in longitudinal community studies.[7,8]

RP remains a widely used treatment for localized PCa, although up to 35% of patients experience relapse postoperatively.[9] Intervention before clinical recurrence gives patients the opportunity for better long-term cancer-free survival.[10] The sensitivity of detecting BCR is directly related to the sensitivity of the PSA assay. The LLD of commercial first generation PSA assays is 0.3 to 0.4 ng/ml and any detectable serum PSA after RP could be rightfully interpreted as residual or recurrent cancer.[11,12]

Since that time, second generation uPSA assays have improved sensitivity with most manufacturers offering assays with a LLD of 0.1 ng/ml or less.[13,14] This sensitivity level satisfies current AUA (American Urological Association) and EAU (European Association of Urology) guidelines that define BCR after RP as PSA 0.2 ng/ml or greater. Further technical advances enabled assays to be developed with a LLD as low as 0.001 ng/ml, which allowed BCR detection months to years earlier compared to standard assays.[15–17]

The use of uPSA is increasing in the urological community. However, no clear guidelines exist on its role in monitoring patients after RP. Earlier detection may translate to more efficacious salvage therapy and potential for improved survival. In this review we systematically analyzed available evidence on uPSA performance in the followup of patients after RP. We also established a practical guideline for using uPSA to monitor patients after RP.

PATIENTS AND METHODS

No clear definition of uPSA exists in the literature. Early reports used the term ultrasensitive for second generation assays with a detection limit of 0.1 ng/ml, which may be misleading in the current era.[13,14] Thus, we considered an assay ultrasensitive only when PSA less than 0.1 ng/ml was reported, in contrast to standard PSA assays for which PSA less than 0.1 ng/ml is reported as undetectable.

In July 2014 we searched the MEDLINE database. Only original articles in English were considered for review. Search terms included ultrasensitive, prostate-specific antigen and prostatectomy. Other descriptive terms that are interchangeable with ultrasensitive (ie supersensitive, hypersensitive and sensitive) were included. Lower limit of detection and other terms that specify the assay sensitivity level (ie lower detection threshold, lower detection sensitivity, lower limit and analytical sensitivity) were also used. To identify relevant reports that may not mention ultrasensitivity or specify a detection limit of the assay we included specific values, ranging from 0.01 to 0.09 ng/ml at 0.01 ng/ml increments. The same strategy was applied for 0.001 to 0.009 ng/ml.

This study was developed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses).[18] Eligibility criteria for study inclusion considered participants, intervention, comparators, outcomes and study design. Eligible studies included patients who underwent RP with serial postoperative uPSA data and standard PSA data or a traditional definition of BCR as comparators. Outcome included one of certain topics, including lead time to BCR diagnosis, BCR PPV, uPSA kinetics, prognostic significance of the undetectable uPSA nadir and implications for adjuvant/salvage XRT. All study designs except case reports were included in analysis. Figure 1 shows the study search and selection flow diagram.

RESULTS

BCR Diagnosis Lead Time

Time from first detectable uPSA to more traditionally defined BCR was based on multiple stored serum samples from patients with known BCR, which was presented as an efficacy uPSA assay end point in earlier studies (table 1).[15,16,19–22] Detection limits of uPSA assays were 2.5 to 25 times lower than those of standard assays used for comparison. Average lead time to BCR diagnosis was 1 year (range 9 to 29 months). Notably tumor characteristics and other factors such as followup, which influence this lead time, were heterogeneous or not mentioned in some studies. Moreover, the BCR definition was not universal, limiting data generalizability.

Ultrasensitive PSA

Positive predictive value. PSA has been detected in men who undergo cystoprostatectomy for bladder cancer without identifiable PCa. This was hypothesized to arise from the periurethral glands.[23] Even in some women serum PSA is detectable by an ultrasensitive assay.[24,25] Several groups reported serum uPSA levels in control populations lacking the prostate (table 2).[14–17,20,24–27] Pooled analysis