Management of an Increasing Prostate-Specific Antigen Level After Negative Prostate Biopsy

Katsuto Shinohara, MD*, Hao Nguyen, MD,
Selma Masic, MD

KEYWORDS

• Repeat prostate biopsy • Transrectal ultrasonography • PCA3 • Anterior cancer
• Transperineal prostate biopsy • Multiparametric magnetic resonance imaging

KEY POINTS

- Percent free prostate-specific antigen (PSA), PSA velocity, PSA density, and PCA3 can suggest further risk of malignancy in patients with previous negative biopsy.
- Repeat biopsy should be directed to areas not previously sampled, such as anterior part, extreme apex and base, and midline.
- Changing the route of biopsy to a transperineal approach may improve the detection of anteriorly located cancers.
- Multiparametric magnetic resonance imaging (MRI) shows the cancer location with higher sensitivity than transrectal ultrasonography (TRUS) and should be considered before repeat biopsy.
- Newer tumor markers, field defect markers and MRI/TRUS fusion technology may improve sensitivity and specificity of detection of prostate cancer.

INTRODUCTION

Persistent increase in prostate-specific antigen (PSA) levels in patients with previous negative biopsies creates a clinical dilemma. Increase in PSA levels is nonspecific and can be associated with benign causes, such as benign prostatic hyperplasia, infection, inflammation, infarction, mechanical stimulation, and so forth. Despite its vague implications, urologists are compelled to evaluate increasing PSA levels to avoid missing a diagnosis of prostate cancer. With the recent increase in septicemia cases associated with prostate biopsies,[1] complications can be costly and potentially life threatening. With conventional transrectal ultrasonography (TRUS) technology, sampling errors are inevitable, and a negative biopsy does not rule out malignancy with certainty. The management of the patient with repeatedly negative prostate biopsies and clinical characteristics suggestive of cancer, such as an increased PSA level or abnormal digital rectal examination (DRE), remains a challenging problem for physicians and patients. The current TRUS-guided prostate biopsy technique may be associated with some discomfort and pain. Further, potential complications associated with biopsies are not negligible. Which findings necessitate repeat biopsy and when repeat biopsies should be recommended is difficult to determine. With low certainty of finding a high-risk cancer on repeat biopsy, the benefits of determining a diagnosis must be weighed against the risks of subjecting patients to rebiopsy-related morbidities.

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Department of Urology, University of California, San Francisco, 1600 Divisadero Street A-634, San Francisco, CA 94143-1695, USA
* Corresponding author.
E-mail address: kshinohara@urology.ucsf.edu

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RISK OF FALSE-NEGATIVE RESULTS WITH PROSTATE BIOPSY

Repeat prostate biopsies detect cancer in 16% to 41% of cases in which the initial biopsy was negative.[2] At the University of California at San Francisco (UCSF), Shinohara and colleagues attempted to identify predictors of positive biopsy to avoid unnecessary biopsy procedures in patients at low risk for malignancy by studying 325 men with a history of 2 or more negative biopsies. The mean age of this patient population was 61 years, with a mean serum PSA level of 13.8. The repeat positive biopsy rate in these patients was 38%. The percentage of patients with a positive biopsy decreased as the number of previous negative biopsies increased: 40% in patients with 2 or 3 previous negative biopsies, 36% in patients with 4 or 5 previous negative biopsies, and 17% in patients with 6 previous negative biopsies. Using a Cox proportional hazards model, predictors of positive biopsy were identified, including higher serum PSA level, increased age, hypoechoic lesions on ultrasonography, and smaller prostates. Abnormal pathology (prostatic intraepithelial neoplasia [PIN], atypical small acinar proliferation [ASAP]) on previous biopsy, abnormal DRE, and transition zone volume were not significant predictors of a positive biopsy (Shinohara K, unpublished data, 2004). Clinical data accumulation now identifies more reliable predictors for patients who need a repeat biopsy in this population. Ploussard and colleagues reported the factors associated with repeat biopsy on longitudinal follow-up among patients who had initially negative biopsy. Of 617 men followed for a mean of 19 months, 31% underwent repeat biopsy. The risk factors for repeat biopsy are high PSA levels, high PSA density (PSAD), and younger age. These investigators also reported PSA levels greater than 6 ng/mL, PSAD greater than 0.15, prostate volume less than 50 mL were associated with positive biopsy results.

PREDICTORS FOR REPEAT PROSTATE BIOPSY

High-Grade PIN and ASAP

High-grade PIN (HGPIN) is found on a varying but significant fraction of prostate biopsies (1%–25%), with most modern series having an average of 5%.[3] PIN is characterized by architecturally begin prostate acini, which are lined by cytologically atypical cells. HGPIN may be a precursor lesion to adenocarcinoma.[4,5] Previously, the discovery of HGPIN on first prostate biopsy prompted repeat prostate biopsy in 3 to 6 months. Published series of those with HGPIN who undergo repeat biopsies show a cancer detection rate of 30% to 50%. However, Lefkowitz and colleagues[6] reported that with an extended biopsy scheme showing HGPIN, repeat biopsy showed cancer in only 2.3% of cases. These investigators recommended that immediate repeat biopsy is not necessary after a 12-core biopsy showing HGPIN. Netto and Epstein[7] reported a higher incidence of cancer diagnosis in patients with initial biopsy showing widespread HGPIN. More recently, Lee and colleagues[8] reported their results of 328 men undergoing repeat prostate biopsy after the initial biopsy showed HGPIN. In their study, these investigators found that a group with multifocal or bilateral HGPIN on initial biopsy had a significantly increased hazard ratio of subsequent prostate cancer compared with the unifocal HGPIN disease group. These investigators found a 3-year cancer detection rate of 29% to 37% in the multifocal HGPIN group.

ASAP, which has also previously been termed atypical adenomatous hyperplasia or atypia, is characterized by the crowding and proliferation of small glands; however, cytologic atypia is minimal.[9] This lesion has been less well characterized than HGPIN, but ASAP alone is identified in 5% of patients undergoing needle biopsy. Iczkowski and colleagues[10] proposed further classification of this lesion into 3 categories (favoring benign, uncertain, and favoring malignant) and suggested correlation of each category with subsequent cancer detection. The association of ASAP with prostate cancer is higher than that of HGPIN. Contemporary biopsy series looking at the influence of ASAP have shown that the probability of detecting adenocarcinoma on repeat biopsy is 40% to 50%. Having both HGPIN and atypia together on the first biopsy may increase the rate of cancer detection on the second biopsy to as high as 75%.[11]

The current indications for repeat biopsy within the first year based on National Comprehensive Cancer Network (NCCN) Guideline Version 2012 include ASAP found on initial biopsy and extensive (multiple biopsy sites, $\geq$2 cores) HGPIN lesions.[12]

DRE, PSA and PSA Derivatives

Abnormal DRE or abnormal PSA values lack specificity for detecting prostate cancer, especially after the first negative biopsy, with the positive predictive value of PSA detecting clinically significant cancer ranging from 25% to 40%. A PSA level in the range between 4 and 10 most often resulted in a 60% to 70% negative biopsy rate. Prostate cancer is also detected in 17% to 27% of patients with PSA levels from 1 to 4 ng/mL.[13] Furthermore,