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Collaborative Review – Prostate Cancer

Optimizing Performance and Interpretation of Prostate Biopsy: A Critical Analysis of the Literature

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Abstract

Context: The number and location of biopsy cores and the interpretation of prostate biopsy in different clinical settings remain the subjects of continuing debate.
Objective: Our aim was to review the current evidence regarding the performance and interpretation of initial, repeat, and saturation prostatic biopsy.
Evidence acquisition: A comprehensive Medline search was performed using the Medical Subject Heading search terms *prostate biopsy, prostate cancer, detection, transrectal ultrasound (TRUS), nomogram,* and *diagnosis*. Results were restricted to the English language, with preference given to those published within the last 3 yr.
Evidence synthesis: At initial biopsy, a minimum of 10 but not >18 systematic cores are recommended, with 14–18 cores in glands ≥50 cm^3. Biopsies should be directed laterally, and transition zone (TZ) cores are not recommended in the initial biopsy setting. Further biopsy sets, either as an extended repeat or as a saturation biopsy (≥20 cores) including the TZ, are warranted in young and fit men with a persistent suspicion of prostate cancer. An immediate repeat biopsy is not indicated for prior high-grade prostatic intraepithelial neoplasia diagnosis given an adequate extended initial biopsy. Conversely, biopsies with atypical glands that are suspicious but not diagnostic of cancer should be repeated within 3–6 mo. Overall recommendations for further biopsy sets (a third set or more) cannot be made. Transrectal ultrasound–guided systematic biopsies represent the standard-of-care method of prostate sampling. However, transperineal biopsies are an up-to-standard alternative.
Conclusions: The optimal prostatic biopsy regimen should be based on the individualized clinical setting of the patient and should follow the minimum standard requirements reported in this paper.

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1. Introduction

The early detection of prostate cancer (PCa) should be aimed at diagnosing significant disease at a curable state. Within the past 2 decades, substantial improvements in early detection have been achieved [1,2]. For example, the increased use of prostate-specific antigen (PSA) has resulted in so-called stage migration, shifting the proportion of pathologically localized curable disease from 20% to 30% in the pre-PSA era to about 70–80% currently [3].

1.1. Challenges of early detection

Despite this significant shift toward curable stages, early PCa detection remains limited in several ways. First, a PSA cut-off level such as 4.0 ng/ml for biopsy indication is characterized by a limited PCa specificity due to the effect on PSA of other underlying prostatic diseases such as inflammation or benign prostatic hyperplasia. Therefore, PSA represents only a surrogate marker of PCa. Additionally, as clearly demonstrated in the Prostate Cancer Prevention Trial (PCPT), instead of cut-off levels, PSA values represent a continuum of PCa risk. Thus single PSA measurements are unable to rule out the presence of disease [4]. In fact, it may be anticipated that the principal early detection driving force, that is, PSA, will weaken its association to PCa because a significant proportion of men who present for prostatic evaluation already have PSA values below specific cut-off levels such as 4.0 ng/ml. Consequently, the benefits of PSA-driven early detection, especially in the light of the most recent data from the European and American PCa screening trials, must be carefully balanced and may also be perceived controversially [1,2].

Second, except for palpable lesions, clinical symptoms on which a urologist may identify early disease are practically absent [5]. Third, despite substantial technological progress, neither visualization nor molecular characterization is currently advanced enough to indicate reliably the presence or absence of underlying malignant disease [6].

Therefore, the significant research effort based on established clinical prebiopsy risk factors such as age, PSA, percentage of free prostate-specific antigen (%fPSA), digital rectal examination (DRE), prostate volume, and the consideration of novel markers such as urinary prostate cancer antigen 3 (PCA3) [7–12] has resulted in multifactorial statistical models to individualize biopsy indication and thus to subject only those men with the highest risk to further prostatic evaluation. In addition to identifying those individuals at high risk for harboring PCa, the combined proper use of prebiopsy clinical risk predictors reduces the proportion of unnecessary biopsies, biopsy-related side effects, and patient anxiety [8,13].

1.2. Challenges of prostate biopsy

Prostate biopsy represents a "hot-spot area" on different levels [14]. For example, the determination of the optimal number of cores and prostate sampling sites stratified according to biopsy session, the systematic versus targeted prostate biopsy approach, the need to quantify certain histologic patterns such as high-grade prostatic intraepithelial neoplasia (HGPIN), the optimal pathologic processing of the biopsy cores, and the expertise-dependent pathologic interpretation are controversial.

Beyond these ongoing debates, it is important to note that "typical" clinical biopsy studies carry a so-called verification bias that makes it difficult to truly assess, for example, the influence of different biopsy schemes due to the unknown proportion of "falsely biopsy-negative" men [15]. Consequently, identification of a prostate biopsy gold standard is almost impossible.

Taken together, these different activities potentially add to the current uncertainty of how to perform and how to interpret a prostatic biopsy. To address this significant and competitive interdisciplinary field, this review considers the current clinical evidence investigating risk factors including novel markers, performance of prostate biopsy in different clinical settings, and pathologic interpretation of prostate biopsy.

2. Evidence acquisition

A systematic review of the literature was performed in December 2009 using the Medline database. The Medline search used a complex search strategy including both Medical Subject Heading (MeSH) search terms and free-text protocols. Specifically, the MeSH search was conducted by combining the following terms retrieved from the MeSH browser provided by Medline: *prostate biopsy, prostate cancer, detection, transrectal ultrasound (TRUS)*, *nomogram,* and *diagnosis*. Subsequently, the search results were restricted to the English language, with preference given to articles published within the last 3 yr.

3. Evidence synthesis

3.1. What to consider before biopsy

3.1.1. Risk stratification models as clinical decision aids for biopsy indication

Risk estimation, patient counseling, and decision making are based on clinical judgment. The major limitation is that clinical judgment is biased at all of these stages of patient management [16–19]. Specifically, PCa risk depends on multiple clinical risk factors. In fact, it is difficult to adequately consider the multitude of these clinical variables followed by weighing each factor's relative importance and to formulate a PCa risk estimation [20–22]. Therefore, statistical models have been developed to circumvent these biases. The currently available decision aids consist of logistic regression-based nomograms, risk groupings, artificial neural networks, probability tables, and classification and regression tree (CART) analyses [23]. With the adoption of these models, only those men at high risk of PCa are being referred for further prostatic evaluation. Thus significant patient-related factors such as anxiety or biopsy-related complications are being reduced, and at the same time, health and economic aspects are being optimized. In