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A review of optimal prostate biopsy: indications and techniques

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***Abstract*:** Prostate biopsy is the gold standard diagnostic technique for the detection of prostate cancer. Patient selection for prostate biopsy is complex and is influenced by emerging use of prebiopsy imaging. The introduction of the magnetic resonance imaging (MRI)–transrectal ultrasound (TRUS) fusion prostate biopsy has clear advantages over the historical standard of care. There are several biopsy techniques currently utilized with unique advantages and disadvantages. We review and summarize the current body of literature pertaining to when and how a prostate biopsy should be performed. We discuss current recommendations regarding patient selection for biopsy and discuss future directions regarding prebiopsy imaging. We offer a description of the MRI–TRUS fusion biopsy technique and a comparison of many of the currently available fusion software platforms. Articles pertaining to the title were obtained via PubMed index search with relevant keywords supplemented with personal collection of related publications. Prostate biopsy should be considered for patients with gross digital rectal exam (DRE) abnormality, patients with a prostate-specific antigen (PSA) greater than 4 ng/ml, and concomitant risk factors for prostate cancer or patients with lesions identified on multiparametric MRI (mpMRI) with Prostate Imaging Reporting and Data System 2 (PI-RADS2) score of 4 or 5. MRI–TRUS fusion biopsy has demonstrated advantages in cancer detection when compared with TRUS-guided biopsy. There are currently several fusion software platforms available with a variety of biopsy approaches. Future efforts should detail the role of prebiopsy imaging as a triage tool for prostate biopsy. Consensus should be sought regarding the preferred modality of fusion biopsy. Additional data describing each fusion software platform would enable a more rigorous comparison of platform sensitivities.

Keywords: imaging, multiparametric magnetic resonance imaging, prostate cancer, prostate specific antigen, techniques

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Introduction

Prostate cancer is the most common form of cancer experienced by men in the United States with 164,690 new cases predicted for 2018.[1] It constitutes a diverse spectrum of disease with clinical behavior ranging from well-differentiated noninvasive tumor to high-grade metastatic cancer with significant morbidity and mortality, and is the second leading cause of cancer death in US men with 29,430 deaths predicted for 2018.[1] Prostate biopsy is the cornerstone of establishing the diagnosis of prostate cancer. Recent advances in imaging technology have lead to improvements in the early detection of prostate cancer. In this literature review, we discuss the indications and techniques for prostate biopsy and summarize recent data concerning the diagnostic performance of several modern techniques.

Prostate biopsy in clinical practice

The decision to proceed with biopsy is complex, evolving, and should be made on an individualized basis. Traditionally, biopsy is performed for three general indications: abnormal digital rectal exam (DRE), increased prostatic-specific antigen (PSA), and clinical suspicion of prostate cancer.

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Prior to the advent of PSA screening, prostate biopsy was performed solely for lesions palpable on DRE.[2] Concerning findings on DRE include nodularity, asymmetry, or diffuse firmness. DRE has a poor positive predictive value (PPV) for detecting cancer (5–30% in one meta-analysis)[3] and is not recommended as a sole screening tool. However, detection of suspicious gross abnormality on DRE may be an indication for biopsy regardless of PSA depending on contextual patient factors.[4]

PSA is an important biomarker that correlates with the risk of prostate cancer. Screening for prostate cancer using PSA has been shown to reduce prostate cancer mortality, but its utility is highly age dependent. The American Urological Association (AUA) provides guidance on who should be screened using PSA. Their recommendations include avoiding screening altogether in men under the age of 40, average risk men age 40–54, men age 70 or older and men with a life expectancy less than 10–15 years. They recommend that for men aged 55–69, the decision to screen using PSA should be shared amongst the physician and patient and that a biennial interval may preserve the benefits of annual screening while reducing overdiagnosis.[5]

The PSA threshold that should prompt a biopsy has not been precisely established owing to the variety of nonmalignant causes of PSA elevation. The AUA does not recommend a single PSA cutoff level that should prompt a biopsy as cancer risk exists at any PSA level. Rather, they recommend that PSA be evaluated in conjunction with PSA density, free, and total values as well as patient specific risk factors such as age and family history.[5] The Prostate Cancer Prevention Trial demonstrated that men with PSA values greater than 4 ng/ml with a normal DRE have a 30–35% risk of having cancer.[6] Men with lower PSA levels still bear a significant cancer risk. Thompson *et al.* demonstrated a 32% sensitivity for cancer detection using a threshold value of 3.1 ng/ml.[7] The American Cancer Society performed a pooled analysis of PSA performance literature and described a 21% sensitivity for 4 ng/ml and 32% sensitivity for 3 ng/ml cutoffs.[8] A reasonable summary of the available evidence suggests that men within the at-risk age group with PSA greater than 4 ng/ml should undergo prostate biopsy.[4]

The AUA recommends considering the use of risk calculators subsequent to a suspicious PSA value to aid in the decision to proceed to biopsy.[5] However, because of the varying populations involved in construction of each specific risk calculator generalizability may be limited. In addition, use of risk calculators has not been shown to improve the benefit to harm ratio in patients being screened. Risk calculators do have use in illustrating to patients that cancer risk varies on a spectrum of PSA values. The traditional approach of DRE and PSA to inform decision to biopsy as described above lacks sensitivity and specificity for cancer leading to a relatively high rate of unnecessary biopsies.[9]

Role of multiparametric MRI in prostate biopsy

Recent advances in imaging techniques including multi-parametric MRI (mpMRI) have enabled non-invasive assessment of the prostate for suspicious lesions. mpMRI is a MRI technique that involves conjunctive use of multiple MRI sequences to more accurately characterize lesions.[10] mpMRI reporting has been standardized by the European Society of Urogenital Radiology through the development of the Prostate Imaging Reporting and Data System (PI-RADS), which was updated to version 2 in 2015. Park *et al.* demonstrated in a retrospective study of patients who underwent both mpMRI and radical prostatectomy that PI-RADS2 score greater than 4 was 77% and 73.8% sensitive for detection of clinically significant cancer for each of the two readers with excellent inter-reader agreement.[11] A recent meta-analysis by Woo *et al.* assessing the diagnostic performance of PI-RADS2 included 3857 patients and found a pooled sensitivity of 89% and specificity of 73% for cancer detection.[12] Lesions with PI-RADS2 scores of 4 or 5 indicate a high or very high likelihood of clinically significant cancer, respectively, and should be biopsied.[13]

Lesions with PI-RADS2 score of 3 are considered to have equivocal likelihood of being clinically significant and no guidance is offered by PI-RADS. Scialpi *et al.* suggest subgrouping these lesions based on tumor volume and recommend targeted biopsy for volume >0.5 ml although this has not been validated.[14] Hansen *et al.* recommend further subjective evaluation by an experienced uroradiologist regarding decision to biopsy.[15] Lesions with PI-RADS2 scores of 1 or 2 have very low and low likelihoods of harboring clinically significant cancer respectively and should not be biopsied based on

imaging findings alone.[13] An *et al.* evaluated the likelihood of a patient having significant cancer despite negative mpMRI. They demonstrated a systemic biopsy detection rate of 3.6% for Gleason 7 or higher lesions with a negative predictive value (NPP) of 96.5% suggesting biopsy may be unnecessary for these patients although more data is needed before a definitive recommendation can be made.[4,16]

The application of mpMRI in prebiopsy lesion characterization has the potential to revolutionize prostate cancer screening and patient selection for biopsy. The PROMIS trial, a large multicenter trial that compared the accuracy of the TRUS-guided biopsy and the mpMRI against a reference test, determined that if used as a triage test the mpMRI could eliminate 25% of patients from undergoing a prostate biopsy.[17] The mpMRI has a sensitivity of 93% (95% CI 88–96), specificity of 41%, PPV of 51%, and NPV of 89%. The TRUS-guided biopsy, on the other hand, demonstrated a sensitivity of 48%, specificity of 96%, PPV 90%, and NPP of 74%,[17] which demonstrates the benefit of using the mpMRI as a triage tool for biopsy naïve patients with an elevated PSA. Furthermore, the PRECISION trial, which looked at 500 men who underwent either mpMRI then targeted biopsy, or standard transrectal biopsy, found that the MRI was superior at limiting the amount of men who needed biopsies and the discovery of more clinically significant cancers.[18]

A recent Cochrane Review by Drost *et al.* sought to compare the diagnostic performance of four index tests to a template guided biopsy reference.[19] The index tests included MRI alone, MRI-guided biopsy, MRI pathway (MRI with or without subsequent MRI guided biopsy), and systemic TRUS biopsy. The analysis included 43 studies of men with suspicion of prostate cancer undergoing either initial or repeat biopsy. The key finding of the study was that the MRI pathway evinced the strongest diagnostic performance in detection of clinically significant (IUSP grade 2) prostate cancer with a pooled sensitivity of 72% and pooled specificity of 96%. The MRI pathway notably outperformed systemic biopsy with a 12% greater likelihood of identifying clinically significant cancer in a mixed group of patients. The authors cite issues pertaining to selection bias and study inconsistency but conclude that the MRI pathway could reduce over diagnosis of low-grade cancer while improving the detection of significant cancer. They suggest that MRI preceding biopsy likely represents the preferred diagnostic strategy for most patients.

Currently, the AUA suggests that mpMRI-based screening should be considered purely investigational and awaiting results of PROMIS and PRECISION trials before making a statement on the change in adoption,[20] but it will be intriguing to see how rapidly it will change clinical practice.

Types of prostate biopsy

Historically, TRUS guided biopsy has been the standard approach. There are a variety of sampling schema with number of cores ranging from 6 to extensive 24 core saturation biopsy. Eichler *et al.* compared the cancer detection rates (CDRs) for several of these schemes and found that increasing number of cores was not associated with better cancer yield.[21] Laterally directed sampling significantly improved detection while 18–24 core sampling did not suggesting that 12 cores provides adequate sensitivity. Later studies demonstrated an improved sensitivity with 24 core saturation biopsy for men with suspicion of prostate cancer in spite of prior negative biopsy and in men with very large prostate volume.[6,22] Brock *et al.* found a clinically significant CDR of 37.5% in men with elevated PSA using 12-core systemic biopsy which is approximate to sensitivity data obtained in similar studies.[23,24]

Contemporary MRI-guided biopsy strategies preferentially detect clinically important lesions and offer clear benefits over the traditional systematic biopsy.[25] MRI-guided biopsy involves selective sampling of lesions identified as suspicious on mpMRI. There are several methods currently in use for targeted prostate biopsy: direct MRI-guided (in-bore) biopsy, cognitive fusion biopsy and MRI–TRUS fusion biopsy.

Direct MRI-guided biopsy involves obtaining an initial mpMRI localization data to describe regions of high tumor suspicion. This dataset is then mapped to a T2 anatomic scan obtained just prior to the biopsy. The regions of tumor suspicion are targeted for biopsy using a nonmagnetic biopsy needle device. Once the needle is placed in the prostate, fast T2 images are obtained to determine accurate delivery.[26] This approach has been shown to be effective in detecting clinically significant cancer in patients with rising PSA and prior negative TRUS biopsy. Hoeks *et al.* demonstrated a

CDR of 41% with 87% being clinically significant.[27] Quentin *et al.* compared in-bore biopsy to standard TRUS biopsy and demonstrated a higher percent of cancer involvement per core with significantly fewer cores required.[28] Although the benefits of this technique are clear, there are several important drawbacks. In-bore biopsy requires a significant upfront investment in MR-compatible biopsy equipment as well as competition for use of MR scanner units. In addition, coordination between urology, radiology, and anesthesiology adds logistic complication and scheduling difficulty making this biopsy technique somewhat less common in modern practice.[29]

Cognitive fusion biopsy is the simplest technique for incorporating mpMRI data into a prostate biopsy. Patients in need of prostate cancer evaluation undergo mpMRI as in other MR-guided techniques and lesions of interest are identified. The operator then manually targets these lesions during TRUS biopsy using anatomical landmarks apparent on ultrasound with reference to the mpMRI scan. This technique was studied by Sciarra *et al.* for patients with persistently elevated PSA and negative TRUS biopsy. They found a significantly better CDR with cognitive fusion biopsy compared with saturation biopsy (45.5 *versus* 24.4%).[30] Puech *et al.* compared cognitive fusion with MRI–TRUS fusion software biopsies and found no significant differences in CDR between the techniques.[31] The lack of special software or technology related to the procedure itself is a significant benefit. This method of fusion biopsy is simple, quick, less expensive with improved accuracy over conventional systemic biopsy. However, there are notable disadvantages including a large dependence on technical abilities of the operator and a presumed reduced accuracy for small lesions.[32]

The MRI–TRUS fusion biopsy was designed to allow for biopsies to be taken in an office setting, as opposed to the direct MRI-guided biopsy. It involves using different software platforms to integrate the MRI data to the ultrasound for a more accurate biopsy.[33] MRI-fusion biopsies have continually been proven to be more effective at detecting clinically significant prostate cancer in comparison with standard systematic biopsy.[34–38] Valerio *et al.* ran a meta-analysis to evaluate the CDR of MRI fusion *versus* standard sextant biopsy. They found a 30% CDR with fusion biopsy per core *versus* 7% with standard biopsy per core.[39] There is current debate over how to best utilize MRI fusion biopsies. Disadvantages associated with this method is that it requires specialized operator training and involves use of an additional device.[40]

The recently published FUTURE trial sought to compare three different MR-guided biopsy techniques with respect to detection of both overall and clinically significant prostate cancer.[41] The multicenter study involved 665 European men with prior negative systemic biopsy and continued suspicion for prostate cancer. All patients underwent mpMRI with lesions classified using the PIRADS2 schema. Patients with PIRADS $\geqslant 3$ lesions were randomized to either MR fusion biopsy, cognitive fusion biopsy or in-bore MRI biopsy and cancer detection rates were compared. The authors did not find any significant differences in both overall and clinically significant cancer detection between the three groups. An important weakness of the trial was the low prevalence of PIRADS $\geqslant 3$ lesions (35%) which was 50% lower than expected and reduced the power for detecting the primary endpoint. As no difference in detection rates was found, the authors recommend evaluating the unique factors related to each technique (expense, local expertise, need for anesthesia) when deciding which technique is best for a patient.

Owing to the cost and potential difficulties in determining thresholds for mpMRI abnormalities, MRI-fusion biopsies are used in conjunction with elevated PSA and DRE.[20] There are multiple software systems available for in office fusion biopsies. We discuss a few of the more commonly used systems below.

Commonly used MRI fusion platforms

Artemis (Eigen) is one of the more popular fusion-biopsy systems used in the world today. It incorporates ProFuse multimodality fusion software to convert the 2D MRI image into a 3D image that is superimposed on the TRUS images.[42,43] This allows for more focused targeting of lesions discovered on the MRI in an office setting. In 2013, Sonn *et al.*[38] performed a study with 171 men using the Artemis system and found that the targeted biopsies found increased rates of Gleason $\geqslant 7$ cancers (36%; $p = 0037$) in comparison with systemic core biopsies (24%). Furthermore, they found that 38 % of Gleason $\geqslant 7$ cancers were detected only with the targeted biopsy.[38] Meng *et al.*[36] also used the Artemis system and found that MRI-fusion

targeted biopsy detected fewer Gleason score 6 prostate cancer (75 *versus* 121; $p < 0.001$) and more Gleason score $\geqslant 7$ cancers (158 *versus* 117; $p < 0.001$) than systemic biopsy. These results are in concordance with other research demonstrating improved CDR with fusion biopsy in comparison with systemic biopsies.[35,37,38] As with every technology, there is a learning curve associated with the urologists using the Artemis system. On an individual level, Kasabwala *et al.*[44] demonstrated that at 150 cases there was improvement in region of interest (ROI) biopsies and a decrease in biopsies without prostate tissue from 18% to 3.3 %. As a system, Demirel *et al.*[45] showed that there was an improved rate of ROI positivity from 41 % at the beginning of the study in 2012 up to 66 % later in the study near 2017 (trend test, $p < 0.001$). When compared with cognitive fusion, the Artemis fusion biopsy technique identified more informative diagnoses (77 *versus* 60, $p = 0.0104$) and demonstrated a multivariate trend towards improved CDR.[46]

UroNav (Invivo) is another fusion biopsy system and was developed in National Institute of Health in Bethesda, MD, USA, in collaboration with Philips Healthcare. UroNav utilizes electromagnetic guidance to target MR lesions.[43] UroNav can be used for both transrectal and transperineal approaches to obtain biopsies. Using the UroNav system, Siddiqui *et al.* found a 30% increase in identification of high-risk cancers with targeted biopsy *versus* standard biopsy ($p < 0.001$) and 17% fewer low-risk cancers ($p = 0.002$).[37] In a follow up of previously nontarget prostate lesions, Chelluri *et al.* elucidated that only 16% of rebiopsied lesions were found to have prostate cancer, and only 1.5% of all lesions were shown to have clinically significant cancer.[47] This demonstrates the low false-negative rate of using the UroNav system for fusion biopsy. Recently, the UroNav system was used to biopsy cancers using the transperineal technique. Overall prostate cancer detection was found at 81.3% with clinically significant cancer detection at 59.4%.[48] The transperineal approach is becoming more popular, even with the need for general anesthesia, because there is no need for antibiotic prophylaxis and no pain.[49] Furthermore, Calio *et al.* demonstrated an improvement over time in detecting clinically significant prostate cancer using UroNav ($p < 0.001$) with each of their successive cohorts between 2007 and 2016.[34]

Another novel device is Urostation (Koelis), which is unique in that it is software imaging based. Urostation uses both real-time 3D TRUS image guidance and 3D MRI-TRUS fusion guidance to allow the urologist to move the ultrasound probe to get the correct biopsies.[42,43] Ukimura *et al.* tested the Urostation system using prostate phantom models with known hypoechoic and isoechoic MR visible lesions. A total of 84% of the fusion biopsies hit the lesion.[42] Mozer *et al.* looked at 152 men with elevated PSA and using the Urostation for targeted biopsies, found an increase in clinically significant prostate cancer detection when compared with the standard protocol.[50] Recently, Bey *et al.* compared Urostation fusion biopsy with standard ultrasound-guided biopsy to help explain any potential differences in cohorts for each technique.[51] With multivariate analysis, they found an odds ratio of 3.00 (95% CI 1.52–6.17, $p = 0.002$) for MR-fusion compared with ultrasound alone.[51]

Other devices include Hitachi/HI-RVS (Hitachi Medical Corporation), BiopSee (MedCom), Virtual Navigator (Esaote), BioJet (GeoScan), Mona Lisa (Biobot Surgical Pte Ltd.), and LOGIQ 9 (GE Healthcare).[32,43]

As described, these platforms have several unique differences in design and clinical execution and all have demonstrated superiority to systemic biopsy with respect to cancer detection. Unfortunately, there is a complete lack of data directly comparing fusion biopsy systems making it difficult to distinguish systems based on published outcomes. As this technology continues to mature and use becomes more widespread research efforts should focus on obtaining direct comparative data to determine which fusion biopsy strategies are superior.

Conclusion

Prostate biopsy remains the cornerstone of prostate cancer diagnosis and TRUS-guided biopsy is widely used in the diagnosis. Indications of prostate biopsy include gross DRE abnormality, PSA greater than 4 ng/ml in the high-risk age group, or lesions with PI-RADS2 score of 4 or 5 on mpMRI. PI-RADS 3 lesions have an equivocal cancer risk; decision to biopsy should be based on subjective evaluation by an expert uroradiologist or patient-specific factors. The application of mpMRI to the diagnosis of prostate cancer has the potential to revolutionize the current practice and emerging data highlight its potential use as a biopsy triage tool. MRI-fusion-guided prostate biopsy techniques have been shown to be superior to the

historical standard of care TRUS biopsy as it is associated with high CDR, eliminating unnecessary systematic prostate biopsies for patients with elevated PSA levels, and repeated tumor-negative TRUS biopsy. There are several fusion software platforms each with demonstrated advantage in cancer detection compared with TRUS although no direct comparisons between platforms have been made. As more data emerges, consensus should be sought regarding the role of prebiopsy imaging in prostate cancer and how this effects patient selection for biopsy and intervention.

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