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Magnetic Resonance-Ultrasound Fusion Prostate Biopsy in the Diagnosis of Prostate Cancer

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Abstract

The advent of multiparametric magnetic resonance imaging (mpMRI) has ushered in a new era for urologists who perform prostate needle biopsies. The fusion of MRI with transrectal ultrasound (TRUS) allows the direct targeting of suspicious lesions, which has been shown to improve the performance of conventional random biopsy techniques by increasing detection of clinically relevant disease while also decreasing detection of low-risk cancer. However, as with any new technology, many questions regarding effectiveness, reproducibility, and generalizability still remain. In this review, we 1) provide a summary of the various sequences that comprise a MRI of the prostate; 2) evaluate the three different ways of incorporating MRI into targeted biopsies of the prostate including in-bore MRI-guided biopsy, cognitive fusion, and device-mediated fusion; 3) review the sensitivity of MR-US fusion in the detection of clinically significant and clinically insignificant disease; and 4) review the barriers to the widespread implementation of MR-US fusion into everyday practice. While other articles in this issue of *Urologic Oncology Seminars* will discuss other aspects of MRI in the management of prostate cancer, the purpose of this article is to provide an overview of MR-US fusion biopsies in the diagnosis of prostate cancer.

Keywords

Magnetic Resonance Imaging; Ultrasound; Fusion; Prostate Biopsy; Prostate Cancer

1. Introduction

With an estimated 1.1 million incident cases in 2012, prostate cancer constitutes 15% of all new cancers diagnosed among men worldwide.¹ Efforts to accurately diagnose clinically relevant prostate cancer early in the disease course has been a public health priority since the

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introduction of prostate specific antigen (PSA) in the 1980s. However, the gold standard diagnostic test for an elevated PSA - the extended sextant TRUS-guided prostate needle biopsy - has significant clinical deficiencies.^{2,3} While TRUS-guided prostate biopsies initially represented a major advancement over older methods in which biopsy needles were guided only by the examiner's finger, the TRUS technique is non-targeted and prone to sampling error. As a result, TRUS biopsies detect many cancers that don't require treatment and, more importantly, fail to diagnose many cancers that do.⁴⁻⁶

In an effort to improve the performance of TRUS-guided prostate biopsies, several commercially available solutions have been introduced to the marketplace over the last decade. One solution that has garnered significant momentum has been the incorporation of prostate MRI into the prostate biopsy armamentarium. Compared to TRUS, multiparametric MRI (mpMRI) has better image resolution, superior visualization of anatomical structures, the capacity for functional assessment, and the ability to assess tumor aggressiveness.⁷⁻¹⁰ As a result, MR-US fusion biopsy systems combine the powerful ability of MRI to visualize clinically relevant prostate cancer with sophisticated probe-tracking software to substantially improve the prostate biopsy technique. In this narrative review, we focus on the fundamentals of MR-US fusion technology, including the basic tenets of mpMRI, cognitive fusion, and MR-US fusion devices. We provide a discussion regarding the sensitivity of MR-US fusion in the detection of clinically significant and clinically insignificant disease and conclude with a review of the potential barriers to the widespread adoption of MR-US fusion into everyday practice.

2. Multiparametric MRI

Hricak et al. was the first to describe the features of prostate cancer on MRI.¹¹ Using a 0.35 T magnet, the authors described malignant prostate tissues as having a higher intensity signal than surrounding benign tissues. Since then, a litany of advancements in MRI technology has improved the ability of MRI to localize prostate cancer *in vivo*. Prostate mpMRIs incorporate a combination of high-resolution T2-weighted images with various functional techniques such as diffusion-weighted imaging (DWI), dynamic contrast enhancement (DCE), and/or MR-spectroscopic (MRS) imaging. The relative clinical value of each component differs and is summarized below.

2.1 T2-weighted imaging

T2-weighted imaging (T2WI), which reflects the tissue water content, provides the best depiction of prostate zonal anatomy and superior tissue contrast for the detection, localization, and staging of prostate cancer.¹² On T2WI, prostate cancer classically manifests as a round or ill-defined, low-signal intensity focus in the peripheral zone. However, this is a very nonspecific finding as myriad conditions such as prostate intra-epithelial neoplasia, prostatitis, hemorrhage, atrophy, scars, and post-treatment changes can mimic cancer on T2WI.¹³ Furthermore, lesion detection is especially problematic in the transition zone because benign prostate hyperplasia can mimic the appearance of cancer.^{14,15} Similarly, biopsy related hemorrhage can cause artifacts that resemble the appearance of cancer, thus the time interval between the biopsy and the prostate MRI should be at least 4–6

weeks.⁹ In our center, we commonly wait 3 months or more. Because of potential false positives, T2WI alone is not recommended as functional parameters, discussed below, improve both the sensitivity and specificity of T2WI (which alone is only 74% and 88%, respectively).¹⁶

2.2 Functional Parameters

DWI is a form of MR imaging that is based upon measuring random Brownian motion of water molecules within tissue.¹⁷ Generally, dense cellular tissues exhibit lower diffusion coefficients and thus diffusion is particularly useful in tumor characterization. The slope of change of the signal, established by the degree of diffusion weighting, is known as the apparent diffusion coefficient (ADC) and generates quantitative maps of molecular mobility. Prostate cancer typically displays high signal intensity on DWI and low values/darkness on ADC maps^{18–20} which dramatically improves the specificity of prostate cancer detection compared to T2WI alone.²¹ Furthermore, ADC values have been shown to correlate with Gleason scores making DWI a potent clinical tool and an essential parameter for all prostate mpMRIs.^{22–25}

Another functional parameter that can improve the performance of T2WI in the detection of prostate cancer is dynamic contrast enhancement. DCE is performed following the administration of gadolinium-based contrast medium and is the most reliable method for evaluating tumor vascularity.²⁶ Similar to other functional techniques, DCE significantly improves both the sensitivity and specificity of prostate mpMRI.²⁷ However, because normal prostate tissue is highly vascular, a pre- and post-gadolinium comparison is usually inadequate to detect prostate cancer without T2WI and DWI.^{28,29} In general, use of DCE in the detection of prostate cancer has demonstrated favorable performance characteristics²⁷ and, although the literature is sparse, DCE may also have an emerging role in the evaluation of post-prostatectomy and post-radiotherapy recurrences.^{30–33}

MR spectroscopy enables the detection of the lower levels of citrate and higher levels of choline in prostate cancer tumors compared to benign tissue.³⁴ MRS can be used to predict the presence or absence of cancer and provide information about the aggressiveness of the disease, but does not give staging information owing to poor spatial resolution.³⁵ Furthermore, it requires a high-level of additional expertise, an endorectal coil at 1.5 T, and adds time to the examination.¹³ Because of these factors, the decision to include MRS in a prostate MRI depends more on local expertise and availability. Figure 1 demonstrates T2WI, DWI, ADC maps and DCE imaging.

2.3 PI-RADS

Prostate Imaging-Reporting and Data System(PI-RADS)TM Version 2 was developed by members of the PI-RADS Steering Committee, several working groups with international representation, and administrative support from the American College of Radiology (ACR) using the best available evidence and expert consensus opinion. Its adoption is designed to promote global standardization and diminish variation in the acquisition, interpretation, and reporting of prostate mpMRI examinations. A comprehensive discussion about PI-RADS is beyond the scope of this article but it can be readily assessed on the ACR website.³⁶

2.3.1 Salient features of PI-RADS

- PIRADS is a system for rating the likelihood of significant cancer in each region of interest, ranging from 1 (very low) to 5 (very high).
- Cancer imaging characteristics are different for peripheral and transitional zone cancers. DWI is the most important sequence in the peripheral zone whereas T2WI is the most important sequence in the transitional zone. DCE adds supportive value to DWI in peripheral zone only whereas DWI adds supportive value to T2WI in the transitional zone. Other sequences like MR spectroscopy are not a part of the PI-RADS criteria.
- Endorectal coils (ERCs) improve image quality by increasing the signal to noise ratio (SNR) at any magnetic field strength, but these have some disadvantages, the most important of which is patient discomfort. For the purpose of cancer detection, satisfactory results have been obtained at both 1.5T and 3T without the use of an ERC but 3T imaging is preferable. Some contemporary 1.5T scanners that employ a relatively high number of external phased array coil elements and radiofrequency channels (e.g., 16 or more) may be capable of achieving adequate SNR in many patients without an ERC but an ERC might be indispensable in older 1.5T scanners. 1.5 T imaging may also be preferable in certain situations like presence of metallic hip implants.

3. Targeted Biopsy Methods

The primary clinical indications for MR/US fusion biopsy are persistently elevated PSAs despite previous negative prostate biopsies and the follow-up of patients on active surveillance. Three different methods of incorporating MRI into targeted prostate biopsies have been described: In-bore MR guided fusion, cognitive MR-US fusion, and device-mediated MR-US fusion. While in-bore biopsies under real-time MRI guidance are quite accurate for targeting areas of interest within the prostate,³⁷ this technique is cumbersome, time-consuming, costly, and impractical since the entire procedure is performed in the MRI gantry.^{38–40} Since MR-US fusion biopsies can be done in the clinic, these techniques are being more widely adopted. Table 1 summarizes the sensitivity of overall cancer detection, clinically significant cancer detection, and clinically insignificant cancer detection among selected studies. While there is substantial variation in the sensitivity of detecting clinically indolent disease across studies, most studies demonstrated that the sensitivity of MR-US fusion (cognitive or device) ranges between 80 and 95% (table 1).

3.1 Cognitive Fusion

Cognitive fusion relies on the ability of the sonographer to localize the region of interest by imagining its location within the prostate after viewing the suspicious lesion on MRI. The advantages of cognitive fusion include speed and parsimony; that is, it involves no extra equipment beyond what is normally required for a TRUS biopsy.⁴¹ However, the disadvantages of cognitive fusion biopsy techniques include the potential for sampling error when attempting to conceptualize the region of interest, especially for smaller tumors. Another downside to cognitive fusion is the inability to track the location of each of the prior

biopsies. Despite that, the tumor detection rate of cognitive fusion is similar to that obtained by device-mediated fusion, and both cognitive and device-mediated fusion appear to be better than random systematic sampling alone in most studies.^{42,43} One interesting study by Haffner et al. did show that cognitive fusion was no better than systematic biopsies among men with suspicious MRIs, which underscores the main concern regarding cognitive fusion: inter-observer variability.⁴⁴ Nevertheless, the current literature on cognitive fusion does demonstrate promise in the hands of expert cognitive fusionists, but because of the lack of tracking and digital overlay, most urologists are now moving toward commercially available device-mediated platforms.

3.2 MR-US Fusion Devices

Device-mediated fusion uses proprietary computer software to overcome the limitations of cognitive fusion. Through a 3D rendering apparatus that superimposes saved MRI images on real-time US images, a process known as co-registration, device-mediated fusion permits the targeting of biopsies into regions of interest that were previously identified on the MRI. While a number of commercial MR-US fusion platforms have become available, they all employ some method of image co-registration and needle/probe tracking (mechanical or electromagnetic). These platforms allow the acquisition, storage, and reconstruction of real-time ultrasound images as well as 3D maps of lesion locations and prior biopsy sites that can be saved for future reference.⁴⁵ Since any movement of the patient or prostate affects the image co-registration, these fusion devices also use dynamic repeat registration methods via motion-compensation software to ensure accurate and reproducible targeting of index lesions.⁴⁶ This review focuses only on Artemis (Eigen/Hitachi) and UroNav (Invivo/Philips) MR-US fusion biopsy platforms, because they are the most extensively studied and are widely available in the US.

3.2.1 Artemis—With the Artemis Device (Eigen, Grass Valley, CA), the position of the US probe is tracked by angle-sensing devices (encoders) built into each joint of the arm.^{47,48} This allows for the reconstruction of the biplanar US into a 3D model, which is then elastically fused with the MRI. The Artemis platform facilitates office-based transrectal prostate biopsies of suspicious regions detected on MRI and tracks the placement of targeted and systematic biopsy cores. The principle advantage of the Artemis platform is the ability of the robotic arm to immobilize the probe from the time of biopsy targeting to the firing of the biopsy gun which theoretically allows for more accurate tracking. The downsides include the cumbersomeness of the Artemis platform compared to other fusion systems, which use freehand biopsies, as well as the increased expense associated with the robotic tracking technology. Nevertheless, in studies of men on active surveillance or those with a prior negative biopsy, the cancer detection rate approaches 55% and up to 94% in patients with highly suspicious lesions on MRI.^{49,50} Furthermore, these studies, and others, consistently demonstrate the preferential detection of significant cancers over clinically indolent tumors.⁵¹

As an aside, while these findings are promising, the concept that targeted biopsies can obviate the need for systematic biopsies should be regarded with caution. In the largest series of Artemis biopsies to date, Filson et al. demonstrated that the combination of targeted

and systematic biopsy resulted in better detection of clinically significant prostate cancer than either method alone.⁵² In 328 biopsy-naïve men, 19% with clinically significant cancers would have been missed with targeted biopsies alone. When the whole cohort is considered, which includes men with both prior negative and positive biopsies (n=1042), 60 men with clinically significant prostate cancer would have been missed with targeted biopsy alone. Taken together, a strong rationale can be made for the continued incorporation of systematic biopsies in combination with targeted biopsies.

3.2.2 UroNav—The UroNav system (Invivo, Gainesville, FL) was developed under a collaborative effort between Invivo, a subsidiary of Philips, and the National Cancer Institute (NCI) in the mid-2000s. UroNav is a modification of the PercuNav system, which was introduced years prior as a GPS for medical instruments.⁵³ The UroNav platform tracks the location of the TRUS probe by following its location in space using a small electromagnetic field generator that is near the patient. The principle advantage of this platform is the freehand use of the US probe during biopsy, which is certainly more familiar to most urologists. This platform also tends to be cheaper than Artemis. The main disadvantage is the probe is tracked using electromagnetic fields instead of mechanical tracking with a robotic arm, which may be less accurate. Despite that, early studies have demonstrated favorable results with cancer detection rates of 28%, 67%, and 89% in men with low-, intermediate-, and high-suspicion MRIs.⁵⁴ Among men with negative prior biopsy, cancer detection rates approached 37%.⁵⁵ Since these initial reports, more than 1000 men have undergone targeted prostate biopsy at the NCI with the UroNav device since it was first developed.⁵⁶ Compared to the standard extended sextant TRUS guided biopsy scheme, the UroNav MR-US fusion biopsy is associated with increased detection of clinically relevant cancer and decreased detection of low-risk cancer.⁵⁶ Whether these rates are significantly different from the Artemis platform is largely unknown since large head-to-head experimental data are not available.

3.3 Cognitive fusion versus fusion device

Whereas the benefits of targeted biopsy compared to random systematic biopsies are clear, the comparative effectiveness of fusion techniques (device versus cognitive) remains unknown. While both device-based and cognitive fusion for targeted biopsies improve the performance of conventional TRUS biopsy, the published studies comparing the effectiveness of each fusion technique report conflicting outcomes. In a study of 391 patients, device-mediated fusion increased the detection of clinically relevant cancer while limiting the detection of insignificant cancers and reducing the number of cores necessary compared to cognitive fusion.⁵⁷ However, a separate prospective study whereby all patients received a 12-core random systematic biopsy and a 4-core targeted biopsy (2 using cognitive fusion and 2 using device-based fusion), found that the cancer detection rate was better than random systematic but similar between fusion techniques.⁵⁸ This finding is supported by similar cancer detection rates in the PROFUS trial, which is a prospective blinded comparison of cognitive versus device-mediated fusion.⁵⁹

4. Barriers to Widespread Implementation

Prior to widespread adoption of MR-US fusion biopsy, several barriers will need to be addressed. First, the accurate interpretation of prostate MRI requires substantial radiological expertise, which may be lacking even in high-volume centers of excellence for prostate cancer care, where prostate MRI is relatively recently adopted. Because the accuracy of MR-US fusion biopsy techniques depends on precise localization of the regions of interest on the prostate MRI, the importance of having experienced radiologists cannot be overstated. With the implementation of the PI-RADS criteria, there is a concerted effort in the radiology world to enable accurate prostate imaging and interpretation. The success of this effort in training the practicing radiologist, who did not receive fellowship training in interpretation of prostate MRIs, remains to be determined.

Second, the cost of device-mediated MR-US fusion prostate biopsy is not inconsequential and is frequently cited as a deterrent to the adoption of this technology. The cost of acquiring the device-mediated platforms in the US ranges between \$200,000 and \$300,000 dollars, which does not take into account the additional cost and expertise required to maintain equipment and perform this procedure.⁶⁰ Furthermore, there is the added costs of time required to integrate the technology into practice as well as the additional time required by the radiologists to define the suspicious lesions. Despite these challenges, emerging data has suggested the use of MRI to aid in the localization of prostate abnormalities for biopsy may be cost-effective by reducing false negatives and the need for subsequent repeat biopsies.^{61–63} Recognizing that cost-effectiveness studies are sensitive to key parameters and assumptions, further investigation in this space is essential to elucidate whether the savings related to the preferential diagnosis of clinically significant cancer is adequate to counterbalance the cost of MRI and fusion biopsy platforms.

Despite these concerns, use of MRI for diagnosis of prostate cancer is on the rise, and is endorsed at least in certain settings by guideline bodies, such as the National Comprehensive Care Network.⁶⁴

5. Conclusions

MR-US fusion represents a promising new tool to address many of the limitations of conventional TRUS biopsy methods. The Artemis and UroNav platforms are the two most widely available commercial MR-US fusion products in the US and both systems demonstrate comparable results in terms of cancer detection rates. Both platforms have the potential to reduce false-negatives, improve risk classification, and contribute to the reduction of repeat biopsies, especially for men with a previous negative biopsy or men on active surveillance. Further comparative studies evaluating the role of MR-US fusion in the diagnosis of prostate cancer are needed.

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Key Points

- Multiparametric MRI is an excellent imaging method to identify clinical relevant prostate cancers. T2WI provides the best anatomic image of the prostate, but functional parameters like DWI and DCE offer insight into the grade and aggressiveness of the index tumor.
- Targeted biopsy, using MRI fused with real-time ultrasound, can be routinely performed in an office-based setting using one of several commercially-available fusion devices equipped with advanced image registration software.
- Targeted prostate biopsy has the potential to improve prostate cancer diagnosis and management through the accurate localization of prostate cancers and preferential identification of significant cancers over indolent cancers. However, changes to the current prostate cancer risk classification systems may be needed to prevent the overtreatment of clinically indolent prostate cancers.
- Men with persistently elevated PSAs in the setting of a previous negative biopsy as well as men considering active surveillance may be the best candidates for targeted prostate biopsies.

Figure 1.

66-year-old male with history of elevated PSA and BPH, status post multiple negative TRUS prostate biopsies and PSA level of 7.46. A 3T prostate MRI without endorectal coil was performed for the purpose of MR-US fusion biopsy. Images show a mildly T2 hypointense lesion in the apex just anterior to the urethra (arrow) which demonstrates markedly increased signal on diffusion weighted image (top right), corresponding darkness on ADC map signifying decreased ADC value (bottom right) and early enhancement on DCE images (asterisk). MR-US fusion biopsied confirmed a Gleason 4+3 lesion.

Table 1

Performance characteristics of MR-US fusion in the detection of prostate cancer for selected studies

First Author	Sample Size	Year	First or subsequent biopsy	Sensitivity, n/N (%) ^a			Field strength, sequence for defining lesion
				Overall Cancer Detection	Detection of significant cancer	Detection of Insignificant cancer	
Artemis							
Sonn ⁶⁵	171	2013	Subsequent	68% (21/31)	86% (19/22) ^b	11% (1/9)	3T, T2/DCE/DWI
Wysock ⁶⁶	125	2014	First	69% (27/39)	88% (22/25) ^c	93% (13/14)	3T, T2/DCE/DWI
UroNav							
Siddiqui ⁵⁶	1003	2015	Both	80% (253/315)	82% (150/184) ^c	65% (85/131)	3T, T2/DCE/MRSI
Rastinehad ⁶⁷	153	2014	Both	80% (53/66)	92% (47/51) ^d	40% (6/15)	3T, T2/DCE/MRSI
Cognitive							
Hafner ⁴⁴	555	2011	First	94% (236/252)	95% (236/249) ^b	0% (0/3)	1.5, T2/DCE
Belas ⁶⁸	71	2012	First	92% (24/26)	96% (23/24) ^b	0% (0/2)	1.5, T2/DCE/DWI

Clinically significant disease defined as:

^aThe sensitivity values are calculated based on the number of cancers detected by targeted biopsy alone compared to the combination of targeted and standard biopsies

^bGleason > 3+3 or Gleason > 3+3 with more than one core positive or 1 core with >4mm

^cGleason > 3+3

^dGleason > 3+3 or Gleason 3+3 with >50% core positivity or >2 positive cores