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Recent advances in image-guided targeted prostate biopsy

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Abstract

Prostate cancer is a common malignancy in the United States that results in over 30,000 deaths per year. The current state of prostate cancer diagnosis, based on PSA screening and sextant biopsy, has been criticized for both overdiagnosis of low grade tumors and underdiagnosis of clinically significant prostate cancers (Gleason score ≥ 7). Recently, image guidance has been added to perform targeted biopsies of lesions detected on multi-parametric magnetic resonance imaging (mpMRI) scans. These methods have improved the ability to detect clinically significant cancer, while reducing the diagnosis of low grade tumors. Several approaches have been explored to improve the accuracy of image-guided targeted prostate biopsy, including in-bore MRI-guided, cognitive fusion, and MRI/transrectal ultrasound fusion-guided biopsy. This review will examine recent advances in these image-guided targeted prostate biopsy techniques.

Keywords

prostate cancer; biopsy; targeted; MRI; TRUS

Introduction

Prostate cancer (PCa) is a very common malignancy, affecting one out of every seven men in the United States [1]. Although PCa is thought to be less aggressive than other cancers due to its propensity for slow tumor growth, it is still the second leading cause of cancer death among American men (1). Despite its high ranking as a cause of cancer death, there is still no good screening tool to accurately identify clinically significant PCa. Prostate specific antigen (PSA) has proven to be too non-specific, as it is elevated in benign prostatic hyperplasia, prostatitis and prostate cancer [2–5]. Nevertheless, PSA is sensitive for cancer;

among 1,000 men screened using PSA, 110 men will be diagnosed with prostate cancer although only 4–5 men will die as a result of their disease [6, 7]. While PSA has recently fallen out of favor as a screening biomarker [8–10], it may still play an important role in determining clinical suspicion for PCa or response or recurrence evaluation to treatment [11–13].

Once PSA tests reveal abnormal results, it is common practice to obtain a prostate biopsy. The current standard of care is to perform random systematic 12-core sextant biopsies (SBx) rather than targeted prostate biopsies. Transrectal ultrasound (TRUS) imaging is used to visualize the prostate gland for SBx. However, the low contrast between malignant and normal tissue on TRUS reduces the ability to identify PCa. For this reason TRUS is used mostly to systematically sample different regions of the prostate. As a result, there is a propensity to detect slow growing indolent microfoci of cancer while potentially missing larger tumors that are outside of the usual biopsy sampling regions. Those in whom the initial biopsy is negative return for serial PSAs. If these continue to go up then the patient may undergo a repeat biopsy. This not only results in unnecessary discomfort and uncertainty for those patients, whose PCa could still remain undiscovered after multiple negative biopsies, but also puts the patient at increased risk for biopsy-induced sepsis [14]. It has been shown that the SBx misses 10–30% of PCa [15] and that more than two SBx sets are required in over 20% of men to diagnose PCa [16, 17].

One promising solution for improving the detection of PCa is targeted biopsy of the prostate using imaging modalities such as multi-parametric MRI (mpMRI), which has been shown to have high positive and negative predictive values for clinically significant cancer [18]. Sequences commonly used to identify suspicious areas on mpMRI are shown in Fig. 1. There are several ways to capitalize on the ability of MRI to visualize PCa, either by performing biopsies directly in the MRI suite or to fuse MRI to ultrasound and perform the biopsy using the latter. In-bore MRI-guided prostate biopsy was described by several groups throughout the 2000s [19–21], but the technique has not been broadly adopted for clinical use for many reasons including its inherent complexity and expense [22]. So-called “cognitive fusion” in which the operator estimates the location of the lesion on ultrasound using the previously obtained MRI as a guide, has been more popular but suffers from a strong operator-dependence that limits its universal application [23–25]. By electronically fusing MRI to ultrasound it is possible to conduct targeted biopsies under TRUS in the usual manner but using the prior MRI for guidance. Multiple studies have shown that the MRI/TRUS fusion guided biopsy (FgBx) improves the detection rate of high-risk cancers previously missed on SBx [26–29]. The relative advantages and disadvantages of each prostate biopsy method are summarized in Table 1. These encouraging approaches for targeted prostate biopsy will be explored further in this review.

Prostate biopsy

Systematic transrectal ultrasound guided sextant biopsy

The current standard of care biopsy for PCa includes a systematic transrectal ultrasound (TRUS) guided biopsy of the prostate following a positive digital rectal exam or an elevated serum PSA. Originally, prostate biopsies were performed under finger guidance during

direct palpation [30]. After the emergence of TRUS in the 1980s, the sextant core approach under TRUS came into use, and this was shown to improve PCa detection over finger-guided nodule biopsy [31]. The sextant core approach refers to using a template-based procedure to obtain biopsy specimens on the right and left side of the apex, mid, and base regions of the prostate. Later on, the sextant approach was extended from one biopsy to two biopsies (medial and lateral) resulting in approximately 12 cores per SBx. This resulted in increased PCa detection rates varying from 40% to 96% depending on the study; however, many of these tumors were low grade and this simply contributed to overdiagnosis compared to the 6-core biopsy [15, 32–34]. This “extended sampling technique” has become a new standard of care, but while contributing to the overdiagnosis of indolent PCa [35] it has continued to underdiagnose about one third of clinically significant PCa [36]. Moreover, the SBx technique is inherently limited in larger prostates where the percentage of prostate tissue that is sampled is lower, particularly in less accessible areas such as the anterior prostate [37, 38]. SBx also misses PCa in up to 24% of patients with cancer in the transition zone [38, 39]. Thus, despite the convenience and simplicity of SBx, a significant portion of PCa may be missed using this method alone.

In-bore MRI-guided biopsy

In-bore MRI-guided prostate biopsy was described by several groups in the 2000s [19–21]. This technique involves obtaining biopsy samples under direct MRI guidance in the MR gantry after lesions have been identified using a diagnostic multi-parametric MRI typically obtained before the biopsy. *MRI*. In the in-bore MRI-guided approach, the patient is placed in the prone position, and then at least one diagnostic MRI sequence is obtained to localize the target lesion(s). This is followed by the insertion of biopsy needles into the target lesion(s) via a transrectal or transperineal approach. Tissue samples are obtained after confirming that the biopsy needle is located within the target lesion [40]. The main advantage of this approach is that it enables precise lesion sampling. For instance, Hoeks et al. performed in-bore MRI-guided biopsies in 265 patients with elevated PSA and prior negative TRUS guided SBx. PCa was detected in 41% of patients and the majority of the detected cancers (87%) were clinically significant [41]. Roethke et al. investigated the tumor detection rate of the in-bore MRI-guided biopsy technique in 100 patients with prior negative TRUS-guided SBx. In their series, the tumor detection rate was 52.0% and 80.8% of the detected PCa were clinically significant [42].

A systemic review by Overduin et al. included 10 studies documenting the clinical results of in bore MRI guided biopsy (MRGB). These studies range in size between 12–265 patients and the majority (9 of 10) of these studies were conducted with a transrectal needle positioning device either using a commercially available (Dynatrim, In Vivo, Schwerin, Germany) or an in-house developed device. Reported PCa detection rates for MRGB ranged from 8 to 59 % (median 42 %) and 81–93 % of detected cancers were clinically significant. The most frequent major complications of in bore MRI guided biopsy were urosepsis (0–2 %) and urinary retention (1 %); whereas common minor complications were transient hematuria (1–24 %) and short-term perirectal bleeding (11–17 %) which are common to all types of prostate biopsy [43].

Direct in-bore MRI-guided biopsies do have considerable limitations, however, such as discomfort related to positioning, increased costs related to long procedures (19 minutes as the reported shortest median procedure duration), and the requirement for special non-magnetic equipment and needles [43, 44]. Another challenge is that there is insufficient MR capacity and expertise to handle the high volume of patients for whom image-guided prostate biopsy is needed. Moreover, this approach has not been popular with urologists as the biopsy is performed in the radiology department and thus interferes with normal workflow. Therefore, although popular in some centers, this technique has not been broadly adopted for clinical use [22]. It became clear that an alternative would be needed if MRI were to play a role in improving the diagnosis of prostate cancer.

Cognitive fusion guided biopsy

Cognitive fusion is the simplest and the most appealing approach, as it requires no extra equipment aside from the TRUS apparatus and MR images. As opposed to solely using TRUS to guide biopsies, cognitive fusion entails a physician reviewing the prostate MR images prior to and during a TRUS biopsy and using this knowledge to then guide the biopsy. Unfortunately, it is highly dependent on the user's expertise and ability to translate MRI findings to TRUS without a physical overlay of the two images. Additionally, ultrasound is performed using a series of oblique planes in contrast to axial planes in MRI that are usually orthogonal to the table, which then introduces further complexity into the procedure. Lastly, cognitive fusion methods lack the ability to track and record biopsy sites in relation to pre-defined targets on US. This is an important consideration for both repeat procedures and active surveillance in which documentation of prior targets and biopsy sites may be highly valuable [45].

In 2011, Haffner and colleagues evaluated a cohort of 555 patients with an abnormal prostate cancer screen (abnormal DRE or elevated PSA). Each patient underwent a pre-biopsy MRI followed by 10–12 TRUS-guided extended systematic biopsies (SBx) plus two targeted biopsies of suspicious areas on MRI. Cognitive fusion biopsy was subsequently found to have improved detection accuracy for clinically significant cancers over SBx ($p < 0.001$). Furthermore, targeted biopsy more accurately estimated tumor burden ($p = 0.002$) while detecting 16% more high grade (Gleason pattern 4 and 5) cases [23]. Park et al. performed a similar prospective study in patients who had an elevated PSA and no previous biopsy. Again, cognitive fusion biopsy had a higher detection rate (29.5% vs 9.8%, $p = 0.03$) and significantly higher positive core rate (9.9% vs 2.5%, $p = 0.00$) [24].

In patients with a prior negative biopsy, the data also appears to favor cognitive fusion biopsy over SBx. In a prospective, single-center study, Sciarra et al. randomized patients with a prior negative biopsy and elevated PSA levels to either the standard-of-care TRUS biopsy or cognitive fusion targeted biopsy (DCE-MRI + MR Spectroscopy + TRUS). Almost twice as many prostate cancers were diagnosed in the targeted biopsy group (46% vs 24%). Moreover, on a patient-by-patient analysis the cognitive fusion biopsy was found to accurately detect 90.7% of clinically significant PCa [46]. However, it should be noted that more cores (mean = 12.17) were taken in the fusion biopsy group compared to the SBx group (mean = 10) accounting for at least some of the difference. In a similar study,

Labanaris and colleagues evaluated 260 patients who had a prior negative biopsy who subsequently underwent multi-parametric MRI, stratifying patients to 18-core TRUS biopsy if the MRI was negative or to 18-core TRUS biopsy + cognitive fusion if MRI was suspicious for cancer. This study found that 65% of patients had suspicious lesions on MRI and that cognitive fusion had a significantly higher PCa detection rate than SBx cores (56% vs 18%), although the MRI arm of the study was clearly enriched for higher risk tumors [25]. Finally, Puech et al. compared targeted MRI/TRUS fusion biopsy (cognitive and software-based) to TRUS-guided SBx in a prospective trial of 95 patients with clinically localized prostate cancer. Patients underwent 12-core SBx followed by 4-core targeted biopsy (two cognitive and two using co-registration software). This study design removes the bias of Lebanaris' study although it is still subject to a bias caused by a larger number of biopsies with MRI guidance. While the study found no difference between cognitive fusion-guided biopsy and MRI/TRUS fusion biopsy results, it should be noted that the authors were highly experienced in cognitive fusion [24]. Targeted biopsy detected a greater percentage of cancers than did systematic biopsy ($p=0.003$).

In summary, the current evidence suggests that cognitive fusion more accurately targets prostate cancer versus TRUS random biopsy. More studies are still needed to compare the efficacy of cognitive fusion to other methods of MRI-guided biopsy. However, limitations remain with regards to adequately training operators to achieve consistent, reproducible results with cognitive fusion.

MRI/TRUS fusion guided biopsy

Multi-parametric MRI provides unique information about the location and size of tumors. TRUS provides real time guidance for biopsy. Thus, the main concept behind MRI/TRUS fusion technology is combining the advantages of MRI with the advantages of real-time ultrasound imaging by using software registration of the two images. MRI scans are performed first, and the prostate boundaries and tumor locations are segmented from the remainder of the scan. This information is then sent electronically to the biopsy suite. There, a three-dimensional ultrasound is done, and the ultrasound scan is segmented and fused to the prostate MRI via registration software. This can be done manually with rigid registration or the software can adapt the two shapes to each other using so-called elastic or deformable registration. Elastically registering the two imaging modalities helps to eliminate any residual "cognitive fusion" necessary to hit the prostate cancer target. The deformable registration stretches the MR image to match the TRUS prostate contour and thus strongly depends on a high-quality ultrasound sweep. Caution must be taken to ensure that the apical to base ultrasound sweep is accurate to avoid misaligned or incorrectly warped registration. The alignment between ultrasound and MRI allows for manipulating the TRUS probe in real time and observing corresponding rotation or translation of the MR image. This approach enables the TRUS operator to guide a precise, targeted biopsy using information from the previously obtained prostate MRI.

This technique has been reported extensively as a method for targeted biopsy of the prostate, and there is some evidence for its use in guiding radiation therapy of prostate cancer as well. In 2002, Kaplan et al. described the successful implementation of MRI/TRUS fusion

prostate visualization using an ultrasound stepper and stabilizer common in brachytherapy procedures [47]. The first practical solution using off-the-shelf components was described in 2007 [48]. Since the late 2000s, multiple MRI/TRUS fusion platforms have been developed and are in current clinical practice [Table 2]. Each of the currently available MRI/TRUS fusion biopsy platforms are briefly described below. The various approaches for fusing MRI to ultrasound are displayed in Fig. 2.

UroNav

The first step with all MRI-TRUS fusion biopsy platforms is to register the MRI to the TRUS image as previously described. The platforms then differentiate from each other in how they link the TRUS to the MRI. The UroNav platform uses passive electromagnetic tracking similar to a global positioning system (GPS) to link the real-time TRUS with the previously obtained prostate MRI. This gives the operator free-hand use of the TRUS probe, which is especially useful at the apex and base of the prostate. This system features elastic (deformable) registration, which helps to reduce the need for cognitive fusion since the MRI and US modalities are in the same orientation rather than simply overlaid, as would be the case with rigid registration. The elastic registration method depends on a reliable ultrasound sweep in order to achieve a good software registration outcome. Another important feature is its ability to document precise biopsy location [49] so that is possible to sample the same exact area in the future, which is very helpful for monitoring patients on active surveillance requiring repeat fusion biopsy and for patients with suspected recurrent disease. For the biopsy itself, lesions are pre-defined on high-resolution MR-viewing stations using multi-parametric MRI sequences [Fig. 1] prior to delineating the target area on the fusion software [Fig. 3].

Initial clinical experience using real-time MRI/TRUS fusion biopsy (FgBx) was reported by Singh et al. and Xu et al. in 2008 using the UroNav system with a spatial tracking sensor to enable real-time registration of TRUS with MRI [50, 51]. This method confirmed the feasibility of using MRI/TRUS fusion to perform targeted prostate biopsy within a reasonable time frame, since the overall procedure time was only 10 minutes. Pinto et al. reported soon afterwards that this system identified more prostate cancers per core than standard TRUS biopsy alone (20.6% vs 11.7%) [27]. Later, Rastinehad et al. demonstrated an overall PCa detection rate of 62.9% using the UroNav FgBx platform. Of the detected cancers, 14.3% were found only on FgBx, and these were largely clinically significant cancers. Furthermore, 23% of the cancers labeled as clinically insignificant on standard TRUS biopsy were upstaged to more aggressive cancers using FgBx samples [52]. Additionally, the UroNav system has also been shown to detect a large proportion of PCa in patients with previously negative SBx results. Vourganti et al. reported a PCa detection rate of 37% using the FgBx in 195 men with prior negative standard biopsy. In this study, very high grade cancers (Gleason 8) were found in 21 patients, all detected on FgBx, whereas SBx missed 12 of these cancers. The UroNav FgBx cores also resulted in pathological upgrading of PCa in 28 patients [53]. The UroNav platform, which was first tested in patients in 2007, served as a model for developing similar systems [45].

Artemis

The Artemis system employs a different method for linking the MRI to the TRUS. After image registration, Artemis uses a fixed mechanical arm for the TRUS probe. The joints of this mechanical arm are embedded with angle-sensing encoders. The position of the needle and probe are tracked by these encoders [54] [Figs 4–5]. Similar to the UroNav platform, the Artemis system uses elastic registration in warping the ultrasound acquisition to the MRI space. This allows real-time movements in ultrasound to synch up with the respective changes in the MRI domain. The initial clinical evaluation of the Artemis platform revealed that the targeted FgBx improved the biopsy yield of cores positive for PCa. As compared to traditional SBx with only 7% positive cores, the FgBx had 33% PCa positive cores. This study further indicated the clinical feasibility of the device by reporting that the FgBx platform added only 5 minutes to the overall biopsy procedure (24).

Further studies have corroborated the clinical utility of the Artemis system for detecting clinically significant prostate cancer. Wysock et al. prospectively found that the Artemis FgBx platform had a detection rate of 32% for clinically significant PCa compared to only 20% using TRUS-guided SBx [55]. Similar results were later reported by Sonn et al. using this system in 2013 [56]. Another study demonstrated that using Artemis improves the detection rate of PCa in patients with elevated PSA who have had multiple negative biopsies in the past. In this study, the Artemis system detected clinically significant PCa in 91% of men compared to only 54% of men undergoing conventional SBx [57]. More recently in July 2014, Sonn and colleagues discussed the ability of Artemis to monitor specific sites of known PCa. This study demonstrated that repeat FgBx sampling of prior MRI targets showed PCa more often than repeat sampling of tumor sites identified by prior systematic TRUS biopsy (61% vs 29%, $p=0.005$). The cancer detection rate on repeat FgBx was also found to be directly associated with the initial core biopsy length of the cancer ($p<0.02$) [58]. While further research is needed in the area of using FgBx for men with PCa who are on active surveillance, the most recent study by Sonn et al. shows promise in the ability of FgBx platforms like Artemis to accurately sample cancer sites even on repeat biopsy.

Urostation

The Urostation platform differs from the others by using real-time TRUS-TRUS registration as the “tracking mechanism” rather than using electromagnetic sensors or encoders. This system also utilizes a freehand TRUS probe and elastic registration methods. Fusion of a 3D ultrasound volume with the previously obtained MRI is performed first, and the targeted biopsy is then performed. Immediately after the biopsy, another 3D TRUS acquisition is obtained to determine whether the biopsy needle position was accurate [59, 60]. Thus, the Urostation does not enable real-time targeting but rather retrospectively can assess the precision of the biopsy site compared to MRI-defined lesion locations. Rud et al. evaluated the accuracy of this platform in detecting PCa and reported a tumor detection rate of 52% [61]. Another study by Delongchamps et al. compared TRUS-guided SBx with the Urostation FgBx system and found that fewer cores were required to detect high grade cancer using FgBx. The authors also concluded that the FgBx system detected fewer microscopic cancers than SBx [28]. This distinction between significant and inconsequential cancers was also explored by other groups using the Urostation system. Mozer and

colleagues have shown that the Urostation FgBx platform has a higher detection rate of significant PCa than SBx alone in the first round of biopsies. In this study, all patients underwent the standard 12-core TRUS-guided SBx with an additional 2–4 targeted cores taken for areas previously marked as suspicious on multi-parametric MRI. The comparative yield of the SBx and targeted FgBx cores was highly significant, with 31% of targeted FgBx cores positive for clinically significant PCa compared to only 7.5% of the SBx cores, $p < 0.001$ [62].

BiopSee

While many of the FgBx platforms are set up for taking transrectal biopsies, it is also possible to perform transperineal biopsies with these systems. One advantage of the transperineal approach is that it may reduce the rate of sepsis after biopsy because it avoids transgressing the rectal mucosa. One fully transperineal platform is BiopSee, which includes a TRUS probe mounted on a stepper that is fixed to the operating table. The TRUS probe movements within the Biopsee platform are tracked using two encoders. A grid mounted on a mechanical stepper is used to place the biopsy needles, akin to the technique used for brachytherapy seed placement [63]. One large study showed that this platform identified PCa in 82.6% of the patients (86 of 104), and 72% of these tumors were clinically significant (Gleason score ≥ 7). Overall, the targeted FgBx cores were more efficient in identifying cancer compared to SBx, with PCa detection rates of 30% compared to 8.2% [63]. A recent study by Radtke et al. reported that FgBx alone using the BiopSee platform detected as many significant PCa lesions as SBx while detecting fewer low-grade tumors. While SBx and FgBx ultimately had similar detection rates for significant cancer, the targeted cores had greater efficiency with 46% FgBx cores positive for Gleason ≥ 7 cancers compared to only 7.5% of the SBx cores. Based on their results, this group concluded that the gold standard for primary biopsy of patients with suspected PCa should be a combination of SBx and targeted FgBx [64].

Virtual Navigator

The Virtual Navigator system for prostate biopsy was customized from a more general imaging fusion system that utilizes fusion technology to combine MR or CT with real-time ultrasound. It is similar to the UroNav since it uses a freehand TRUS probe movement and electromagnetic tracking sensors [45]. However, it is only capable of rigid registration between MRI and TRUS and does not create a deformable image that can be manipulated by the operator. Instead, the prior T2W MRI is overlaid on top of the ultrasound image on a per-slice basis. This system depends on matching internal anatomical markers in order to overlay the MRI and TRUS images. Due to the rigid, nondeformable nature of this registration method, the overlay may be inaccurate due to prostate shape differences in TRUS images compared to MRI and the potential for motion artifact in TRUS [28]. Suspicious lesions are first defined on MRI studies (T2W, DCE, and DWI using a 1.5 T magnet) after they have been loaded into the Virtual Navigator system. These areas are then targeted in real-time using a freehand TRUS probe after the rigid registration overlay is available [45]. Delongchamps et al. showed that the Virtual Navigator platform found PCa in 82% of the patients studied (64 of 78), and this FgBx system detected 9% more medium-to-high risk PCa than SBx. The FgBx system also found 18% fewer Gleason 6 cancers than SBx [28].

Puech et al. corroborated these findings, demonstrating that the Virtual Navigator system found clinically significant PCa in 67% of patients compared to 52% with SBx [29]. A caveat to this study is that results included targeted biopsy obtained via both cognitive and software fusion approaches. These non-uniform methods could underestimate the reported detection rates, as the stated detection rate of 67% is lower than that reported by Delongchamps (82%) using the same system. Nonetheless, these reports support findings from other studies that the MRI/TRUS software fusion technology detects more clinically significant PCa while avoiding the overdiagnosis of indolent disease.

HI-RVS/Real-Time Virtual Sonography

Similar to the Virtual Navigator platform, the HI-RVS system is an example of a general fusion platform that has been adapted to perform targeted prostate biopsy. The HI-RVS uses a freehand TRUS probe with electromagnetic tracking sensors similar to the UroNav system. However, it is dissimilar in that only rigid registration is used to fuse MRI with ultrasound [54]. The MRI-suspicious lesions are also marked only after the MRI data has been uploaded onto the biopsy platform rather than on an MR-viewing station. Thus, this system most resembles the Virtual Navigator as it employs rigid registration methods to produce an image overlay that is used to guide the targeted biopsy, in which MRI targets are delineated on the software fusion platform. Clinical testing of the HI-RVS system revealed that PCa was detected in 61% of patients with 87% of the PCa detected by targeted cores alone. The targeted FgBx cores were also more efficient at obtaining samples with PCa on a per-core basis, as 32% of the FgBx cores contained PCa compared to 9% of the SBx cores [65].

These findings corroborate results from studies of other FgBx platforms that describe greater efficiency in obtaining PCa positive biopsy cores using FgBx compared to SBx. It has been difficult to actually compare these systems head-to-head as these are single center studies with unique populations of patients with differing prevalence of clinically significant disease. Nonetheless, some themes emerge: targeted biopsies result in a higher rate of clinically significant disease and a lower rate of indolent disease while increasing the relative efficiency (measured in needle biopsies/diagnosis) of the biopsy. This intuitively makes sense, as targeted FgBx cores are obtained by utilizing the more precise localization methods of MRI whereas TRUS-guided SBx cores are performed “blindly” in a systematic fashion. The improved relative efficiency of FgBx is an important consideration moving forward in the shifting paradigm of prostate biopsy, since it will potentially enable shifting away from the trend of ever-increasing numbers of biopsy cores. Instead, fewer cores may be needed in the future to definitively diagnose prostate cancer. Thus, FgBx platforms demonstrate promising findings of improved detection of clinically significant prostate cancer with greater efficiency. Therefore, using multiparametric MRI as an effective screening method may ultimately reduce the burdensome cost of unnecessary and repeat biopsies, biopsy-related sepsis, and unnecessary treatment. This has the potential to ultimately achieve cost-effective outcomes with multi-parametric MRI and targeted biopsy to direct management efforts at men with clinically significant disease [66]. However, it is also important to note that there is a learning curve involved in using MR guided biopsy methods, whether by MRI-US fusion or by in gantry biopsy. Care should be taken to carefully train new users of these techniques to achieve the best results.

Conclusion

The 12-core random TRUS biopsy is still the standard of care for prostate cancer diagnosis, but there is increasing awareness of its limitations and the value of targeted prostate biopsy using more advanced imaging techniques like MRI. Targeted prostate biopsies utilizing multi-parametric MRI to identify suspicious lesions have shown promising results for detecting more clinically significant cancer. They also have the ability to detect this cancer with greater efficiency, requiring fewer cores and decreasing the number of inconsequential cancers detected that do not ultimately drive decisions about patient care. Currently the targeted biopsies are performed in conjunction with standard biopsies, except for in-bore MRI-guided biopsy. However, due to recent advances in the capability of MRI and targeted techniques to detect significant lesions, it is possible that fewer biopsy cores will need to be taken in the future. This could reduce the rate of post-biopsy sepsis that has been a growing problem. It is also important to identify the best patient population to undergo multi-parametric MRI and targeted biopsy so that this expensive resource is used most appropriately as a cost-effective means of detecting clinically significant prostate cancer. Nonetheless, the ultimate acceptance of image fusion guided prostate biopsy awaits the results of large-scale multi-center, randomized studies that will be needed for this approach to be adopted as the new standard of care.

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Fig. 1.

A 62 year old male with serum PSA of 23.85 ng/dL and previous TRUS-guided prostate biopsy showing Gleason 6 disease was followed by four subsequent TRUS-guided biopsies that were all negative despite substantially rising PSA levels. Axial T2-weighted MR image shows a hypointense area in the right mid base anterior peripheral zone also affecting the adjacent transition zone (**a**). The apparent diffusion coefficient (ADC) map shows a corresponding hypointense area (**b**), and the high $b=2000$ diffusion weighted MR image demonstrates hyperintensity (**c**). The dynamic contrast enhancement (DCE) sequence indicates early strong enhancement within the lesion as well (**d**)

Fig. 2. Three different approaches for fusing prostate MRI with ultrasound

The use of electromagnetic tracking on a freehand transrectal ultrasound (TRUS) probe is found in three platforms, the UroNav, HI-RVS, and Virtual Navigator systems. Two of the platforms, Artemis and Biopsee, utilize an articulated approach with a mechanical stepper used to mount the ultrasound probe and embedded with encoders relating the position of the probe to the biopsy platform to aid with fusion. One other system, the Urostation, employs an image-based registration algorithm in which TRUS images are fused to the MRI to determine the appropriate biopsy location, and then TRUS is performed following biopsy sample acquisition to verify placement of the biopsy needle. Whereas the first two approaches (electromagnetic tracking and articulated) allow for real-time prospective targeting of suspicious areas, the TRUS-TRUS registration method only allows for retrospectively assessing the accuracy of the biopsy needle location. All of these systems enable operators to target lesions pre-identified on MRI in the realtime ultrasound suite in a more precise fashion than cognitive fusion, since images are either overlaid or deformably shaped to match contours from both modalities. Permission was obtained from InVivo, Eigen, and Koelis as indicated for use of their representative images

Fig. 3.

TRUS/MRI fusion guided biopsy procedure snapshot of a 62 year old male with serum PSA of 23.85 ng/dL (same patient in Fig. 2). The patient underwent MRI/TRUS fusion-guided biopsy using the UroNav platform. This figure shows a screen capture of the operator's view during the biopsy procedure. The ultrasound and MRI scans have been co-registered elastically. The operator can freely rotate the ultrasound probe, and this will change the view of both the ultrasound image (superior) and the previously acquired MRI (inferior). The red dot with concentric green circle identifies the target lesion, which this operator has correctly 'pierced' with the biopsy needle. The location of the biopsy needle is shown by the yellow line, which can be documented for later retrieval on the UroNav system. Currently the routine prostate biopsy procedure for patients at the National Cancer Institute includes both conventional TRUS-guided biopsy and targeted biopsy performed at the same time. On histopathology, this patient was found to have high-grade Gleason 4+4=8 prostate adenocarcinoma (75% and 40% in 2 targeted cores) in this lesion. Only the targeted biopsy cores were positive for this patient, while all of the TRUS-guided biopsy cores showed benign prostatic tissue

Fig. 4.

Demonstration of the biopsy planning process for the Artemis system. The lesion is outlined in yellow at top left on the T2-weighted sequence and corresponds with the hypointense area on the ADC map shown at top right. The whole prostate outline is shown on the DCE image at bottom left, which demonstrates enhancement in the anterior region where the lesion is located. The bottom right panel shows a sagittal view of the MRI with lesion outlined

Fig. 5. Longitudinal view of the output of the Artemis system following prostate biopsy, with the target lesion volumes shaded in gray and lines representing biopsy needle locations. The blue and purple dots represent the center of the biopsy needle where the cores were taken. Additional cores have been taken for the systematic biopsy locations, with the green dots (1–12) representing a template for the systematic biopsy sites

Table 1

Comparison of TRUS-guided, In-bore MRI-guided, Cognitive Fusion, and MRI/US Fusion Prostate Biopsy Techniques

Prostate Biopsy Comparison	Random systematic TRUS-guided	In-bore MRI-guided	Cognitive Fusion	MRI/TRUS Fusion
Real-time prospective targeting
Spatial resolution
Cost-effectiveness
Biopsy and target location documentation
Ease of use by urologist
Time-consuming
Steep learning curve

Table 2

Comparison of the different commercially available MRI/ultrasound fusion-guided prostate biopsy platforms

Fusion system (manufacturer)	Principal investigator location(s)	Year of published clinical validation	Type of US probe	Tracking mechanism	Biopsy route	Allows for real-time prospective targeting?	Comments
CytoNav (Philips/InVivo)	Bethesda, MD, USA	2008 (45)	Freehand manipulation of US probe	Electromagnetic tracking	Transrectal	Y	<ul style="list-style-type: none"> Integrated with existing US device Stores biopsy location for easy retrieval Real-time rigid and elastic MRI/TR US registration
Artemis (Eigen)	Los Angeles, CA, USA	2013 (51)	Manual rotation along fixed axis	Mechanical arm with encoders	Transrectal	Y	<ul style="list-style-type: none"> Stabilized TRUS probe on a tracking arm Elastic image registration Can overlay systematic biopsy template
Urostation (Koelis)	Paris, France Oslo, Norway Grenoble, France	2012 (54) 2012 (56)	Automatic US probe rotation	TRUS-TRUS registration	Transrectal	N	<ul style="list-style-type: none"> Real-time elastic MRI/TR US registration Does not allow for real-time biopsy targeting
BiopSee (Pi Medical/MedCom)	Heidelberg, Germany	2013 (58)	Biplanar US probe mounted on a stepper	Stepper with built-in encoders	Transperineal	Y	<ul style="list-style-type: none"> Rigid image registration Automated documentation of biopsy location

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Fusion system (manufacturer)	Principal investigator location(s)	Year of published clinical validation	Type of US probe	Tracking mechanism	Biopsy route	Allows for real-time prospective targeting?	Comments
VirtualNavigator (Esaote)	Paris, France Lille, France	2013 (23,24)	Freehand rotation of US probe	Electromagnetic tracking	Transrectal	Y	<ul style="list-style-type: none"> Rigid image registration only End-fire endorectal biopsy probe
HiRVIS/Real-time Virtual Sonography (Hitachi)	Chiba, Japan	2010 (60)	Linear transrectal probe	Electromagnetic tracking	Transperineal or Transrectal	Y	<ul style="list-style-type: none"> Integrated with existing US device Rigid image registration only