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Radiology



# The Current State of MR Imaging–targeted Biopsy Techniques for Detection of Prostate Cancer[1]

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Systematic transrectal ultrasonography (US)–guided biopsy is the standard approach for histopathologic diagnosis of prostate cancer. However, this technique has multiple limitations because of its inability to accurately visualize and target prostate lesions. Multiparametric magnetic resonance (MR) imaging of the prostate is more reliably able to localize significant prostate cancer. Targeted prostate biopsy by using MR imaging may thus help to reduce false-negative results and improve risk assessment. Several commercial devices are now available for targeted prostate biopsy, including in-gantry MR imaging–targeted biopsy and real-time transrectal US–MR imaging fusion biopsy systems. This article reviews the current status of MR imaging–targeted biopsy platforms, including technical considerations, as well as advantages and challenges of each technique.

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Prostate cancer is the most common nonskin cancer and the second leading cause of cancer-related death among men in the United States (1). The best current measure of prostate cancer aggressiveness is the Gleason score, which is typically determined at prostate biopsy. Systematic transrectal ultrasonography (US)–guided biopsy is currently the standard procedure for sampling the prostate in patients with an elevated prostate-specific antigen (PSA). In the United States, this technique generally uses a 12-core sampling schema. However, this approach is prone to substantial undersampling of the prostate, leading to underdiagnosis of clinically significant prostate cancer (which has been variably defined in the literature, although some authors include any tumor with Gleason score ≥7) (2). Even the use of a saturation biopsy that obtains a larger number of cores, as is occasionally performed in the repeat biopsy setting, is prone to undersampling. Meanwhile, the systematic biopsy approach has been criticized for the overdetection of Gleason score 3 + 3 tumors that have virtually no risk of metastasis, yet are associated with substantial overtreatment with considerable morbidity (3,4). Although the transrectal US-guided approach helps to visualize the gland to guide systematic sampling of different regions of the prostate, it is unable to reliably localize prostate cancer for targeting. The standard transrectal US-guided approach is particularly poor at sampling cancers in the anterior and apical locations, contributing to the underdetection of clinically significant disease. A major limitation of transrectal US-guided biopsy is that up to 40% of cases classified at transrectal US-guided biopsy as low grade are found to be of higher grade disease in surgical histologic specimens (5). Uncertainty of the results of transrectal US-guided biopsy can lead to more aggressive therapy than is needed given a justifiable concern that the biopsy is underestimating the disease. This uncertainty, in turn, leads to increased patient anxiety, compelling patients to elect unnecessary therapies with associated morbidity, decreased quality of life, and increased cost of care.

One promising solution for improving prostate cancer detection is targeted biopsy of the prostate by using multiparametric magnetic resonance (MR) imaging (hereafter, MR imaging–targeted prostate biopsy). Multiparametric MR imaging incorporates anatomic (T1- and T2-weighted) and functional imaging (diffusion-weighted, dynamic contrast material–enhanced) and tends to increase the detection of clinically significant disease while reducing the detection of inconsequential tumors. Multiparametric MR imaging can be used to define a suspicious area for targeted prostate biopsy (Fig 1) and to better represent the underlying tumor location and volume than does standard transrectal US-guided biopsy. Consistent with the recommended terminology of an earlier consensus statement, this review uses *MR imaging–targeted biopsy* to refer generically to any prostate biopsy in which a prebiopsy MR image is used to define the location of the biopsy target, whereas *MR imaging–guided biopsy* infers the use of MR imaging for needle guidance at the time of biopsy (6). Multiparametric MR imaging–targeted biopsies result in higher detection rates of clinically significant cancer with a reduced upgrading of cancers at surgery, improving confidence in the biopsy results (7,8).

Given the ability of MR imaging–targeted prostate biopsy to help detect clinically significant cancer in essentially any patient undergoing biopsy, the range of indications for multiparametric MR imaging–targeted prostate biopsy corresponds with those for systematic prostate biopsy. These indications include patients suspected of having or known to have prostate cancer (whether biopsy-naïve or those with prior negative prostate biopsy findings) as well as patients with a known prostate cancer diagnosis (whether undergoing biopsy for treatment planning, guidance of active surveillance [9], or detection of local recurrence after therapy). The criteria of a positive finding at multiparametric MR imaging are not discussed in this review. Instead, here we will assume that a suspicious lesion is identified and it is determined that a biopsy is needed. All multiparametric MR imaging–targeted biopsies are performed either in gantry (ie, by using MR imaging) or in combination with US as the navigational system for biopsy. In this review, we will summarize the current applications of MR imaging–targeted prostate biopsies, including technical considerations, and also review advantages and challenges of each technique.

## Essentials

- Targeted prostate biopsy by using multiparametric MR imaging results in higher detection rates of clinically significant cancer with a reduced upgrading of cancers at surgery, improving confidence in the biopsy results.
- The main advantage of in-gantry MR imaging–targeted biopsy compared with other targeted biopsies is improved targeting of the lesion and more accurate documentation of the biopsy site and sample location.
- The main advantage of transrectal US–MR imaging fusion biopsy is short procedure time and ease of performing concurrent systematic biopsy.

## Patient Preparation

A high-quality multiparametric MR image of the prostate should be obtained prior to the biopsy to identify the potential target. A radiologist locates suspicious targets on the multiparametric MR image and assigns a score based on the Prostate Imaging Reporting and Data System (PI-RADS) version 2 (10,11) (Table 1). To ensure optimal results,

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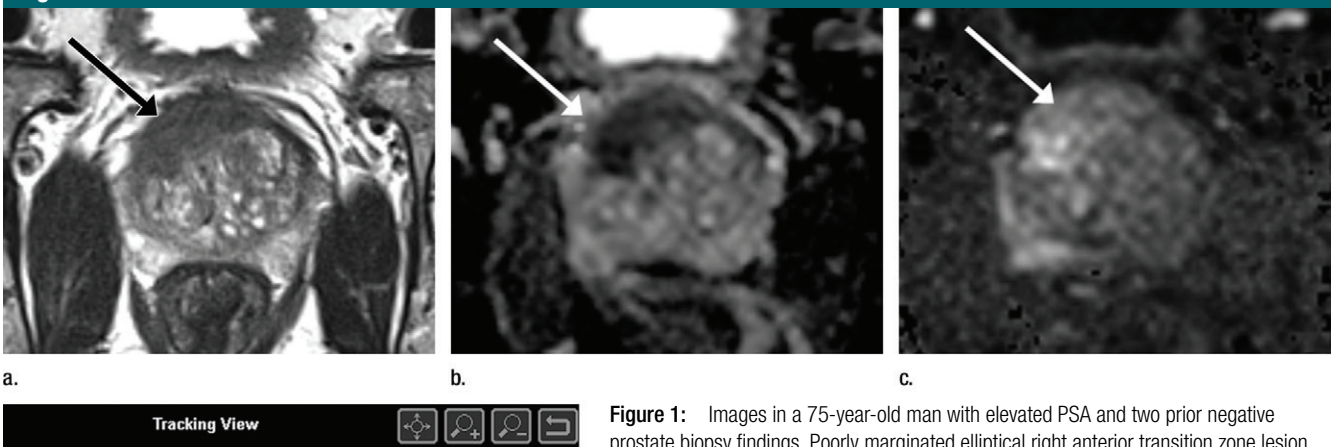
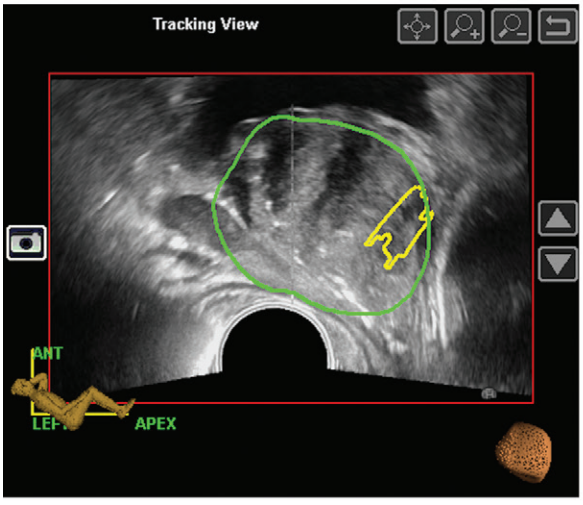
**Abbreviations:**
PI-RADS = Prostate Imaging Reporting and Data System
PSA = prostate-specific antigen

Conflicts of interest are listed at the end of this article.

**Figure 1**




d.

**Figure 1:** Images in a 75-year-old man with elevated PSA and two prior negative prostate biopsy findings. Poorly marginated elliptical right anterior transition zone lesion (arrow) exhibits **(a)** decreased T2 signal, **(b)** decreased apparent diffusion coefficient, and **(c)** increased high-*b*-value signal. **(d)** Screen capture from real-time transrectal US–MR imaging fusion biopsy of the lesion indicates segmented boundary of the prostate (green circle) and segmented boundary of the lesion (yellow outline). Targeted biopsy demonstrated tumor with Gleason score of 5 + 4 in the lesion.

such assessment should be performed by a radiologist with experience in prostate imaging given the established impact of reader experience on the diagnostic performance of prostate MR imaging interpretation (12). PI-RADS categories of both 3 and 4 have been proposed as thresholds for warranting targeted biopsy; the patient's individual risk profile may help to guide the decision whether to perform targeted biopsy of PI-RADS category 3 lesions. Targeted biopsy can be performed for lesions of any size and location within the prostate. Finally, the diagnostic study and the biopsy can be tentatively scheduled on the same day, if a credible target is identified.

Antimicrobial prophylaxis is mandatory for all transrectal prostate biopsies and is highly recommended for transperineal or transgluteal biopsies. Septicemia requiring hospitalization following transrectal US-guided biopsies has been reported in up to 4% of patients (13), although the risk of infection is lower for transperineal or transgluteal biopsies because of the fewer number of cores in addition to the avoidance of transrectal puncture. Prophylaxis, generally including oral fluoroquinolones 12 hours prior to and 48 hours following the biopsy procedure, is often used. However, because of growing resistance of bacteria to fluoroquinolones, usually a second antibacterial agent such as a cephalosporin or aminoglycoside is also added to the prophylaxis regimen. For example, this step may be performed by using intravenous gentamicin 1.5 mg/kg at 2 hours prior to the biopsy. A cleansing enema may be administered the day before the examination but is not mandatory. Evaluation of the patient before the procedure includes assessment for contraindications such as serious bleeding diathesis, suspected acute bacterial prostatitis, or active perianal disease. Anticoagulation and anti-inflammatory medications should be appropriately managed. A discussion with the patient regarding the rationale of the biopsy and level of suspicion of the lesion is warranted during the consent process and helps to improve patient compliance.

## In-Gantry MR Imaging–targeted Biopsy of the Prostate

In-gantry MR imaging–targeted prostate biopsy involves obtaining tissue samples with direct MR imaging guidance while the patient is in the MR imaging gantry and allows direct visualization of the MR imaging target and the needle at the same time. These biopsies were initially performed in low-field open systems about 2 decades ago (14–19) but with the development of faster (14) pulse sequences and advanced visualization tools for needle tracking, they started to be performed with closed 1.5-T and 3-T systems in which the lesions could be better visualized (20). Open systems allow easier access to the patient, whereas high-field-strength systems offer better

signal-to-noise ratio and target visualization. Although the most commonly preferred biopsy approach is transrectal, in-gantry MR imaging–targeted prostate biopsy can also be performed by using a transperineal or transgluteal approach. Initially, because in-gantry biopsy was the only method for MR imaging–targeted biopsies, *MR imaging–targeted biopsy* was widely used to describe this procedure. Recently, *in-gantry MR imaging–targeted biopsy* has been embraced to differentiate this technique from other targeted prostate biopsies (transrectal US–MR imaging fusion or cognitive MR imaging–targeted biopsy.).

## Advantages and Challenges of In-Gantry Biopsy

The main advantage of in-gantry MR imaging–targeted biopsy compared with other targeted biopsies is improved targeting of the lesion and more accurate documentation of the biopsy site and sample location. MR image guidance during the biopsy procedure helps to ensure that the designated lesion is sampled. Anecdotal experience suggests that this advantage can be particularly valuable for biopsy of small lesions, although there is a lack of data indicating a specific size threshold at which the in-gantry method yields more reliable targeting in comparison with other targeting methods. In addition, because only the target lesion is biopsied rather than the entire prostate, fewer cores are obtained for each patient, which can minimize the risk of complications. Transperineal in-gantry MR imaging–targeted biopsy of the prostate can be the only approach for patients without a rectum, which precludes transrectal US-guided biopsies. Also, as previously noted, the transperineal route has much lower rates of infection compared with those of transrectal biopsy (21).

Limitations of in-gantry MR imaging–targeted biopsy are its restricted availability, long duration of the procedure, absence of real-time feedback, steep learning curve for the operator, requirement for MR imaging–compatible needles, and opportunity cost of using MR imaging resources for the biopsy. Moreover, in-gantry MR imaging–targeted biopsy is not compatible with urologists' current workflow because the biopsy is performed in the MR imaging unit of the radiology department rather than an office setting, presenting logistical and economic disadvantages for urologists. Finally, depending on the patient's pelvic anatomy or size of the prostate, in rare occasions, far lateral lesions or lesions at the prostate base may be impossible to target by using the transrectal approach; the transperineal approach may be preferred in such patients.

## Performance of In-Gantry MR Imaging–targeted Biopsy and Comparison with Systematic Transrectal US–guided Biopsy

In-gantry MR imaging–targeted biopsies allow detection of more clinically significant cancer with fewer cores compared with systematic transrectal US-guided biopsies in patients with elevated PSA in both primary (biopsy-naïve) and secondary biopsy settings (13,22–26). In a recent systematic review including 10 studies, Overduin et al reported prostate cancer detection rates of 8%–59% (median, 42%) by using in-gantry MR imaging–targeted biopsies (13). The majority of cancers detected with in-gantry MR imaging–targeted biopsy were clinically significant (81%–93%). The reported missed cancer rates of in-gantry MR imaging–targeted biopsy were low (6%–10%). Hoeks et al performed in-gantry MR imaging–targeted biopsy in 256 patients who had elevated PSA (>4.0 ng/mL) and one or more prior negative systematic transrectal US-guided biopsy findings (23). The prostate cancer detection rate was 41% and the majority of cancers detected were clinically significant (87%) (23). In a separate study, Quentin et al performed in-gantry MR imaging–targeted biopsy in 128 biopsy-naïve men with elevated PSA and compared results with those of transrectal US-guided biopsy (25). In-gantry MR imaging–targeted biopsy achieved similar high detection rate of cancer (53.1%) with transrectal US-guided biopsy with significantly fewer cores and revealed a significantly higher percent of cancer involvement per biopsy core (25). In a prospective study, Pokorny et al compared the performance of MR imaging and in-gantry MR imaging–targeted biopsy diagnostic pathway with the results of standard transrectal US-guided biopsies (24). They found that in-gantry MR imaging–targeted biopsy reduced the detection of low-risk prostate cancer and reduced the number of men requiring biopsy while improving the overall rate of detection of intermediate- or high-grade prostate cancer. In a more recent study, Schimmoller et al evaluated the performance of in-gantry MR imaging–targeted biopsy in both biopsy-naïve patients and in patients with at least one prior negative systematic transrectal US-guided biopsy finding and reported high detection rates both in primary (55.6%) and secondary biopsy (43.1%) settings (26). Prostate cancer detection rates were significantly higher for patients with larger lesions and smaller prostate glands. Another important advantage of in-gantry MR imaging–targeted biopsy is that specimens obtained by using in-gantry MR imaging–targeted biopsy are found to be highly representative of true tumor grade,

**Table 1**

**PI-RADS Version 2 Is the Scoring System Endorsed by the American College of Radiology and the European Society of Urogenital Radiology That Enables Consistent Interpretation, Communication, and Reporting of Multiparametric MR Imaging Findings**

| Parameter | Assessment Categories |
|---|---|
| PI-RADS 1 | Very low (clinically significant cancer is highly unlikely to be present) |
| PI-RADS 2 | Low (clinically significant cancer is unlikely to be present) |
| PI-RADS 3 | Intermediate (the presence of clinically significant cancer is equivocal) |
| PI-RADS 4 | High (clinically significant cancer is likely to be present) |
| PI-RADS 5 | Very high (clinically significant cancer is highly likely to be present) |

Note.—Assignment of a PI-RADS assessment category for each lesion is based on separate scores assigned to the lesion on T2-weighted, diffusion-weighted, and dynamic contrast-enhanced images. The criteria for deriving the overall lesion score based on these individual pulse sequence scores depends on the zonal location of the lesion.

exactly matching prostatectomy Gleason score in 88% of the cases (7,27). This is in contrast to Gleason scores based on transrectal US-guided biopsy, which (as previously noted) undergrades up to 40% of tumors relative to findings from radical prostatectomy (5).

## Technique

### Transrectal In-Gantry MR Imaging–targeted Biopsy

The transrectal approach by using 1.5-T or 3.0-T MR imaging systems is the most common technique used for in-gantry MR imaging–targeted biopsy. Several different manual and automated MR imaging–compatible biopsy devices have been used (20). A commonly used biopsy device for the transrectal approach is the DynaTRIM (Invivo, Gainesville, Fla) (28). This portable device consists of a fixed stable base placed underneath a patient in the prone position and an adjustable needle guide that can be attached to the base and can be manipulated with three degrees of freedom (back and forth, up and down, and right to left). Following the placement of the patient in the prone position on the MR imaging table, a phased-array coil is placed and the needle guide is set to its default neutral position setting. Then, a disposable rectal needle sleeve is lubricated with lidocaine gel and inserted into the patient's rectum. Sagittal T2-weighted turbo spin-echo images are obtained and sent to the DynaTRIM workstation for calibration and registration of the neutral position of the needle sleeve over the images (Fig 2a). Then, an axial T2-weighted turbo spin-echo image is obtained through the prostate to help visualize the target lesion. Diffusion-weighted MR images can also be used for identification of the target if the target is better seen on diffusion-weighted images or the apparent diffusion coefficient map. Upon identification and marking of the target on the axial images, the three coordinates (back and forth, up and down, and right to left) are used to determine the appropriate position of the needle guide by using the advanced visualization and intervention planning software. The needle guide is adjusted accordingly and correct orientation of the needle guide is verified with a fast T2-weighted turbo spin-echo image (single-shot fast spin-echo or steady-state free precession sequences can be other options) (Fig 2b). If the orientation of the needle is not ideal, then additional adjustments are made as needed for optimal positioning. Upon verification of the correct alignment of the needle sleeve, an MR imaging–compatible 18-gauge double-shot core needle (150 cm or 175 cm; Invivo) is inserted through the needle guide and triggered (Fig 2c). Before pulling out the needle, the same quick oblique axial pulse sequence in the same plane as the needle sleeve is repeated to document the tip of the needle in the target. Additional cores can be obtained from the same region after minimal manipulation of the needle location, although the benefit of a second targeted biopsy core per suspicious lesion at MR imaging is generally minimal with regard to prostate cancer detection rate and Gleason score upgrading (29). After a learning curve of 25–30 patients, the in-gantry MR imaging–targeted biopsy can typically be performed in a 30-minute time slot with 15 additional minutes for each additional target.

After the procedure is complete, the patient is helped to rise slowly from the table to minimize the risk of a fall because of vasovagal syncope. The patient is then typically discharged after 30 minutes of observation and given instructions to complete the antibiotic prophylaxis regimen. Reported complications from in-gantry MR imaging–targeted biopsy are rare and usually mild, including self-limiting hematuria and rectal bleeding and urinary tract infection (which may lead to bacteremia and urosepsis in rare cases) (13,30).

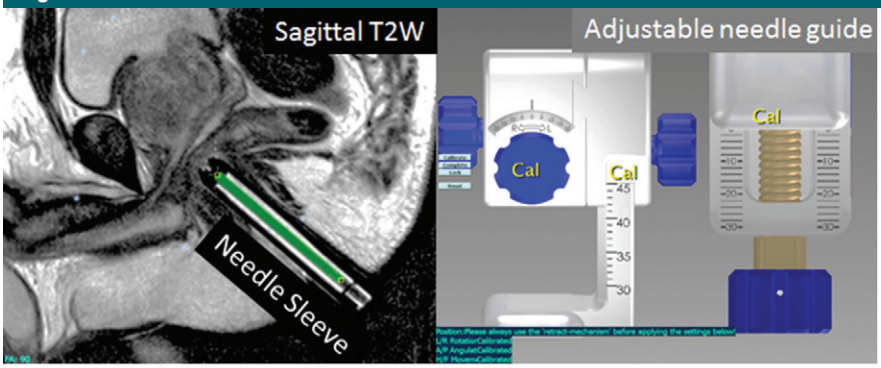
### Transperineal In-Gantry MR Imaging–targeted Biopsy

Transperineal in-gantry MR imaging–targeted biopsy was first reported in 2001 by using a 0.5-T MR imaging system (17). In the United States, where the transrectal approach predominates, the main application of transperineal in-gantry MR imaging–targeted biopsy is in patients with either limited or no rectal access because of previous proctocolectomy or rectal stenosis because of previous radiation therapy. In addition, because the needle does not go through the rectum, the transperineal approach is considered a sterile biopsy with a substantially reduced risk of infection (31). In some countries, the transperineal approach has been adopted as a standard of care although it generally requires more time than does the transrectal approach. Patients also require moderate sedation because of the greater sensitivity of percutaneous puncture by using the transperieal technique. Several different manual and automated templates can be used (32–34). Penzkofer et al recently published their experience in 90 biopsies by using their custom-made tabletop device and template and concluded in-gantry transperineal biopsy is safe and well tolerated (33). Menard et al performed transperineal in-gantry MR imaging targeted–biopsy in 28 patients by using a prototype stereotactic transperineal interventional system (Hologic, Bedford, Mass) and showed that the integration of targeted biopsy with diagnostic MR imaging alters delineation of tumor target boundary in a substantial proportion of patients considering focal salvage (32). A commercially available grid and software (Visualase; Medtronic, Minneapolis, Minn) can also be used for transperineal in-gantry prostate biopsies. The patient is placed in the supine position with a needle-guide template containing MR imaging–detectable fiducial markers secured tightly against his perineum. Upon registration of the template by using the fiducial markers and selection of the target in the prostate, the open-source software identifies the correct hole in the template and depth of insertion. Following insertion of the needle (same MR imaging–compatible needle as used in transrectal approach), repeat imaging followed by adjustments is performed until adequate needle positioning is confirmed. After firing the needle, additional images confirming intralesion needle placement are again obtained.

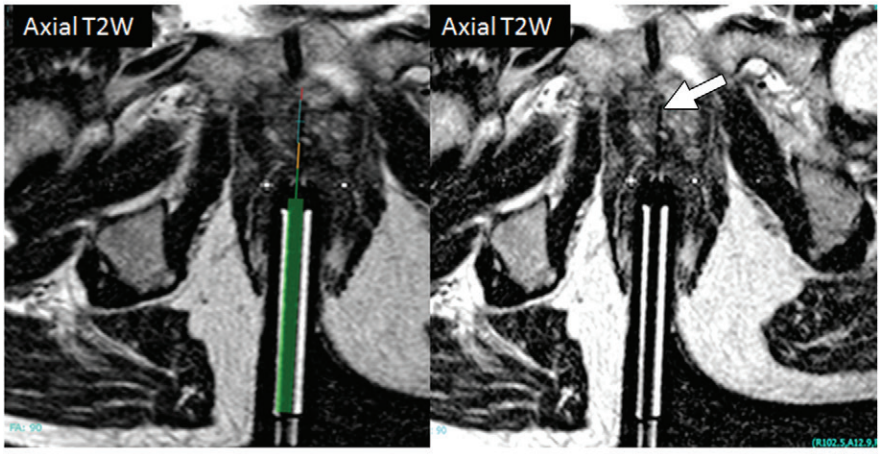
## Cognitive MR Imaging–targeted Biopsy

The definition of *cognitive* is simply "by means of using your brain." The concept of cognition, when applied to

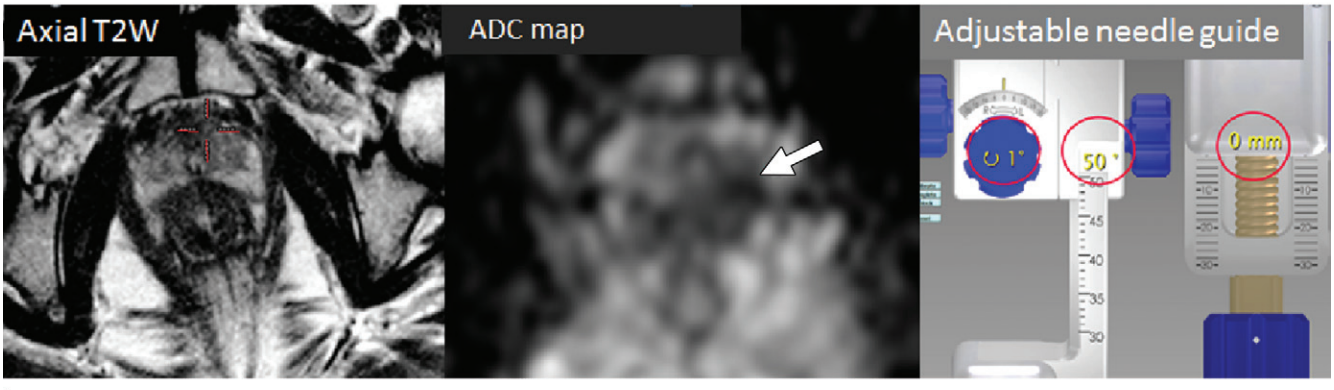
**Figure 2**




a.




c.




b.

**Figure 2:** Images in a 67-year-old man with elevated PSA and negative transrectal US-guided prostate biopsy finding. Prebiopsy multiparametric MR imaging examination depicts large anterior tumor in prostate apex. Patient decided to undergo MR imaging–targeted biopsy. At the time of biopsy, **(a)** sagittal T2-weighted image shows rectal needle sleeve in rectum and registered over the MR images. Adjustable needle guide is calibrated at neutral default position. **(b)** Axial T2-weighted image and apparent diffusion coefficient map show large anterior cancer in apex (crosshair and arrow), which was initially missed by using transrectal US-guided biopsy. Upon identification of target in the prostate, interventional planning software suggested coordinates for needle sleeve orientation. **(c)** Axial T2-weighted image confirms appropriate orientation of needle sleeve, and three cores are obtained from the target. After biopsy, axial T2-weighted image confirms tip of needle (arrow) within the target. Biopsy results demonstrated prostate cancer with Gleason Score 3 + 4 in the target. *T2W* = T2-weighted. *ADC* = apparent diffusion coefficient.

a complex task such as MR imaging–targeted biopsy, incorporates various mental processes including memory, measurement calculation, three-dimensional spatial reasoning, and pattern recognition. In essence, the operator of transrectal US-guided biopsy reviews in detail the location of a target lesion identified at multiparametric MR imaging and translates the site within the gland to the anatomic site to be targeted by transrectal US-guided biopsy. This method has also been called visual estimation. When using this approach, it is important for the radiologist's report to clearly and specifically detail the anatomic location of the targets within the prostate, which can be accomplished with a combined series of detailed terms of localization (ie, left or right, anterior or posterior, lateral or medial, peripheral or transition zone, base or mid or apex), maps, and images. For instance, maps incorporating 24–36 anatomic sectors can be used to communicate the location of a lesion (Fig 3) (35). Key images, which are

**Figure 3**

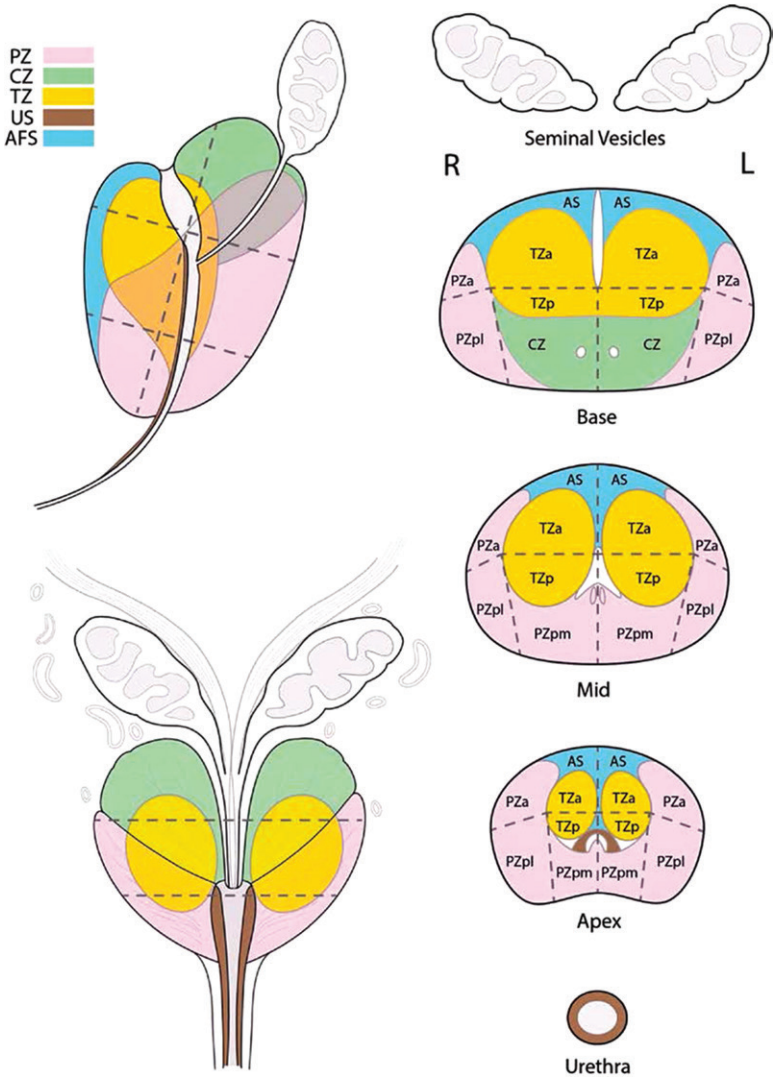



**Figure 3:** Images show standardized anatomic localization map from PI-RADS version 2 to designate a suspected cancer lesion seen at prostate MR imaging, consisting of 36 prostate sectors (18 on each side) with designations for left (L) and right (R) seminal vesicles and urethral sphincter (US). *a* = anterior, *AFS* = anterior fibromuscular stroma, *CZ* = central zone, *p* = posterior, *pl* = posterolateral, *pm* = posteromedial, *PZ* = peripheral zone, *TZ* = transition zone. For example, left anterior transition zone within the apical one-third of the gland would be sector L, TZa; right posterolateral peripheral zone of the mid gland would be R, PZpl. Source.—Reference 11.

annotated with arrows in three planes and saved to the picture archiving communication system, assist the operator in confident understanding of the target locations to be sought at transrectal US biopsy. This method depends on the skill of the operator in translating the targets identified at MR imaging to the anatomy recognized at evaluation of transrectal US. This can be especially challenging because the planes of section for MR imaging and transrectal US may be quite different.

Existing studies on the results of cognitive MR imaging–targeted biopsy suggest it is superior to systematic prostate biopsy and, in the proper hands, potentially comparable to other fusion methods (35–38). For example, cognitive MR imaging–targeted biopsy has been applied to men with prior negative biopsy findings with advantages over systematic rebiopsy. Sciarra et al reported a prospective study of 180 men divided into two groups, one undergoing systematic 10-core rebiopsy and another undergoing systematic 10-core rebiopsy plus cognitive MR imaging–targeted biopsy (37). Cancer was detected in 24.4% and 45.5% of the two groups, respectively ($P$ = .01). In addition, Lee et al studied 87 men with increasing PSA following initial negative 12-core biopsy findings who underwent multiparametric MR imaging prior to 12-core systematic rebiopsy with additional cognitive MR imaging–targeted biopsy of lesions suspicious for cancer (38). Cancer was reported in 28.8% of MR imaging–targeted cores versus 3.6% of systematic cores ($P$ = .012). Authors also noted a high proportion of anterior and apical cancers in 86% of those patients that underwent prostatectomy, reflecting MR imaging targets traditionally missed by systematic biopsies.

Although the previous studies show cognitive MR imaging–targeted biopsy to be superior to standard systematic transrectal US-guided biopsy, a randomized prospective clinical trial by Tonttila et al demonstrated these two methods to be similar in prostate cancer detection (39). However, one of the major limitations of this study was the skill level of the operators. Radiologists involved were not experienced in prostate MR imaging and the urologists had differing levels of experience in cognitive MR imaging–targeted biopsy. This operator dependence and lack of standardization remains a challenge for cognitive MR imaging–targeted biopsy.

## Transrectal US–MR Imaging Fusion Methods and Techniques

Transrectal US–MR imaging fusion biopsy is becoming a highly utilized method for targeted biopsy of the prostate, with one recent review identifying

more studies using this approach than either cognitive or in-gantry approaches (40). Transrectal US–MR imaging fusion biopsy combines the superior lesion detection of multiparametric MR imaging with the real-time capabilities of transrectal US. This technique is performed by coregistering previously acquired MR images with real-time transrectal US and then tracking the US probe as it is moved through space. Then, the biopsy is performed with US guidance, allowing the operator to target the lesions identified at multiparametric MR imaging, but outside the MR imaging gantry (Fig 4).

Several available commercial systems designed specifically for fusing MR imaging and transrectal US for prostate biopsy are summarized in Table 2. One of the fusion platforms is known as UroNav (Invivo), which uses electromagnetic tracking to follow the motion of the real-time transrectal US probe to multiparametric MR imaging and allows the user to sample the prostate via a freehand approach. This system combines rigid and elastic registration to achieve reliable and accurate image fusion, registration, and ultimately tissue sampling (41). The reported accuracy of the UroNav platform was 2.3 mm ± 0.9 (standard deviation) in a phantom study and is probably slightly less accurate in humans (42).

Another fusion platform is the Artemis (Eigen, Grass Valley, Calif) system. This platform initially performs image registration between multiparametric MR imaging and transrectal US images by using a fixed mechanical arm holding the transrectal US probe. The mechanical arm includes joints with angle-sensing encoders to track the needle and probe in space for targeting. The Artemis also uses elastic registration to optimize image fusion. After the two images are fused, the position of the US probe is monitored by position sensors on the mechanical arm. The reported accuracy of this system was 1.2 mm ± 1.1 in humans in an initial study (43). A third transrectal US–MR imaging fusion biopsy platform to be introduced was the Urostation (KOELIS, Meylan, France), which differs from the first two platforms because it uses transrectal US to transrectal US registration as the tracking method. The system initially fuses multiparametric MR imaging to transrectal US images; then, right after the biopsy core is taken, additional transrectal US imaging is performed to determine the accuracy of needle deployment within the target lesion. This platform enables a freehand approach, although the targeting during the biopsy is retrospective rather than in real time. The accuracy of this system was reported as 2.35 mm and 2.92 mm for hypoechoic and isoechoic lesions, respectively (44). Because of recent increased concerns of higher infection and sepsis rates following transrectal US-guided prostate biopsies, the transperineal route has been suggested as an alternate approach to decrease such risks (21). The BiopSee platform (MedCom, Darmstadt, Germany) is one of the few systems to enable transrectal US–MR imaging fusion biopsy through the transperineal route. BiopSee uses a transrectal US probe that is attached to a mechanical stepper fixed to the operating table. This transrectal US probe has two degrees of freedom that allow for adjustments in probe depth and rotation along the main axis. These movements and rotations are tracked by two encoders to ensure accurate lesion targeting and sampling. Biopsy needles are guided through a perineal brachytherapy grid mounted to the mechanical stepper (45).

A main strength of transrectal US–MR imaging fusion biopsy is the capability to perform MR imaging–targeted biopsy while in an office setting. In addition, most fusion platforms record the biopsy core locations, which can both aid active surveillance biopsies and assist quality assurance regarding sampling accuracy in the event of inconclusive targeted biopsy results.

## Challenges of Transrectal US–MR Imaging Fusion Biopsy

A number of challenges exist regarding the implementation of transrectal US–MR imaging fusion biopsy in clinical practice. First, the method entails substantial upfront costs for the initial investment in the MR imaging–US fusion technology. Data indicate the presence of a steep learning curve, with operators exhibiting improved performance as experience increases. For example, in a study of 340 patients who underwent transrectal US–MR imaging fusion biopsy by using a transperineal approach over a 22-month period, the cancer detection rate increased between the first and last groups of 70 patients from 27% to 63%, as did the negative predictive value from 67% to 89% (46). In an additional study of 429 patients undergoing prostate MR imaging interpreted by a single radiologist with subsequent fusion biopsy performed by a single urologist, the cancer detection rate in highly suspicious lesions increased over 33 months from 63% to 86% (47). This method requires continuous feedback between the urologist, pathologist, and radiologist during the learning period and then at intervals to ensure maintenance of quality. Another substantial concern is the quality of the fusion between MR imaging and transrectal US. Inaccurate segmentation of the MR images or transrectal US images can lead to misregistration, as can poor manual registration of accurately segmented MR imaging and transrectal US. Martin et al performed a simulation-based study to assess needle delivery error accounting for discrepancies relating to guidance system error, image misregistration, or irregular tumor shapes. The authors reported a root mean square error of 3.5 mm (48). A separate phantom study suggested a registration accuracy of 2.4 mm ± 1.2 (43), both of which are best-case scenarios. Because of the small registration error that is apparent based on the available literature, it is generally advised to obtain at least two spatially distributed cores from each target.

## Comparison of MR Imaging–targeted Prostate Biopsy Methodologies

All three methods of performing MR imaging–targeted prostate biopsy (cognitive, in-gantry, and transrectal US–MR imaging fusion biopsy [hereafter, software fusion–targeted biopsy]) outperform standard biopsy in various measures of cancer detection. A more challenging issue, with far less data available, is how these methods

**Figure 4**

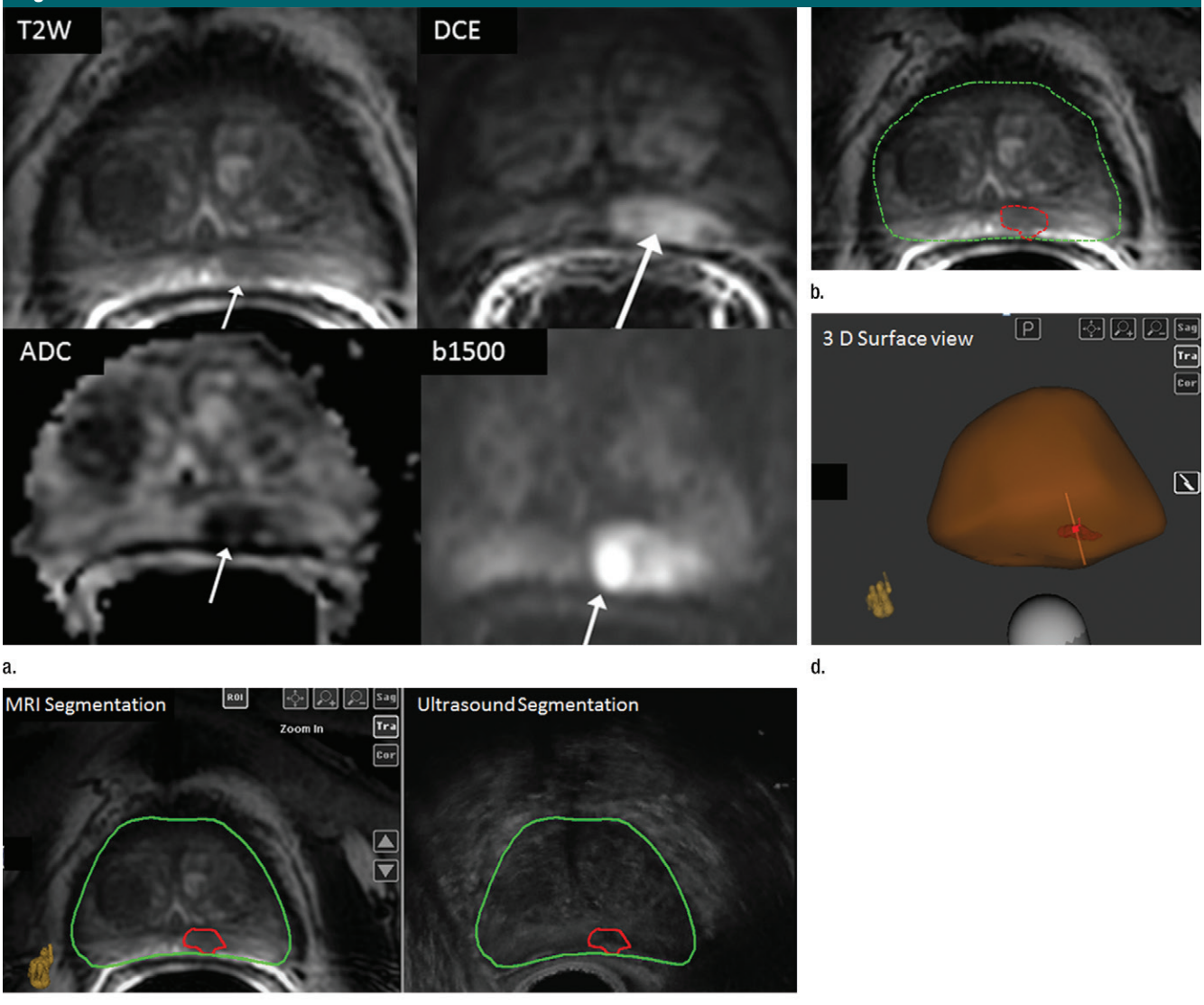



**Figure 4:** Images in a 68-year-old man with rising PSA to 9.9 ng/mL and two negative transrectal US prostate biopsy findings. **(a)** A 10-mm poorly marginated nodule in left mid gland peripheral zone (arrow) with decreased T2-weighted signal intensity, decreased apparent diffusion coefficient of 0.773 × 10–3 $mm^2$/sec, increased high-*b*-value signal of 1500, and focal early enhancement on dynamic contrast-enhanced images yielding an overall score of 4 on PI-RADS version 2. **(b)** Prostate segmentation is performed by using MR imaging data set to produce a three-dimensional model of the prostate. The prostate (green circle) is outlined by using a semiautomated segmentation tool and delineated as a target (red circle). **(c)** During fusion biopsy, real-time three-dimensional US model of the prostate is acquired and used to outline the prostate (green circle). The MR imaging and transrectal US three-dimensional models are dynamically fused and visualized side by side. This data set facilitates transrectal US–MR imaging registration and allows projection of the suspicious area seen at MR imaging (red circle) on the transrectal US screen. **(d)**. Finally, targeted biopsies can be performed to generate a final three-dimensional model. Targeted biopsy demonstrated a tumor with Gleason score of 3 + 4. Follow-up prostatectomy confirmed transrectal US–MR imaging fusion biopsy findings. *T2W* = T2-weighted. *DCE* = dynamic contrast enhanced. *ADC* = apparent diffusion coefficient. *3D* = three-dimensional.

compare with one another (Table 3). Such comparative studies are difficult to perform. Ultimately, as further data emerge regarding all of the approaches, systematic reviews and meta-analyses pooling data across centers may be required to achieve meaningful comparisons of the relative performance of the three methods. The ultimate decision on which method is superior may rest with practical issues such as which method has higher throughput, which is less costly, and which better conforms to existing workflows. In this regard, software fusion–targeted

biopsy methods are likely to prevail in the future.

Currently, the two methods with the highest number of comparative studies are cognitive and software fusion–targeted biopsy. In the earliest published such study, Puech et al performed an intraindividual comparison of systematic, cognitive-targeted, and software fusion–targeted biopsy (49). Both cognitive and software fusion–targeted biopsy had significantly greater detection of clinically significant cancer than did systematic biopsy, and tumor detection and grading were similar between cognitive and software fusion–targeted biopsy. On the other hand, Wysock et al conducted an intraindividual study in which two different urologists performed cognitive and software fusion–targeted biopsy in a given patient (50). Software fusion–targeted biopsy achieved slightly higher detection rate of Gleason score of 7 or greater cancer (20% vs 15%; $P = .052$), as well as a significantly higher number of informative nonbenign histologic results (77 vs 70 targets among a sample of 172 targets in 125 patients; $P = .001$). Moreover, multivariable analysis identified smaller target size to be a significant independent predictor of a lesion being positive for cancer at software fusion–targeted biopsy, but not cognitive fusion biopsy ($P = .005$). A separate study by Delongchamps et al randomized patients to undergo either cognitive or software fusion–targeted biopsy, both in combination with concurrent standard biopsy (51). Of the two targeting methods, software fusion targeting outperformed standard biopsy in terms of tumor detection. Additional studies indirectly address the comparison of the two fusion targeting methods. In a study by Cool et al, three operators performed cognitive-targeted biopsies exclusively of targets that represented clinically significant cancer by using a previously validated prostate biopsy simulator with fusion software (52). For all operators, cognitive-targeted biopsy missed a substantial fraction of cancers detected by using fusion biopsy, regardless of the operator's level of experience, with the rate of missed tumors associated with the anatomic location of the lesion in the prostate. Also, in a study by Kwak et al of patients undergoing fusion biopsy, the same operators also recorded target locations from attempted cognitive targeting, although no actual cognitive-targeted biopsies were performed (53). The locations of the cognitive targets had a mean distance of 10.6 mm from the locations of the software fusion targets, with only 15.3% of cases having a discrepancy of less than 5 mm and 12.5% of cases having a discrepancy of greater than 20 mm. The degree of misregistration between cognitive MR imaging–targeted and software fusion –targeted biopsy was high regardless of the lesion location in the prostate, although it did vary somewhat based on both the location and degree of operator experience. Given the findings of these studies, it is concluded that both

**Table 2**

**Food and Drug Administration–approved Multiparametric MR Imaging Supported Biopsy Systems**

| System | Manufacturer | Tracking Mechanism | Transrectal US–MR Imaging Fusion Mechanism |
|---|---|---|---|
| In-gantry MR imaging–targeted biopsy | | | |
| DynaTRIM | Invivo, Gainesville, Fla | … | … |
| Robotic-assisted MR imaging–targeted biopsy | | | |
| MrBot | Johns Hopkins University, Baltimore, Md | … | … |
| Transrectal US–MR imaging fusion biopsy | | | |
| UroNav | Invivo, Gainesville, Fla | Prospective targeting, electromagnetic tracking with rigid motion compensation | Rigid and elastic |
| Artemis | Eigen, Grass Valley, Calif | Prospective targeting, mechanical tracking with rigid motion compensation | Rigid and elastic |
| Urostation | KOELIS, Meylan, France | Retrospective targeting, real-time elastic registration | Elastic |
| Real-Time Virtual Sonography | Hitachi, Tokyo, Japan | Prospective targeting, electromagnetic tracking | Rigid |
| BioJet | DK North America, Naples, Fla | Prospective targeting, mechanical arm with encoders track | Rigid |
| LOGIQ 9 | GE Healthcare, Buckinghamshire, United Kingdom | Prospective targeting, electromagnetic tracking with rigid motion compensation | Rigid |
| Fusion Bx | Focal Healthcare, Toronto, Canada | Prospective targeting, electromagnetic tracking with rigid motion compensation | Rigid |

**Table 3**

**MR Imaging–targeted Prostate Biopsy (In-Gantry Targeted, Robotic-assisted, Cognitive Targeted, and Software Fusion Targeted) Strengths and Weaknesses**

| Biopsy Approach | Strengths | Weakness |
|---|---|---|
| In-gantry MR imaging–targeted biopsy | Greater detection of clinically significant cancer than systematic biopsy | Restricted availability |
| | Direct visualization of MR imaging target and needle concurrently | Long duration of procedure |
| | Fewer cores biopsied and lower risk of complications | Steep learning curve for operator |
| | Transperineal route has lower rate of infection and can be the only approach for patients without a rectum or hard-to-target lesions | High costs for acquiring technology |
| Robotic-assisted MR imaging–targeted biopsy | Greater detection of clinically significant cancer than systematic biopsy | Lack of commercially available systems |
| | … | Demanding to design and build the machines |
| Cognitive MR imaging–targeted biopsy | Conforms to existing workflows | Highly dependent on operator skill |
| | Greater detection of clinically significant cancer than systematic biopsy | Lack of standardization |
| | Ease of performing concurrent systematic biopsy | Misses some challenging targets in comparison with other targeted biopsy methods |
| | <30 minutes to perform 12-core systematic biopsy in addition to targeted biopsy | Concurrent systematic cores increase procedure time and risk of complications |
| | Less expensive with no additional platforms needed | … |
| Transrectal US–MR imaging fusion biopsy | Greater detection of clinically significant cancer than systematic biopsy | High costs for acquiring technology |
| | Conforms to existing workflows | Steep learning curve for operator |
| | Ease of performing concurrent systematic biopsy | Concurrent systematic cores increase procedure time and risk of complications |
| | <30 min to perform ≥12-core systematic biopsy in addition to targeted biopsy | … |

cognitive and software fusion–targeted biopsy improve tumor detection compared with systematic biopsy. However, software fusion seems to have an incremental benefit compared with cognitive fusion, with the extent of this benefit dependent on operator experience in the two targeting methods, as well as lesion size and location. Finally, further data remain necessary to compare the performance of various methods of software fusion targeting (eg, mechanical, electromagnetic, and organ-based navigation) with one another.

Less data are available comparing in-gantry MR imaging–targeted biopsy with either of the other two targeting methods. Arsov et al randomized patients to undergo either in-gantry fusion biopsy or concurrent standard and software fusion–targeted biopsy (22). The two arms were not significantly different in terms of tumor detection or assessment of tumor grade or volume. However, significantly fewer cores were obtained by using the in-gantry approach (5.6 vs 17; $P < .001$). In a separate study of the same two biopsy approaches, Arsov et al reported that the approach of combined systematic and software fusion–targeted cores required significantly less time (28 minutes vs 42 minutes; $P < .001$) and significantly less subjectively reported procedural pain by using a 0–10 visual analog scale (1.95 vs 2.95; $P < .001$) (54). The decreased pain noted in patients undergoing software fusion targeting was attributed to the use of a periprostatic nerve block, which is recognized to achieve effective pain control and can be easily administered outside of the MR imaging suite. In comparison, an intrarectal anesthetic gel was administered prior to in-gantry MR imaging targeting because of the need to use MR imaging–compatible equipment. Based on the limited available data, it is not possible at this time to draw firm conclusions regarding the performance of in-bore targeted biopsy versus the other targeting methods, or of the impact of such factors as operator experience and lesion size and location. Such comparisons may also be influenced by whether the in-gantry approach is performed by using a transrectal or transperineal approach. Further investigations addressing these issues therefore remain warranted.

Finally, because current clinical assessment tools are typically based on the results of a 12-core biopsy (percentage of positive cores, length of cancer in each core, etc), it may be unclear how to perform optimal risk assessment based on biopsy results solely from an MR imaging–defined target, regardless of targeting methodology. In addition, because a negative finding at multiparametric MR imaging has false-negative rate of approximately 5%–15% for clinically significant cancer (55), a concurrent systematic 12-core biopsy may be considered warranted to reduce the chance of missing significant cancers compared with the lesion-only biopsy. (However, performing concurrent

**Figure 5**


a. b.

**Figure 5:** Images show MR imaging–compatible prostate biopsy robot. **(a)** Transperineal needle placement robot is shown **(b)** in position between patient's legs in 70-cm bore 3.0-T magnet.

systematic biopsy increases discomfort, risk of complication, and the likelihood of detection of insignificant tumor, while still not fully avoiding the risk of missing clinically significant cancer.).

## Robotic-assisted MR Imaging–targeted Biopsy

Only a single targeting device for robotic-assisted MR imaging is approved by the U.S. Food and Drug Administration (56). These devices are mainly used in research settings, and therefore are only briefly discussed here. Robotic technology has been developed and tested for both transperineal and transrectal in-gantry MR imaging–targeted biopsies to remotely steer a needle guide to the target from outside the imager room (17,33,57). The goal is to decrease the duration of the procedure and improve its accuracy. Several studies have demonstrated the feasibility of robotic assisted in-gantry MR imaging–targeted prostate biopsy with promising initial clinical results (34,58–60). However, image-targeted robots are technically demanding to design and build because of the requirements of compatibility, safety, accuracy, size (must fit into the imager, generally between the legs of the patient), ergonomics, and sterility of MR imaging (61). The two major clinical indications for such devices are MR imaging–targeted prostate biopsy (Fig 5a, 5b) and therapeutic indications including thermal therapy and placement of interstitial radiation sources (62–64).

## Conclusion

Conventional systematic (transrectal US-guided) biopsy of the prostate contributes to the frequent overdiagnosis of indolent prostate cancers while missing potentially lethal tumors. However, the advent of multiparametric MR imaging has enabled the more reliable detection of clinically significant cancers than was possible with systematic biopsy and has resulted in an increasing trend toward incorporating multiparametric MR imaging into clinical paradigms for the diagnosis of prostate cancer. However, just as vital as cancer detection is the accurate characterization of its biology with a needle biopsy. For this task, MR imaging–targeted biopsies of the prostate are necessary, and a variety of methods have been developed including in-gantry MR imaging–targeted biopsy, cognitive biopsy with transrectal US guidance (without use of dedicated targeting technology), and transrectal US–MR imaging fusion biopsy. Despite these promising developments, a number of limitations remain. Multiparametric MR imaging has a recognized false-negative rate for significant cancers, ranging from approximately 5%–15% in the best of centers (55), and no guidance system can overcome the lack of a target. This problem may be exacerbated by poor image quality or interpretation, as well as by inaccurate image segmentation or registration for fusion biopsies. Current efforts within the field to establish guidelines for standardization of prostate MR imaging reporting and interpretation, as well as to improve the precision of fusion technologies, are expected to improve upon these challenges. Nonetheless, as with all human-guided procedures, a degree of operator variability will remain inevitable. Investigators in the field are thus currently evaluating this "chain of quality," seeking methods to improve outcomes of MR imaging–targeted prostate biopsies. Ultimately, it is anticipated that MR imaging–targeted prostate biopsy will become established as the preferred approach for many, if not all, men suspected of having prostate cancer.

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