Targeted Biopsy in the Detection of Prostate Cancer Using an Office Based Magnetic Resonance Ultrasound Fusion Device

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Abbreviations and Acronyms

3D = 3-dimensional
ADC = apparent diffusion coefficient
CaP = prostate cancer
DCE = dynamic contrast enhanced
MR = magnetic resonance
MRI = magnetic resonance imaging
MR-US = magnetic resonance ultrasound
PSA = prostate specific antigen
ROI = region of interest
TRUS = transrectal ultrasound
US = ultrasound

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Purpose: Targeted biopsy of lesions identified on magnetic resonance imaging may enhance the detection of clinically relevant prostate cancers. We evaluated prostate cancer detection rates in 171 consecutive men using magnetic resonance ultrasound fusion prostate biopsy.

Materials and Methods: Subjects underwent targeted biopsy for active surveillance (106) or persistently increased prostate specific antigen but negative prior conventional biopsy (65). Before biopsy, each man underwent multiparametric magnetic resonance imaging at 3.0 Tesla. Lesions on magnetic resonance imaging were outlined in 3 dimensions and assigned increasing cancer suspicion levels (image grade 1 to 5) by a uroradiologist. A biopsy tracking system was used to fuse the stored magnetic resonance imaging with real-time ultrasound, generating a 3-dimensional prostate model on the fly. Working from the 3-dimensional model, transrectal biopsy of target lesions and 12 systematic biopsies were performed with the patient under local anesthesia in the clinic.

Results: A total of 171 subjects (median age 65 years) underwent targeted biopsy. At biopsy, median prostate specific antigen was 4.9 ng/ml and prostate volume was 48 cc. A targeted biopsy was 3 times more likely to identify cancer than a systematic biopsy (21% vs 7%). Prostate cancer was found in 53% of men, 38% of whom had Gleason grade 7 or greater cancer. Of the men with Gleason 7 or greater cancer 38% had disease detected only on targeted biopsies. Targeted biopsy findings correlated with level of suspicion on magnetic resonance imaging. Of 16 men 15 (94%) with an image grade 5 target (highest suspicion) had prostate cancer, including 7 with Gleason 7 or greater cancer.

Conclusions: Prostate lesions identified on magnetic resonance imaging can be accurately targeted using magnetic resonance ultrasound fusion biopsy by a urologist in clinic. Biopsy findings correlate with level of suspicion on magnetic resonance imaging.

Key Words: prostatic neoplasms, magnetic resonance imaging, ultrasonography, biopsy

BIOPSY detection of prostate cancer remains imperfect, limited by over detection of indolent tumors and under detection of clinically relevant cancers. Nearly 50% of currently detected CaP cases may be insignificant,[1] while 22% to 47% of saturation or template biopsies reveal cancer after an initial

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negative biopsy.[2] In addition, studies showing an approximately 25% to 40% rate of upgrading on final surgical pathology indicate that conventional prostate biopsy often fails to detect the highest grade lesion.[3] Thus, current methods of prostate biopsy, largely unchanged since 1989, deserve reevaluation.

Magnetic resonance imaging offers the potential to improve CaP diagnosis. Stronger magnets and multiparametric protocols have improved the usefulness of prostate MRI since its initial description in 1982. Compared to TRUS, MRI provides superior resolution and may even be used to assign CaP grade.[4–6] At NIH (the National Institutes of Health) Turkbey et al recently described a 98% positive predictive value for prostate MRI, and found improved sensitivity for higher grade tumors and those larger than 5 mm in diameter.[7] Such preferential diagnosis of clinically significant tumors comprises a potential advantage of MRI. While the technology exists to biopsy prostate tumors under direct MRI guidance,[8] such procedures are time-consuming, costly and impractical in most settings. Magnetic resonance ultrasound systems that fuse stored MR images with real-time ultrasound combine the resolution of MRI with the ease and practicality of ultrasound,[9–11] offering a savings in time and cost, while potentially retaining the accuracy of MR guided biopsy. However, these systems have been limited by the need for monitored anesthesia care[9] or a transperineal approach and general anesthesia.[10]

We previously described the initial clinical use of MR-US fusion using a mechanically assisted prostate biopsy device (Artemis, Eigen, Grass Valley, California), permitting targeted prostate biopsy with the patient under local anesthesia.[11] This technology, validated in phantom studies in 2008,[12] 1) enables office based transrectal biopsy of prostate lesions via MR-US fusion, 2) maps the precise location of systematic biopsies to ensure thorough sampling of the entire organ, and 3) tracks biopsy site locations, permitting accurate return to the same location within the prostate in cases when re-biopsy is necessary. In this study we report CaP detection rates in 171 consecutive outpatients who underwent MR-US fusion biopsy.

MATERIALS AND METHODS

Patients

A total of 171 consecutive outpatients with clinical stage T1c disease who underwent MR-US fusion biopsy between March 2010 and September 2011 provided informed consent. The UCLA (University of California Los Angeles) institutional review board approved this study. Patients were scheduled to undergo MR-US fusion biopsy for the indications of 1) persistently increased PSA but prior negative TRUS biopsy and 2) active surveillance yearly protocol biopsy. All MRIs were followed by fusion biopsy regardless of the MRI result. Ten men underwent multiple fusion biopsy sessions according to the UCLA active surveillance protocol. For the purpose of this study only the most recent biopsy result was used for analysis.

Multiparametric MRI

Subjects underwent multiparametric MRI on a Siemens SOMATOM® Trio™ Tim 3T magnet with high performance gradients using a multichannel external phased array coil. Following the latest international recommendations on prostate MRI for detection purposes, no endorectal coil was used.[13] MRI was performed 1 to 3 weeks before biopsy. Our MRI and biopsy protocol have been described previously,[11] and included T2-weighted imaging, diffusion weighted imaging and dynamic contrast enhanced imaging. Each parameter was interpreted by a uroradiologist (DJAM) with 8 years of experience reading prostate MRI who was blinded to clinical data, including the location of prior positive biopsies. Suspicious regions of interest were identified on a DICOM (Digital Imaging and Communications in Medicine) workstation (Merge CADstream™). Each ROI (ie lesion or target) was assigned an image grade on a 1 to 5 scale ranging from normal to highly suspicious and outlined in 3D on an open source workstation (OsiriX, www.osirix-viewer.com). This previously published classification system has been updated (see table).[11]

MR-US Fusion Biopsy Procedure

Each patient received ciprofloxacin for 1 day, a cleansing enema and intramuscular ceftriaxone before biopsy, followed by 3 additional days of ciprofloxacin. The MRI with documented ROIs was loaded into the image processing component of the Artemis device, a 3D US guided prostate biopsy system. The left lateral decubitus position was used. After insertion of the standard US probe (Hitachi HI VISION™ 5500, 7.5 MHz end fire) and administration of periprostatic 1% lidocaine, the tracking arm was attached to the US probe. Figure 1 demonstrates the work flow in a representative patient. During scanning of the prostate, the US feed is captured by the device and reconstructed as a 3D prostate model on the monitor. The stored MRI data set was manually aligned and automatically fused with the real-time US, overlaying the ROIs on the virtual 3D prostate model. A systematic array of 12 preselected biopsy sites, generated by the Artemis device and independent from the MRI result, was loaded along with the ROI

Classification system for targets identified on MRI[11]

Image Grade	T2-Weighted Imaging	ADC ($\times 10^{-3}$ m^2/sec)	Dynamic Contrast Enhancement
1	Normal	Greater than 1.4	Normal
2	Faintly decreased signal	1.2–1.4	Early or intense enhancement
3	Distinct low signal	1.0–1.2	Early + intense enhancement, or early enhancement with washout
4	Markedly decreased signal	0.8–1.0	Early + intense enhancement with washout
5	Focal low signal with mass effect	Less than 0.8	Early enhancement is intense with immediate washout

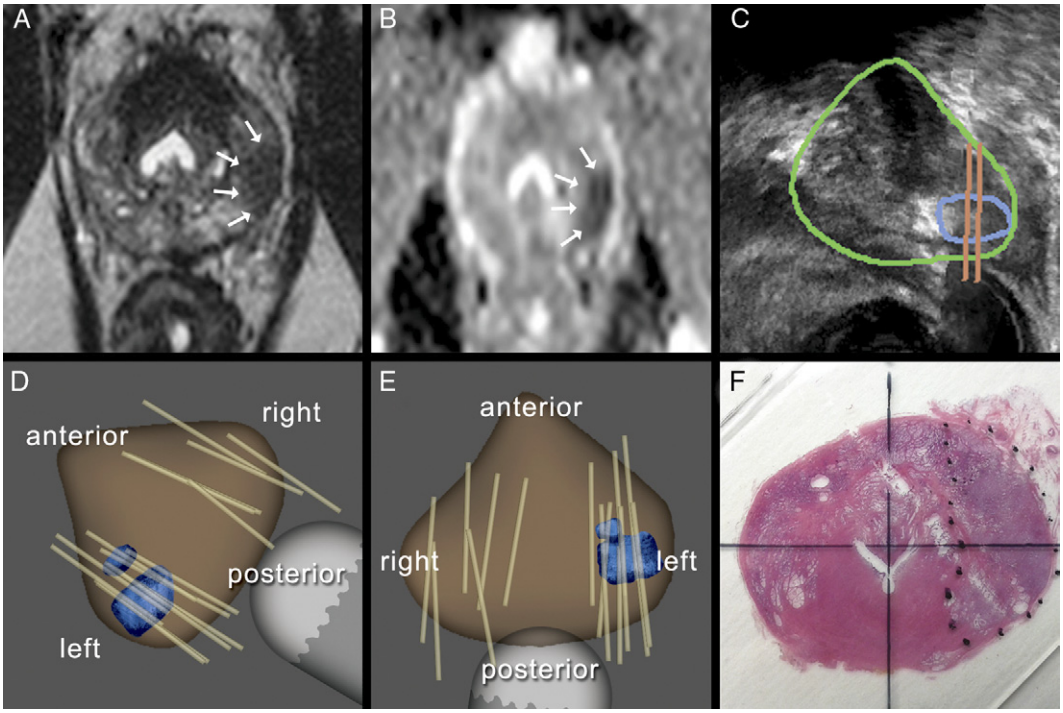


Figure 1. Sample case of 59-year-old man with PSA 7.4 ng/ml and 1 prior negative biopsy. T2-weighted axial MR image demonstrates lesion in left peripheral prostate with focal low signal (*A*). Diffusion weighted axial MR image with ADC value of 0.562×10^{-3} m^2 per second in corresponding area (*B*). Lesion was classified as image grade 5 based on multiparametric features. Radiologist outlined lesion in each axial image. Open source imaging software then produced 3D model of prostate including 3D target. Real-time ultrasound image of area of interest (outlined in blue, *C*). Note absence of ultrasound abnormality. 3D model is generated based on ultrasound. Two models were then dynamically fused, generating composite virtual 3D model (*D* and *E*). Prostate is mapped in brown and target identified in blue. Systematic and targeted biopsies were obtained, generating final 3D model demonstrating location of all biopsy cores (light brown cylinders). Targeted biopsies in this patient revealed Gleason 7 CaP. Radical prostatectomy whole mount pathology confirmed presence of 2 cm Gleason 7 cancer in left peripheral zone (*D*).

targets identified on MRI. A multi-panel image was generated on the monitor showing real-time US, the corresponding axial and sagittal MR images, and the virtual 3D model. Working from the 3D model (fig. 1, *D* and *E*), transrectal biopsies of target lesions and 12 systematic biopsies were performed by a single urologist (LSM) with a conventional reusable spring-loaded gun and 18G needles in the urology clinic. Targets were biopsied at 3 mm intervals, based on prior experience demonstrating 1.2 ± 1.1 mm tracking accuracy on repeat biopsy.[11] Discordance from the 3D model due to patient or prostatic movement was corrected using a motion compensation function in the biopsy tracking software. All biopsies were performed in outpatients under local anesthesia at the UCLA Clark Urology Center.

Statistical Analysis

Descriptive statistics were used to analyze patient characteristics such as age, PSA, prostate volume and previous biopsy results. Comparison of cancer percentages within groups was made using the chi-square statistic. The 95% CIs based on the exact binomial distribution are presented in parentheses where appropriate. Comparison of tumor length between systematic and targeted cores was made using a simple t test. The results of the fusion biopsies were stratified according to the MRI scoring system (image grade 2 to 5). The nonparametric Spearman rank correlation was used to assess the relationship between image grade and the presence of cancer. A statistician (FJD) performed all calculations.

RESULTS

A total of 171 subjects (median age 65 years) underwent fusion biopsy. At the time of biopsy, median PSA was 4.9 ng/ml and median prostate volume was 48 cc. Mean time from probe insertion to last biopsy was approximately 20 minutes. On average, 1.6 targets were identified per patient (range 0 to 4) and 2.2 cores were taken per target (range 1 to 6). Of the men 106 underwent biopsy for surveillance while 65 had an increased PSA but prior negative biopsies. Of 293 MRI targets 257 (88%) were successfully sampled with at least 1 targeted core traversing the ROI. On average, 13.4 biopsy cores were taken per patient. No patient required hospitalization for fever or sepsis after biopsy.

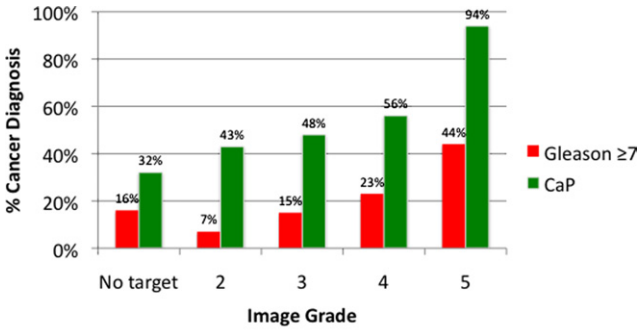
Biopsies demonstrated CaP in 90 of 171 men (53%). Of these 90 men 34 (38%) had Gleason grade 7 or greater cancer. In subjects with at least 1 prior

negative biopsy (median PSA 7.3 ng/ml) the rate of cancer diagnosis was 37%. In men on active surveillance (median PSA 4.1 ng/ml) the rate was 63%. In men with an image grade 2, 3, 4 or 5 ROI, the rate of cancer diagnosis on targeted or systematic biopsy was 43%, 48%, 56% and 94%, respectively. Gleason grade was 7 or greater in 7%, 15%, 23% and 44% of those with an image grade 2, 3, 4 or 5 ROI, respectively (fig. 2). Prostate cancer was diagnosed on systematic biopsies in 6 of the 19 (32%) men with no ROI identified on MRI (3 Gleason 3 + 4, 3 Gleason 3 + 3).

A total of 279 targets were identified in the 171 men. The mean maximal diameter of the ROI identified on MRI was 11.4 mm (range 4 to 45). The rate of cancer diagnosis overall and the rate of detection of clinically significant CaP increased with increasing suspicion on MRI (fig. 3).

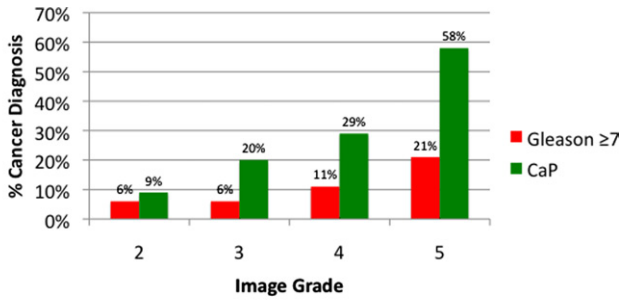
Targeted biopsies were more likely to reveal CaP (20.8% of 486 targeted cores) than systematic biopsies (7.3% of 1,741 systematic cores, p = 0.001). The mean cancer length from cancer positive targeted cores exceeded that from systematic cores (5.1 vs 3.3 mm, p = 0.003). The distribution of Gleason 7 or greater tumors was also greater for targeted cores compared to systematic cores, as 36% of tumors identified on targeted cores were Gleason 7 or greater vs 24% of tumors identified on systematic cores (p = 0.037).

Of the 151 subjects who underwent systematic and targeted biopsies, 84 had CaP diagnosed. Of these, 31 had detection only by systematic biopsy, 15 only by MR-US targeted biopsy and 38 by both. Of the 29 men (35%) found to have Gleason 7 or greater CaP, these numbers were 9 for systematic, 11 for targeted and 9 for both. Thus, 11 of 29 men (38%) with Gleason grade 7 or greater cancer had disease detected only on targeted biopsy.



# Patients	19	14	61	61	16
# Any CaP	6	6	29	34	15
# Gleason ≥7 CaP	3	1	9	14	7

Figure 2. Prostate cancer detection rate in 171 men undergoing MR-US fusion biopsy.



# Targets	34	142	84	19
# Any CaP	3	29	24	11
# Gleason ≥7 CaP	2	9	9	4

Figure 3. Prostate cancer diagnosis by target for 279 targets identified on MRI in 171 men.

DISCUSSION

Our study yielded 3 key findings. 1) We demonstrated the ability to accurately target and biopsy lesions seen on MRI using MR-US fusion technology in an office based setting with the patient under local anesthesia. 2) The addition of targeted biopsies to systematic biopsies increased the rate of diagnosis of all cancers and, more importantly, Gleason 7 or greater cancer. In fact, 38% of men with Gleason 7 or greater cancer had disease detected only via targeted biopsies of lesions identified on MRI. 3) The level of suspicion on MRI correlated with cancer diagnosis overall and diagnosis of Gleason 7 or greater prostate cancers. Biopsies revealed CaP in 16 of 17 (94%) men with an image grade 5 lesion on MRI.

Two recently published investigations using different MR-US fusion devices for targeted prostate biopsy yielded results similar to ours. Pinto et al described a fusion technique incorporating electromagnetic tracking, and found cancer in 28%, 67% and 89% of men with low, moderate and high suspicion on MRI.[9] Hadaschik et al incorporated MR-US fusion technology via a transperineal approach in the operating room, and found CaP in 59% of men overall and in 96% of men with highly suspicious lesions on MRI.[10] The similarity of these results to those presented here substantiates the advantages of image guided targeted biopsy using MR-US fusion.

Other recent studies involve targeted prostate biopsy under direct MRI guidance. Among 68 men with 2 or more prior negative TRUS biopsies and a median PSA of 13 ng/ml, Hambrock et al detected cancer in 59%.[14] Of those with cancer 45% had Gleason grade 7 or greater. The authors contrasted these results to a reference database at their institution in which the tumor detection rate during the third TRUS biopsy session (without MRI) was just 15%.

The same group published results evaluating the concordance of highest Gleason grade from biopsy to prostatectomy specimens in 98 patients.[8] The exact concordance rate for MR guided biopsy was 88% vs 55% for TRUS guided biopsy ($p = 0.001$). Anastasiadis et al performed MRI guided biopsy on men with a suspicious MRI and 1 or more prior negative TRUS biopsy.[15] The cancer diagnosis rate in 27 men (median PSA 10.2 ng/ml) was 55%.

In the present study we applied a 5-point semiquantitative scoring system to assess the degree of cancer suspicion to lesions seen on MRI. The scoring system is based on T2 characteristics, quantitative ADC and dynamic contrast enhancement curve analysis (see table). The scoring system, similar to that used by Hambrock et al,[14] allows for graded levels of suspicion, as opposed to other protocols in which a binary score of normal or abnormal was assigned.[10,15] Thus, the present scoring system follows the guidelines recently released by the European Society of Uroradiology.[13]

Targeted prostate biopsy may be useful in the 3 key situations of active surveillance, increased PSA but negative TRUS biopsy, and selection for focal therapy. While surveillance has proven to be a safe approach for low risk CaP,[16–21] use remains low[22] and rates of progression to active treatment in the major surveillance series range from 14% to 41%.[23] Targeted prostate biopsy may improve patient selection, making surveillance a more attractive option to patients while reducing progression to active treatment. Furthermore, the tracking feature of the Artemis device allows the urologist to return to the exact area of prior positive biopsies, enabling the physician to follow individual tumors over time. In addition, conventional TRUS biopsy may miss tumors in the apex and anterior prostate.[2,24,25] MR-US fusion targeted biopsy may identify tumors missed by TRUS biopsy, sparing patients the discomfort of numerous negative biopsies and reducing the risk of delayed diagnosis of aggressive tumors. Our 37% diagnosis rate in the prior negative biopsy population, 67% of whom had Gleason 7 or greater cancer, is considerably higher than would be expected with repeat conventional biopsy[26,27] and compares favorably with detection rates seen using saturation biopsy.[28] Finally, focal therapy has become an area of keen interest. Current strategies for patient selection for focal therapy often entail perineal template mapping biopsy,[29] a more invasive, morbid, resource intensive and expensive procedure than MR-US fusion biopsy.

This study has several limitations. Given the low risk patient population in our study (median PSA 4.9 ng/ml, all with prior biopsies), relatively few patients subsequently underwent radical prostatectomy. It remains possible that some significant tumors may be missed by targeted and systematic biopsies. Whole mount data would enable a more definitive analysis of the nature of lesions identified on MRI and biopsied using MR-US fusion. In addition, while the yield of biopsies from image grade 5 lesions is excellent, the concordance between lower image grade lesions and biopsy histology is suboptimal. Further analysis may determine if this stems from inaccurate MR-US registration or if many abnormal areas on MRI are actually benign. While some studies show a high sensitivity and specificity of contemporary multiparametric MRI,[7,30] prostate MRI remains difficult to interpret, and requires dedicated training and expertise to approach the accuracy of expert radiologists. The yield of targeted biopsies relates directly to the ability of the radiologist to accurately identify targets on MRI. Until the sensitivity of prostate MRI is confirmed, we view the ability to obtain systematic biopsies along with targeted biopsies as an advantage of MR-US fusion technology compared to direct MRI guided biopsy. Finally, image fusion technology is evolving rapidly and clinical experience with fusion devices remains in its infancy. Advances in hardware and software are certain to change the usability of fusion devices in the future.

Despite these limitations, MR-US targeted prostate biopsy has the potential to improve the contemporary diagnosis and treatment of CaP. The present data, obtained using an office based procedure in patients under local anesthesia, demonstrate better CaP detection than with systematic biopsies alone. These results compare favorably to those obtained using transperineal template biopsy techniques requiring general anesthesia. In contrast to direct MRI guided biopsy, the present method allows systematic and targeted biopsies to be obtained efficiently. Further work, including a detailed study correlating MRI, targeted biopsy results and prostatectomy specimens, is ongoing.

CONCLUSIONS

Prostate lesions identified on MRI can be accurately targeted with MR-US fusion biopsy in a clinic setting using local anesthesia. Biopsy findings correlate with the level of suspicion on MRI. Targeted prostate biopsy has the potential to improve the diagnosis of CaP, and may aid in the selection of patients for active surveillance and focal therapy.

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EDITORIAL COMMENTS

Can MR-US fusion targeted biopsy better characterize prostate cancer based on the degree of MR image suspicion compared to image blind (systematic random) biopsy? To use MR data in office urological practice, MR-US fusion biopsy is proposed.[1,2] This requires image acquisition, segmentation, image fusion, US guided biopsy and confirmation of biopsy trajectory. There are potential errors in each of these steps. Since the MR fused lesion is only a virtual image, the fundamental question is whether the virtual lesion biopsied was even in fact the real MR lesion. TRUS is important because its image is real, not virtual. When the MR lesion is also visible on US, real-time US can precisely guide the needle, relying on the reality of the US image. However, when the MR suspected lesion is completely invisible (isoechoic) on US, or when a concerted effort has not been made to interpret the real-time US image, biopsy accuracy becomes challenging because real-time guidance then relies exclusively on a virtual image. Every effort should be made to minimize potential errors at each step of the MR-US fusion

process.[2] The practicing urologists' understanding of the technical steps in MR-US fusion and facility with TRUS are essential for meaningful use of this technology in the outpatient clinic.

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MR-US fusion biopsy unblinds the blind biopsy, and in this study Sonn et al have continued the process of validating image fusion for TRUS biopsy. MR ultrasound fusion guided biopsies provide more accurate needle localization than "blind" TRUS alone, and do not require the physical presence of a MR gantry. The MR-US fusion biopsy could soon become an important tool for certain patient populations. Clearly defined indications remain speculative, but could include T1c lesions, prior negative TRUS biopsy in the setting of an increasing PSA or lesions identified on MRI. However, standardization and reporting criteria for MR-US fusion are needed, especially to determine whether old criteria validated during the era of TRUS will remain true for MR-US.

However, significant hurdles remain to broad adoption. Reproducibility, indications, throughput, standardization and cost remain to be defined. MRI itself can be subjective and more standardized interpretations are needed. The system described by Sonn et al relies on a mechanical arm attached to ultrasound, while others have electromagnetic tracking, optical tracking and image based fusion. The best approach is yet to be determined.

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Our group performed our first fusion guided biopsies on outpatients in the office setting in 2005 with optional mild oral sedation in approximately 15 minutes using electromagnetic tracking.[1,2] Since then, we have performed MR-US fusion guided biopsy in more than 650 outpatients with more than 11,000 needle core locations. Although monitored anesthesia was used in an early cohort (101 patients), the majority have been outpatients without anesthesia, and with only lidocaine nerve blocks. The cancer detection rate markedly increased with the addition of MR-US fusion biopsy (reference 9 in article). MR-US fusion guided biopsy has great potential to supplement or replace "blind" TRUS prostate biopsies.

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