Published in final edited form as:
Curr Opin Urol. 2013 January ; 23(1): 43–50. doi:10.1097/MOU.0b013e32835ad3ee.

MRI–ultrasound fusion for guidance of targeted prostate biopsy

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Abstract

Purpose of review—Prostate cancer (CaP) may be detected on MRI. Fusion of MRI with ultrasound allows urologists to progress from blind, systematic biopsies to biopsies, which are mapped, targeted and tracked. We herein review the current status of prostate biopsy via MRI/ultrasound fusion.

Recent findings—Three methods of fusing MRI for targeted biopsy have been recently described: MRI–ultrasound fusion, MRI–MRI fusion ('in-bore' biopsy) and cognitive fusion. Supportive data are emerging for the fusion devices, two of which received US Food and Drug Administration approval in the past 5 years: Artemis (Eigen, USA) and Urostation (Koelis, France). Working with the Artemis device in more than 600 individuals, we found that targeted biopsies are two to three times more sensitive for detection of CaP than nontargeted systematic biopsies; nearly 40% of men with Gleason score of at least 7 CaP are diagnosed only by targeted biopsy; nearly 100% of men with highly suspicious MRI lesions are diagnosed with CaP; ability to return to a prior biopsy site is highly accurate (within 1.2 ± 1.1 mm); and targeted and systematic biopsies are twice as accurate as systematic biopsies alone in predicting whole-organ disease.

Summary—In the future, MRI–ultrasound fusion for lesion targeting is likely to result in fewer and more accurate prostate biopsies than the present use of systematic biopsies with ultrasound guidance alone.

Keywords

MRI–ultrasound fusion; prostate cancer; prostate imaging; targeted biopsy

INTRODUCTION

Prostate biopsy to diagnose or exclude cancer is currently performed an estimated one million times annually in the USA [1]. Nearly all are performed by the transrectal, ultrasound-guided technique, which was introduced some 25 years ago by Hodge and colleagues [2]. Using this technique, tissue cores are obtained under ultrasound guidance systematically throughout the prostate, a method shown in 1989 to be just as accurate as when the operator used ultrasound to aim at a nodule [3]. The Stamey technique was performed without knowing the tumour location within the prostate (i.e. a blind biopsy), but

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Conflicts of interest
There are no conflicts of interest.

it was still a major advance over older methods in which biopsy needles were guided only by the examining finger. The systematic method gained widespread adoption, and prostate cancer (CaP) became the only major cancer, in which diagnosis is now routinely made by blind biopsy of the organ.

However, many of the currently performed prostate biopsies yield misleading information. Microfocal 'cancers' of little clinical significance are frequently detected [4], whereas the incidence of falsely negative biopsies, that is serious tumours not detected, may in first-time biopsies be as high as 35% [5]. Part of the problem may be that the average index CaP is smaller today than it was in the 1980s, making serious cancers more difficult to detect [6]. Further, as 12 cores are now routinely obtained, compared with six cores previously, overdetection of small, indolent tumours has become problematic [7]. Up to 50% of currently detected CaP cases may not be clinically relevant [4]. Conversely, 28 000 deaths are expected this year from CaP; thus, early detection of clinically significant CaP would very likely save many lives.

MRI of the prostate, particularly if performed with multiparametric imaging, is capable of detecting clinically relevant CaP [8▪▪]. Accuracy parameters are not yet clear, but for the first time, localized CaP may in many cases be identified, measured, selectively sampled and treated, or if appropriate, followed [9▪▪]. Potentially, many such cancers may be observed and resampled in active surveillance programmes, or perhaps in the future, focally ablated. The ability to visualize some CaP on MRI has brought the opportunity to use those images as targets for needle biopsy by incorporating (i.e. fusing) MRI into a needle-aiming or targeting method [10▪▪].

USE OF MRI TO VISUALIZE PROSTATE CANCER

The first published report, in which MRI was used to visualize CaP within the organ, was probably that of Hricak *et al.* [11]. In that 1983 report, the authors showed, using an MRI unit with a magnet operating at 0.35 T, that malignant prostate tissue had a higher intensity signal than surrounding benign tissues. They concluded that the 'greatest potential (of prostate MRI) seems to be its capability to detect pathology confined to the gland' [11].

Since that time, magnets have become stronger, resolution has improved dramatically and multiparametric enhancements, such as diffusion-weighted imaging and dynamic contrast studies, have become available. In a study of men with prior negative biopsies and persistently elevated PSA levels, Hoeks *et al.* [9▪▪] – working with multiparametric MRI, a machine with a 3-T magnet, and a body coil (not endorectal) – detected twice as many cancers with targeted biopsy as others have reported with conventional ultrasound guidance (detection rate of 41 vs. 18%). In this large series (N=265), 87% of the MRI-detected tumours found on biopsy were important cancers. Conversely, using MRI-targeted biopsy, the detection rate of insignificant cancers, that is those that would best be left undetected, should be lower than with systematic blind biopsy [12▪]. Further, when MRI findings have been correlated with pathologic findings, tumour localization appears to be significantly better with MRI than with digital rectal examination (DRE) or blind biopsy [13]. In the detection of CaP, multiparametric MRI appears superior to all other imaging modalities evaluated to date.

METHODS OF MRI-GUIDED PROSTATE BIOPSY

Three methods of MRI guidance are available for performance of targeted prostate biopsy: cognitive fusion, in which the ultrasound operator simply aims the biopsy needle at the prostate area where the reviewed prior MRI demonstrates a lesion; direct MRI-guided biopsy, performed within an MRI tube; and software coregistration of stored MRI with real-

time ultrasound, using a fusion device. Each method has its advantages and disadvantages. To date, no prospective comparison of the three methods has been made.

Cognitive fusion is simple, quick and requires no additional equipment beyond the MRI and a conventional transrectal ultrasound (TRUS) facility. Specialized training beyond conventional TRUS biopsy is not required for the ultrasound operator. In the comprehensive review of Moore *et al.* [10■■], cognitive fusion was used in some 22 separate studies. Although data are limited, cognitive fusion does appear to yield improved accuracy over conventional systematic, blind biopsy.

Disadvantage of cognitive fusion is the potential for human error in the extrapolation from MRI to TRUS without an actual overlay.

Direct MRI-guided biopsy is performed 'in-bore', that is within the MRI tube, by a radiologist, who fuses a prior MRI demonstrating a lesion with a contemporaneous MRI to confirm biopsy needle localization. The transrectal route is employed. After each biopsy sample, the patient is rescanned to confirm localization. Typically, only a few targeted cores are taken; systematic sampling is not performed. A large experience with in-bore biopsy has been published by the Barentsz group at Radboud University in Nijmegen, the Netherlands [9■■]. The advantages of this method are the limited number of cores taken, the exact localization of the biopsy and the reduced detection of insignificant tumours. The disadvantages of this method include the time and expense required, including the in-bore time and the two MRI sessions necessary to obtain the biopsy specimens. Further, as only suspicious lesions are sampled, tissues with a 'normal' appearance on MRI are not obtained, which is problematic, as any false-negative aspects of prostate MRI are not yet known.

The third method for MRI guidance of prostate biopsy is MRI–TRUS fusion. In this method, the operator images the prostate using ultrasound, as performed for the past several decades; while thus viewing the prostate, the MRI of that prostate, which is performed beforehand and stored in the device, is fused with real-time ultrasound using a digital overlay, allowing the target(s), previously delineated by a radiologist, to be brought into the aiming mechanism of the ultrasound machine. The fusion results in creation of a three-dimensional reconstruction of the prostate, and on the reconstructed model, the aiming and tracking of biopsy sites occurs. The disadvantage of this method is that it is indirect, involves use of an additional device and requires specialized operator training. The advantage is that it can be performed within minutes in an outpatient clinic setting under local anaesthesia, using techniques familiar for several decades. Results using a fusion device are very promising.

MRI–ULTRASOUND FUSION TECHNOLOGIES

Image fusion is the process of combining relevant information from two or more images into a single image, which is more informative than either of the images separately. In medical usage,MRI–ultrasound image fusion is a product of the last decade, first in central nervous system applications [14] and subsequently in prostate brachytherapy [15]. In 2002, Kaplan *et al.* [16] in Boston performed MRI–ultrasound fusion for targeted prostate biopsy, thereby establishing the concept that 'this technique has the potential to increase the yield of the biopsy procedure'. In 2007, researchers at the National Cancer Institute, working in collaboration with scientists from Philips Research North America and Traxtal, Inc., showed in five patients that MRI–ultrasound fusion for targeted prostate biopsy was not only possible, but it could also be quick and accurate [17].

Technologies to perform image fusion are evolving rapidly. As of this writing, five devices providing MRI–ultrasound fusion for targeted prostate biopsy have been approved by the US Food and Drug Administration (FDA), all via the 510(k) route (Table 1). The Philips/

PercuNav system (Royal Philips Electronics, Amsterdam, the Netherlands) has undergone more years of clinical testing than the others; development has been entirely done at the NCI. This system employs an external magnetic field generator to perform biopsy site localization and tracking. Among the first 101 men undergoing MRI–TRUS fusion biopsy with this system, CaP detection correlated with the degree of suspicion on MRI [18■■]. Cancer was detected in nearly 90% of cases, in whom a highly suspicious lesion on MRI was targeted. In this work, targeted biopsies were twice as likely to show cancer as systematic biopsies. The Hitachi HI-RVS system (Hitachi Medical Systems America, Inc., Twinsburg, Ohio, USA) also employs magnetic field localization; clinical experience with this system is limited [19, 20].

The Urostation (Koelis, Grenoble, France) has been studied extensively by Ukimura *et al.* [21■■]; in a preclinical study, ability of this system to navigate to targets within prostate phantoms was highly accurate. Similar to the in-bore biopsies, confirmation of needle location with Urostation is retrospective, that is the biopsy is taken and then the scan is made to confirm placement position. At the 2012 American Urology Association meeting, Ukimura presented a body of clinical work with the Koelis device, showing that tumour localization was highly accurate and that progression of lesions in men undergoing active surveillance could be determined by targeted biopsy.

Work with the Artemis device (Eigen, Grass Valley, California, USA) began at the University of California, Los Angeles (UCLA) in 2009, soon after the FDA approval [22■■]; a multiyear National Institutes of Health (NIH)-supported evaluation is in progress.

The Artemis device differs from the others in that it incorporates a robot-like mechanical arm used to scan and digitize the prostate; the needle and probe positions are tracked by angle-sensing devices (encoders) built into each joint of the arm. A prototype of the device was developed in the laboratories of Professor Aaron Fenster *et al.* at Robarts Research Institute in London, Ontario, California, USA [23]. In Figure 1, the Robarts prototype and the commercially available Artemis device v2.0 are shown. The essential components of the device, as described by Bax *et al.* [23], are as follows:

1. Passive mechanical components for guiding, tracking and stabilizing the position of a commercially available end-firing transrectal ultrasound transducer;
2. Software components for acquiring, storing and reconstructing in real-time a series of two-dimensional ultrasound images into a three-dimensional ultrasound image; and
3. Software that displays a model of the three-dimensional scene to guide and record the biopsy core locations three-dimensionally.

These generic software features are also employed by all other prostate fusion devices.

A summary of the working experience with the Artemis device at UCLA Clark Urology Center is shown in Table 2. In brief, a multidisciplinary team was assembled in early 2009 to try to bring MRI/TRUS fusion biopsy to clinical utility. A urologist, a radiologist expert in prostate MRI, a prostate pathologist and a biomedical engineer were included. NIH grant support (R01) was received via an industry/academic collaborative channel, and imaging scientists from Eigen were also involved. The Artemis device was delivered in March 2009, and its clinical usage commenced in September 2009. Early clinical application of the device at our institution has been detailed previously by Natarajan *et al.* [22■■]. An online video explains rationale and methods of the work (YouTube: ‘UCLA BIOPSY’). In a subsequent publication, results of the first 171 men undergoing a MRI/TRUS fusion biopsy at UCLA are detailed [24■■]. Results of that study are summarized in Table 3.

PATIENT EXAMPLES

In the following patient examples, the value of MRI/ultrasound-targeted prostate biopsy is illustrated.

Anterior prostate cancer

A 60-year-old man was referred to UCLA because eight sets of conventional ultrasound-guided biopsies over a 10-year period were all negative, despite serum PSA level increasing from 4 to 50 ng/ml over that period of time. Prostate volume was 64 ml. mpMRI revealed the lesion causing increased PSA (Fig. 2a–c). Targeted biopsy, using MRI–ultrasound fusion, confirmed the diagnosis of a large, high-grade anterior CaP (Fig. 2d and e) [25].

Anterior CaPs, while once thought to be rare, accounted for more than 80% of tumours found on saturation biopsy in one recent study [26]. The growing concern about 'evasive anterior tumours', and the role MRI can play in diagnosis, were addressed recently by Lawrentschuk *et al.* [27]. When anterior tumours become large (pT3), the likelihood of a positive surgical margin appears to increase substantially [28]. Thus, early diagnosis of anterior tumours has important clinical implications. MRI/ultrasound fusion biopsy provides visualization and access to anterior tumours not possible with conventional biopsy, especially in large prostates.

Active surveillance

A 70-year-old man was enrolled into the UCLA Active Surveillance programme after an early Artemis-guided biopsy (systematic, nonfusion) showed a small amount of well differentiated CaP. Six months later, a confirmatory biopsy was performed using MRI/ultrasound fusion, targeting a high-grade lesion seen on MRI; the prior positive site was also targeted. The target and the prior positive sites were near each other on MRI, as shown in the Artemis imagery (Fig. 3). Fusion biopsy revealed extensive Gleason 3+4=7 CaP in multiple cores obtained from the target and a lesser amount of Gleason 3+3=6 CaP in the prior positive site. Patient was counselled to proceed with active treatment; he elected brachytherapy.

The confirmatory, or first surveillance biopsy, is considered the most important follow-up study in men entering active surveillance [29]. In such cases, information derived from PSA testing is of limited value, compared with that gained via repeat biopsy [30]. Among six large programmes reviewed by Dall'era *et al.* [29], the confirmatory biopsy showed absence of cancer in 24–50% of cases, grade progression in 2.5–28% of cases and no change in 42–61% of cases. Barzell *et al.* [31▪] showed recently that, when confirmatory biopsy was performed via a transperineal template mapping technique (28–34 cores, general anaesthesia), disease reclassification to a clinically important status occurred much more frequently than when conventional TRUS-guided biopsy was used. Many important cancers in such cases can be identified by MRI [32]. Thus, using MRI/ultrasound fusion and targeted biopsy, confirmatory results, which are comparable with those obtained with template biopsy, may potentially be obtained in a clinic setting under local anaesthesia [24▪▪].

CONCLUSION

Multiparametric MRI (3 T) holds great promise of prospectively identifying clinically important cancer within the prostate. Targeted biopsy through magnetic resonance guidance or MRI–ultrasound fusion offers a way to localize and sample suspected cancers with precision. Image fusion using specialized devices offers the practicing urologist an accurate and efficient way to diagnose and manage CaP in an office-based setting. Biopsy results obtained with the fusion devices compare favourably with results obtained with template

perineal biopsy performed under general anaesthesia in the operating room. In the future, MRI/ultrasound fusion technology may be used for targeting and following lesions appropriate for focal therapy.

Acknowledgments

The project described was supported by Award Number R01CA158627 from the National Cancer Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the NIH. Additional support was provided by the Beckman Coulter Foundation, the Jean Perkins Foundation and the Steven C. Gordon Family Foundation.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 100).

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KEY POINTS

- Multiparametric MRI (3 T) appears to be an excellent method to identify clinically important prostate cancers.
- Targeted biopsy, using MRI fused with real-time ultrasound, can now be performed in an office setting using one of several devices equipped with advanced image registration software.
- Targeted prostate biopsy has the potential to revolutionize CaP diagnosis and management through accurate localization of many prostate cancers.
- Men with prior negative biopsy and persistently elevated prostate-specific antigen (PSA) levels and men in active surveillance may be the best candidates for targeted prostate biopsy.

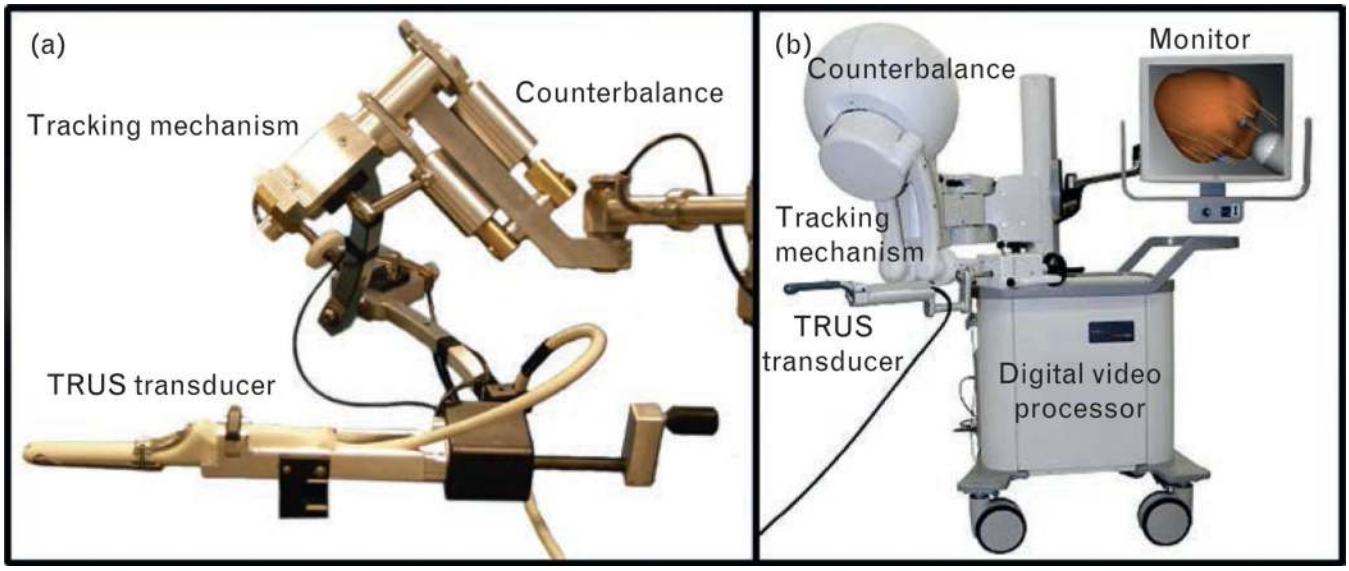

FIGURE 1. Artemis fusion device

(a) Robarts prototype and (b) FDA-approved commercial model (Eigen). When the TRUS probe is rotated, encoders in the tracking mechanism transmit orientation and position of the transducer tip to software that displays and records location on the monitor. The tracking arm is stabilized and held stationary during the rotation, preventing change in pitch, yaw and depth of penetration. During the scan, 2D images are digitized with a frame grabber and reconstructed into a 3D image. A model of the prostate is then generated from the 3D image; biopsy, tracking of biopsy site and MRI fusion are then performed on the reconstructed model [23]. 2D, two-dimensional; 3D, three-dimensional; FDA, US Food and Drug Administration.

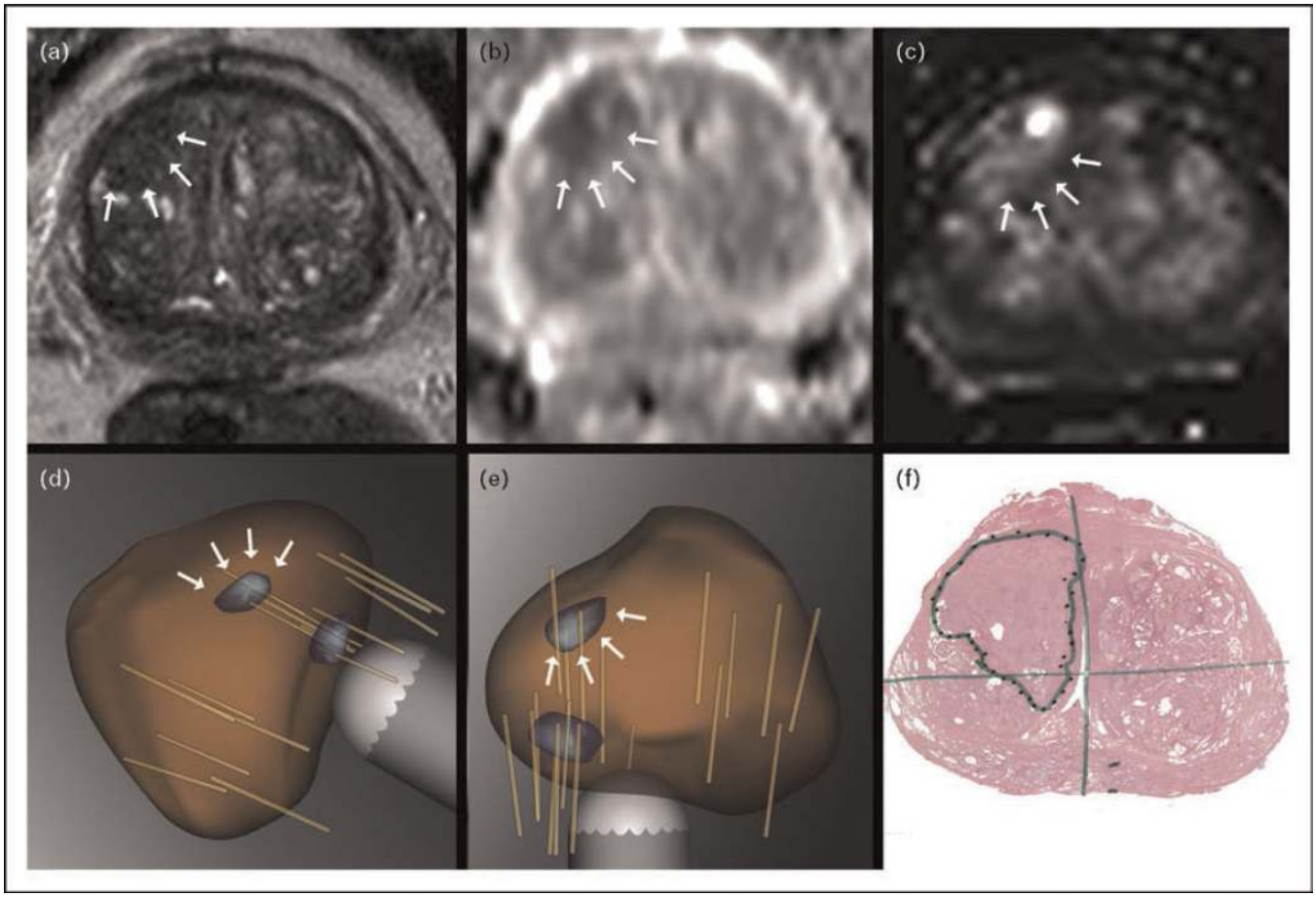

FIGURE 2. A 60-year-old man with eight prior negative biopsies over a 10-year period

During that time, a PSA increase from 4 to 50 ng/ml was observed. Arrows show regions of interest (a) T2-weighted axial MR image demonstrating a dominant lesion in the right anterior prostate with a focal low signal. (b) Diffusion-weighted axial MR image with an ADC value of $0.865 \times 10^{-3} m^2/s$ in the corresponding area. (c) Dynamic contrast enhancement image of the corresponding area showing increased local perfusion. The lesion was classified as an image grade 4 on the basis of multiparametric features [22■■]. The radiologist outlined the lesion in T2 axial images. Open-source imaging software [25] was then used to produce a 3D model of the prostate including the target. A second 3D model was then generated on the basis of an outline of the prostate on ultrasound. (d) and (e) The two models were then dynamically fused, generating the composite virtual 3D model seen in a sagittal (d) and axial (e) views. The prostate is mapped in brown and the target identified in blue. A second, smaller target located peripherally was also identified. Systematic and targeted biopsies were obtained, generating the final 3D model demonstrating the location of all biopsy cores (light brown cylinders). Targeted biopsies in this patient revealed Gleason 3+4=7 CaP in the primary target. (f) Radical prostatectomy specimen demonstrated the presence of a 4.5-cm Gleason 3+4 cancer in the anterior prostate, confirming biopsy localization of the lesion. 2D, two-dimensional; 3D, three-dimensional; MR, magnetic resonance; PSA, prostate-specific antigen.

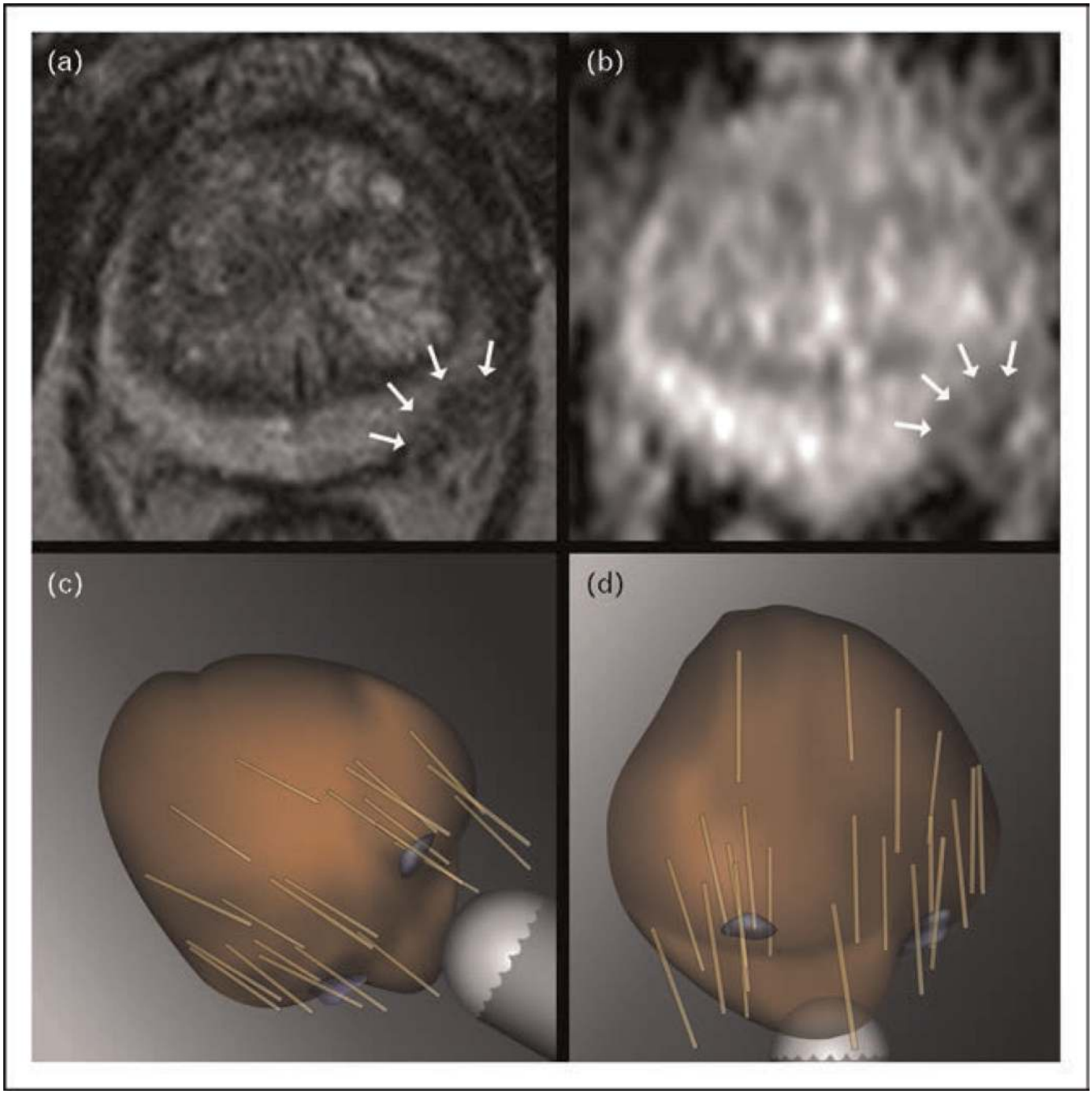

FIGURE 3. A 70-year-old man enrolled in active surveillance with a PSA of 4.1

(a) T2-weighted axial MR image demonstrating a dominant lesion (arrows) in the left posterior prostate with a focal low signal. (b) Diffusion-weighted axial MR image with an ADC value of $1.071 \times 10^{-3} m^2/s$ in the corresponding area. The lesion was classified as image grade 3 on the basis of multiparametric features [22■■]. 3D image processing was performed as in Figure 2. Systematic and targeted biopsies were obtained, generating the final 3D model demonstrating the location of all biopsy cores (light brown cylinders). Targeted biopsies in this patient revealed Gleason 3+4=7 CaP in the primary target. 2D, two-dimensional; 3D, three-dimensional; MR, magnetic resonance.

Table 1

MRI/ultrasound fusion devices approved by US Food and Drug Administration

Manufacturer/ trade name	US image acquisition	Biopsy route	Tracking mechanism	Year of FDA approval	Comments
Philips /PercuNav	Manual US sweep from base to apex	Transrectal	External magnetic field generator	2005	Prospective targeting, integrated with existing ultrasound device, freehand manipulation
Eigen/Artemis	Manual rotation along fixed axis	Transrectal	Mechanical arm with encoders	2008	Prospective targeting, stabilized TRUS probe
Koelis/Urostation	Automatic US probe rotation, three different volumes elastically registered	Transrectal	Real-time TRUS-TRUS registration	2010	Retrospective targeting, real-time elastic registration
Hitachi/HI-RVS (real-time virtual sonography)	Real-time biplanar TRUS	Transrectal or transperineal	External magnetic field generator	2010	Prospective targeting, integrated with existing ultrasound device
BioJet/Jetsoft/GeoScan	Manual US sweep in sagittal	Transrectal or transperineal	Mechanical arm with encoders; uses stepper	2012	Prospective targeting, rigid registration

FDA, US Food and Drug Administration; US, ultrasound.

Curr Opin Urol. Author manuscript; available in PMC 2013 February 26.

Table 2

The University of California, Los Angeles, experience with Artemis device, 2009–July 2012

All biopsy-tracking patients (*N* = 606)	**Tracking and fusion biopsy patients (*N* = 360)**
No. of biopsy sessions: 893	Active surveillance: 188 (52%)
No. of biopsy cores:	Previously negative biopsy: 102 (28%)
With MRI fusion (360 patients):	First-time biopsy: 70 (20%)
Targeted: 1586 (690 targets)	
305 positive (19.2%)	
Systematic: 4263	
374 positive (8.8%)	
Without MRI fusion (246 patients):	
Systematic: 2952	
Total = 8801 biopsy cores obtained and tracked	

Biopsy procedures begun in September 2009, and fusion biopsies begun in March 2010.

Table 3

Summary of results at the University of Caifornia, Los Angeles [24■■] (March 2010–September 2011)

Tracking and fusion biopsy patients (*N* = 171)	**Biopsy cores**
Median age: 65 years	Targeted: 486 (257 targets)
Median prostate volume: 48 ml	101 positive (20.8%)
No. of positive biopsies: 90 (53% of all), 34 Gleason ≥7 (20% of total)	Systematic: 1741
Active surveillance: 106 patients (62%), PSA 4.1 ng/ml	127 positive (7.3%)
Previously negative biopsy: 65 (38%), PSA 7.3 ng/ml	