Multiparametric MRI/TRUS Fusion Biopsy, Outcomes, and Commercial Systems

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Introduction

In current practice, prostate cancer suspicion is confirmed with transrectal ultrasound (TRUS)-guided 12-core biopsy directed at various regions of the prostate in a systematic manner. These biopsies are, in essence, blinded and random by nature as they are not directed toward a specific target, but rather to various geographic regions of the prostate. The widespread use of prostate-specific antigen (PSA) screening and TRUS-

guided prostate biopsy has resulted in the overdiagnosis and overtreatment of low-risk prostate cancers and the underdetection/under-treatment of high-risk cancers, leading to unwarranted interventions without definitive benefit. The introduction of multiparametric magnetic resonance imaging (mpMRI) has revolutionized the way we visualize prostate cancer, as it helps delineate and characterize specific lesions that are potentially malignant. Extending from mpMR imaging, a novel and potentially transformative technique, named MRI/TRUS fusion-guided biopsy, has recently emerged as an option for a more precise prostate biopsy.

TRUS offers the ability to acquire imaging in real time but is limited by poor spatial resolution and low sensitivity for prostate cancer, as lesions can often appear isoechoic on TRUS imaging, making them difficult to distinguish from background [1]. Conversely, MR imaging presents prostatic lesions with striking detail and possesses high sensitivity, yet does not offer the capability for real-time image acquisition and guidance for biopsy in a timely or cost-efficient manner. Developers have strategically created "fusion" platforms to combine MR and TRUS imaging, thus allowing individuals performing biopsy to take advantage of the essential information and features offered by both modalities [2]. Utilizing these fusion biopsy platforms, a targeted fusion biopsy allows for sampling of specific regions within the prostate with lesions

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pre-identified on MRI, thus providing the future possibility of circumventing the need for random "blinded" biopsies throughout the gland.

Herein, we provide a comprehensive review of the current MRI/TRUS fusion-based targeting strategies, indications as well as general workflow for the fusion biopsy technique, and an overview of commercially available software-based registration platforms and their respective strengths, limitations, and patient outcomes.

Magnetic Resonance Imaging-Based Targeted Biopsy Techniques

Three methods of MRI guidance are currently utilized for performance of targeted prostate biopsy: cognitive fusion, direct MRI-guided biopsy ("in-bore" biopsy), and MRI/TRUS fusion-guided biopsy (software-based registration).

Cognitive Fusion

Cognitive fusion (visual targeted biopsy) is a technique in which the ultrasound operator simply aims the biopsy needle in the general region of the prostate where a prior MRI demonstrates a lesion [3]. Therefore, prostate MR imaging is acquired prior to a TRUS-guided biopsy procedure, and "cognitive registration" is performed using knowledge from the MRI to guide the biopsy needle to the appropriate area(s) of the prostate with MRI-identified cancer-suspicious lesions. This method is appealing as it is simple and time efficient and does not require any additional equipment beyond an MRI scanner and traditional TRUS biopsy setup. Furthermore, cognitive fusion does not necessitate significant upfront capital investment or additional training modules/sessions with unfamiliar hardware and software. Several studies have compared cognitive fusion to the conventional systematic biopsy technique and to software-based registration platforms. Haffner et al. showed, in a cohort of 555 patients with suspicion of prostate cancer, that cognitive fusion biopsy had higher detection accuracy of clinically significant prostate cancer

relative to extended systematic biopsy involving 10–12 cores ($p < 0.001$) [4]. Furthermore, targeted biopsy with cognitive registration detected 16 % more grade 4/5 cancers and more accurately quantified tumor burden ($p = 0.002$). Similarly, Park et al. demonstrated in a prospective evaluation in patients with elevated PSA and no prior biopsy history that cognitive fusion had higher cancer detection rates (29.5 % vs. 9.8 %, OR 3.9, $p = 0.03$) relative to TRUS biopsy alone [5]. In the prospective PROFUS trial, Wysock et al. compared targeted biopsy outcomes between MRI/ultrasound fusion biopsy and cognitive fusion biopsy and found similar cancer detection rates (CDRs) for all cancers (32.0 % vs. 20.3 %, $p = 0.1374$) and Gleason sum ≥7 cancers (26.7 % vs. 15.1 %, $p = 0.0523$) [6]. Another study compared targeted MRI/TRUS fusion biopsy (both cognitive fusion and software based) to TRUS-guided systematic biopsy in a prospective trial of 95 patients who had suspicious images at mpMRI [7]; they found that positivity rates for prostate cancer (69 % vs. 59 %, $p = 0.033$) and sampling quality (maximum cancer length per core, Gleason grade) were superior with targeted biopsy relative to systematic biopsy, regardless of visual (cognitive)-based registration or software-assisted registration.

Nevertheless, it appears that results with cognitive fusion biopsy are mixed, as a few studies have shown cognitive fusion biopsy to be no better than systematic TRUS biopsy [8, 9]. Delongchamps et al. tested accuracy of visual targeted biopsy in 127 patients and found no difference when compared to systematic biopsy with respect to cancer detection rate ($p = 0.66$) [8]. In the only Level I evidence to date comparing cognitive fusion biopsy to systematic 10- to 12-core TRUS biopsy, Tonttila et al. found no difference in cancer detection rates for both overall (64 % vs. 57 %, $p = 0.5$) and clinically significant (55 % vs. 45 %, $p = 0.8$) cancers; therefore, the authors concluded that additional prostate MRI before prostate biopsy did not add significant value [9]. However, rather than inferring that no benefit is achieved from MRI, this study may signify that there is limited benefit in biopsy-naïve patients. Lastly, in direct comparison of MRI/

TRUS fusion versus cognitive registration, one study found cognitive registration to be inferior to software-based MRI/TRUS fusion, as fewer than 50 % of clinically significant prostate cancer lesions were successfully sampled with cognitive registration, regardless of experience level [10].

Cognitive fusion biopsy is heavily operator dependent and requires extensive knowledge of prostate anatomy in order to extrapolate lesion location from MRI to TRUS without an actual overlay and registration of imaging. One study highlights the difficulty in performing visual registration, as TRUS 2D images project in a fan-shaped pattern and can be markedly different from the axial imaging plane on MRI, making it difficult to accurately estimate lesion location during TRUS biopsy [11]. This imaging disparity is most evident in anterior base and anterior apical lesions. Inaccurate lesion location estimation can be partially overcome by utilization of anatomical landmarks, such as prostatic cysts, benign prostatic hyperplasia (BPH) nodules, and/or calcifications as internal reference points to help further guide the biopsy needle. However, these "internal fiducials" are not always present, and heterogeneous echogenicity on TRUS may falsely lead the reader to misregister images, small differences of which can dramatically alter the results. As a final limitation, cognitive fusion methods do not offer the ability to track and record biopsy coordinates for later reference.

In-Bore MRI-Guided Biopsy

In-bore MRI-guided biopsy entails acquiring biopsy samples within the MRI gantry under direct guidance after prostate lesions have been pre-identified with a prior diagnostic mpMRI. During biopsy, the patient is placed prone in the MRI apparatus, and biopsy needles are directed toward suspicious lesions via a transrectal or transperineal (TP) approach [12]. Core samples are obtained with serial MRI scans to confirm biopsy needle placement [13]. The primary advantages for this approach are precise lesion sampling due to elimination of registration error and less total number of cores relative to

systematic 10–12-core biopsy, as only suspicious lesions are targeted [14].

In a study of 100 patients with prior negative TRUS biopsy, persistently elevated or rising serum PSA, and at least one suspicious lesion on MRI, Roethke et al. found a CDR of 52 % overall and 80.8 % for clinically significant prostate cancer utilizing the in-bore MRI-guided biopsy technique [15]. Similarly, another report demonstrated the utility of MRI-guided in-bore biopsy in patients with prior negative biopsies and biopsy-naïve patients, with overall CDRs of 43.1 % and 55.6 %, respectively [16]. Hambrock et al. compared the ability of in-bore mpMRI-guided biopsies versus 10-core TRUS biopsy to match true Gleason grade as determined by the gold standard of radical prostatectomy specimens; they showed that the highest Gleason grade from in-bore biopsy matched final pathology in 88 % (30 of 34) patients, whereas the highest Gleason grade from 10-core TRUS biopsy matched final pathology in only 55 % (35 of 64) of patients ($p = 0.001$) [17].

Despite initial success with several studies demonstrating its efficacy, in-bore MRI-guided biopsy has not been embraced clinically due to several limitations. Firstly, the procedure is relatively lengthy and often requires sedation as patients have to remain still for the duration of the procedure. Moreover, the technique is costly and requires trained personnel and specialized MR-safe equipment. Lastly, the biopsy is performed in the radiology department and thus interferes with normal day-to-day workflow. Its unique benefit would be in patients unable to undergo TRUS (e.g., abdominoperineal resection), where an in-gantry approach would provide reliable imaging and targeting [18]. Thus, although accurate and utilized in some centers, this technique has not been broadly adopted for clinical use [19].

Software-Based Registration

The next step in the evolution of MRI-targeted biopsy has involved "fusion" of mpMRI to TRUS imaging utilizing software-based platforms that

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allow for digital overlay. MpMRI provides detailed lesion information such as size and location, while TRUS provides real-time guidance for biopsy. Thus, MRI/TRUS fusion technology allows the user to combine advantages provided by both for sampling, such that lesion(s) previously delineated on MRI can be brought into view via manipulation of the TRUS probe and directly targeted. Furthermore, these software-based strategies enable prostate biopsy to be performed in the clinical outpatient office-based setting, much like the cognitive technique. This strategy, although it requires users to become familiar with additional software and hardware, is quick, efficient, and cost-effective.

Henceforth in this chapter, we will focus on MRI/TRUS fusion-guided biopsy as it is currently the most widely utilized MRI-based targeted biopsy approach. Since the late 2000s, multiple MRI/TRUS fusion platforms have been developed and are currently utilized in clinical practice (Table 17.1). While the workflow begins similarly with MR image acquisition and analysis, biopsy planning, and MR/TRUS image fusion (registration), the available platforms primarily differ in the following ways: the image registration algorithm, method of needle tracking, the hardware and software interface to pres-

ent fused MR/TRUS imaging, additional software functionality, and route of biopsy.

Additionally, the major commercially available software-based registration platforms, their similarities, and differences for targeted biopsy of the prostate as well as outcomes are reviewed.

Indications for Fusion Biopsy

As adoption of fusion biopsy has steadily increased over the last several years, the indications for its use have expanded [20–22]. Targeted biopsy currently has an established role in the following three scenarios: (1) patients with continued suspicion for prostate cancer despite prior negative systematic TRUS biopsies, (2) patients with apparent low-risk prostate cancer interested in active surveillance, and (3) patients with mpMRI-defined lesions in locations of the prostate that are traditionally missed with systematic 12-core biopsy.

In the context of rising PSA and continued cancer suspicion despite multiple negative standard TRUS biopsies, current standard of care is to perform saturation biopsy with >20 cores, which is often associated with increased patient discomfort and need for general anesthesia [23]. One

Table 17.1 Summary of commercially available MRI/ultrasound fusion-guided prostate biopsy platforms

Platform (manufacturer)	FDA approval year	US probe manipulation	Tracking method	Registration method	Route of biopsy
UroNav (Philips/Invivo)	2005	Freehand	Electromagnetic	Rigid or elastic	Transrectal or transperineal
Virtual Navigator (Esaote)	2014	Freehand	Electromagnetic	Rigid	Transrectal
Real-time Virtual Sonography (Hitachi)	2010	Freehand	Electromagnetic	Rigid	Transrectal or transperineal
Artemis (Eigen)	2008	Rotation of articulated arm	Mechanical arm with encoders	Elastic	Transrectal
BiopSee (Pi Medical/MedCom)	–	Mechanical stepper movement in two planes	Stepper with encoders	Rigid	Transperineal
BioJet (D&K Technologies)	2012	Rotation of articulated arm	Mechanical arm with encoders	Rigid	Transrectal or transperineal
Urostation (Koelis)	2010	Freehand	TRUS-TRUS registration	Elastic	Transrectal

FDA Food and Drug Administration, *US* ultrasound, *TRUS* transrectal ultrasound

early study demonstrated the utility of targeted prostate biopsy in men with prior negative biopsy and elevated PSA, as fusion biopsy revealed prostate cancer in 34 % (36/105) of men, with 72 % of men with prostate cancer detected harboring clinically significant disease [24]. Similarly, Vourganti et al. showed in a prior negative TRUS biopsy cohort of 195 men that MRI/TRUS fusion biopsy picked up all high-grade cancers (21 men, 11 %), whereas standard TRUS biopsy missed 12 of these high-grade cancers (55 %) [25]. Furthermore, in a prospective study by Salami et al. in 140 patients with at least one prior negative biopsy, the CDRs for clinically significant prostate cancer utilizing MRI/TRUS fusion biopsy were significantly higher than that of 12-core biopsy (47.9 % vs. 30.7 %, $p < 0.001$) [26].

With respect to active surveillance (AS), mpMRI- and MR-targeted fusion biopsy has proven utility in confirmation of candidacy for AS and continued monitoring [27]. In a study of 113 men enrolled in an AS protocol, confirmatory fusion biopsy resulted in reclassification in 36 % of patients, including 26 (23 %) due to Gleason grade 6 or greater and 15 (13 %) due to high-volume Gleason 6 disease [28]. Similarly, Stamatakis et al. found 29 % of their cohort (25/85 men) no longer met AS criteria after a confirmatory MRI/TRUS fusion-guided prostate biopsy [29]. In this study, number of mpMRI lesions, lesion density, and highest MRI lesion suspicion score were the significant MRI predictors of patients who would be poor AS candidates. In addition, in a study of 111 patients on AS, researchers showed that the use of mpMRI with subsequent fusion biopsy significantly increased the rate of AS termination relative to standard template biopsy alone (27 vs. 10, $p = 0.015$) [30]. Furthermore, early work has shown successful monitoring of cancer in patients on AS using MRI to electronically track specific cancer sites within the prostate, allowing for the return to that specific site with subsequent targeted biopsies [31]. Repeat sampling of cancerous sites within MRI targets was more likely to show cancer than resampling of tumors at systematic sites (61 % vs. 29 %, $p = 0.005$), suggesting improved accuracy in MRI-aided resampling methods over TRUS-guided methods. Walton

Diaz et al. illustrated the utility of serial mpMRI and MRI/TRUS fusion biopsy in monitoring patients on AS, as stable findings on mpMRI were associated with Gleason score stability [32]. In this study, the number needed to biopsy to detect one Gleason progression was 8.74 for systematic 12-core biopsy vs. 2.9 for MRI/TRUS fusion biopsy. While further work is necessary, these initial studies help validate the use of serial imaging and targeted fusion biopsy with limited number of cores as tools to monitor patients on AS.

Lastly, MRI/TRUS fusion biopsy has demonstrated utility in targeting regions of the prostate that are typically missed with systematic 12-core biopsy, such as the anterior prostate, distal apical, and subcapsular regions [33–35]. Therefore, MR-targeted fusion biopsy should potentially be employed in patients in which MR imaging illustrates the presence of lesions in regions that are traditionally outside the systematic 12-core biopsy template.

Workflow of MRI/TRUS Fusion-Guided Biopsy

The workflow of MRI/TRUS fusion-guided biopsy in general involves the following steps in a sequential manner: MR image acquisition, MR prostate and lesion segmentation, ultrasound prostate segmentation, and image registration, followed by fusion-guided biopsy (Fig. 17.1).

MR images of the prostate are acquired first, followed by prostate boundary surface rendering and tumor location marking by the radiologist. An mpMRI study typically consists of T2-weighted (T2W), diffusion-weighted imaging (DWI), and dynamic contrast-enhanced (DCE) sequences, with or without the use of an endorectal coil while acquiring images, as well as other sequences required for completion of a standard pelvic MRI. Utilizing T2W imaging, the prostate is semiautomatically contoured with imaging software and manually adjusted where necessary [36]. The MR slice with the largest lesion diameter is utilized to define biopsy targets as a centroid marker or alternatively can be segmented on multiple slices to produce a three-dimensional (3D)
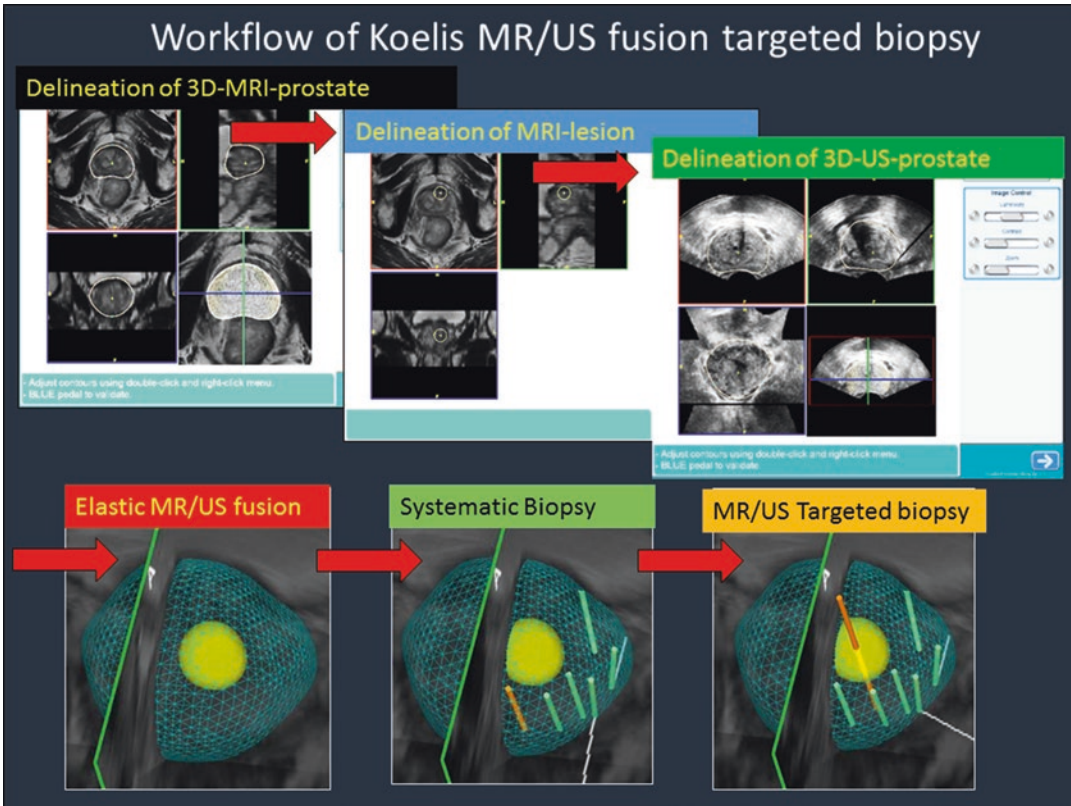
Fig. 17.1 Workflow of Urostation (Koelis) software-based registration platform

volume. This information is then sent electronically to the biopsy suite. Next, at the time of biopsy, a 3D TRUS volume model of the prostate is constructed from a series of two-dimensional (2D) TRUS images obtained via a sweep of the entire prostate with the TRUS probe. The TRUS 3D model is then segmented semiautomatically (with manual adjustments if necessary) and "fused" to the prostate MRI with registration software. This fusion or "registration" can be completed manually utilizing rigid registration; alternatively, the software can co-register the two prostate shapes to each other using a deformable or elastic registration algorithm depending on the fusion system being utilized (discussed in greater detail later). After registration of the two imaging modalities, the TRUS probe can be manipulated in real time, which allows the user to observe corresponding rotation or translation of the MR image. Thus, this technique enables the TRUS operator to guide a precise targeted biopsy of

lesion(s) utilizing information from the previously acquired prostate MRI.

Registration Algorithms

The major technological challenge with MRI/TRUS fusion biopsy is the registration process that fuses MRI to the ultrasound image. Because the prostate on MRI (with an endorectal coil in place) often differs in shape from the same prostate on TRUS due to deformation, adjustments are necessary for optimal registration. This process can partly involve indirect alignment of prostate landmarks/internal fiducials (calcifications, cysts, BPH nodules, fixed bony points, etc.) that can be identified on both corresponding images and/or manual adjustment of probe pressure. Registration can be completed in one of two manners: rigid registration or elastic registration. In rigid registration, the surface rendering of the

prostate generated from MR and TRUS sweep is not altered in any manner; the prostate contours are simply manipulated to allow for rotational or translational alignment between images using a mathematical algorithm. Thus, with rigid registration, the internal anatomy of the prostate is preserved at the expense of prostate borders that may not appear to perfectly align. If images are suboptimally aligned during the procedure due to patient movement and/or prostate deformation, registration can be manually adjusted in real time by re-aligning the prostate contour edges or adjusting probe pressure. In elastic registration, the software algorithm stretches or "warps" the MR image prostate shape to match the TRUS prostate contour. Therefore, internal prostate anatomy is altered in an attempt to more properly match the two images with respect to surface contours. As the MR prostate contour is artificially altered to match the TRUS-generated 3D model of the prostate in elastic transformation, the quality of the ultrasound segmentation becomes highly critical. Robust US image acquisition helps to avoid misaligned or incorrectly warped registration.

After registration is completed, the graphical user interface of the different platforms vary and present fused MR-US images to the operator in different manners depending on the specific platform and user preference. Some platforms have the fused images displayed separately side by side in a "co-display" fashion, while others display a blended fusion image with MR and TRUS overlaid on top of each other in different color schemes. Lesions are typically marked with an indicator/"bullseye" or 3D region of interest to guide sampling.

A few fusion platforms currently are equipped with both rigid and elastic registration algorithms, allowing the user to potentially take advantage of both options depending on the specific circumstances encountered with a given patient. Regardless of the registration method, real-time operator input throughout the biopsy procedure and manual adjustments of the registration are of critical importance to fine-tune registration and optimize the targeting before and between core sampling.

Biopsy Needle Tracking

An additional functional aspect of several of the fusion platforms is the ability to track and record the position of the TRUS biopsy probe in real time in 3D space. This allows the user to track and navigate the needle to the appropriate slices with marked targets. There are currently three main methods for tracking: (1) electromagnetic (EM) tracking ("medical GPS"), (2) position-encoded joints in smart robotic arms, and (3) image-based software tracking.

Electromagnetic tracking (e.g., UroNav, Invivo Corp., Gainesville, FL, USA; Virtual Navigator, Esaote SpA, Genoa, Italy; Real-time Virtual Sonography, Hitachi Ltd., Tokyo, Japan) refers to a process by which the position of a small sensor attached to the TRUS biopsy probe within an external magnetic field (produced by a EM field generator) is relayed continuously to the computer. This form of tracking operates on Faraday's law of induction, which is the idea that a moving sensor located in the midst of an electromagnetic field emits an electrical current, which can then, in turn, be converted by software into a 3D position in space. This position in space can then be translated onto the fused imaging. The exact position of the TRUS probe is utilized to guide the operator toward the planned approach trajectory for each target as defined on pre-procedure mpMRI. The major advantage of this tracking technique is that it allows conventional freehand manipulation of the probe in multiple degrees of freedom, a process familiar to most urologists who routinely perform TRUS biopsy [37]. A potential disadvantage with this tracking method is the possibility for introduction of human error due to unsteady hands at time of needle deployment, leading to inaccurate sampling of the target lesion (mechanical error). Additional ferromagnetic interference from metallic objects can affect the accuracy of tracking, and care must be taken to minimize the proximity of these to the electromagnetic field.

Robotic fusion platforms (e.g., Artemis, Eigen, Grass Valley, CA, USA; BiopSee, Pi Medical, Athens, Greece; BioJet, BK Ultrasound, Analogic Corp., Peabody, MA, USA) operate

with mechanical devices that directly control the TRUS biopsy probe's movement. The probe is mounted on either a basic mechanical stepper with position sensors or a more complex self-articulating mechanical arm with built in angle-sensing encoders [38, 39]. Throughout the procedure, these sensors automatically relay angle and positional information to software that tracks the position of the probe and biopsy needle in 3D space. These robotic platforms allow for limited degrees of freedom along a fixed axis when manipulating the probe—mainly forward/backward and rotational. This technology offers improved probe stability during target acquisition, thereby reducing human mechanical error. However, the machine itself is bulkier relative to freehand devices and does not allow the user to review the MR images during procedure. Also, one is not able to turn off elastic deformation to review the raw MR image dataset and optimize the biopsy approach compared to other systems.

Image-based software tracking (Urostation, Koelis, Meylan, France) is unique in that it relies on TRUS-TRUS registration as the tracking mechanism and thus does not require additional hardware such as electromagnetic field generators or robotic arms. An initial 3D TRUS sweep of the prostate is performed, and then serial 3D TRUS images acquired after each biopsy are sequentially registered with the initial 3D TRUS panoramic volume to confirm needle position. Prior to the acquiring of targeted biopsies, elastic image fusion of real-time 3D TRUS volume from the sweep with previously acquired MR imaging is performed to allow for the identification of isoechoic lesions [40]. This technology was initially designed to map the 3D location of biopsy tracks within a 3D prostate model but then subsequently evolved to allow for prospective navigation of a TRUS probe to predefined suspicious areas within the prostate. This system offers potential advantages in that tracking can be achieved in a cost-effective manner without need for any additional hardware, and the use of the freehand biopsy technique is preserved, which should be familiar to most urologists. However, this technology is limited in that it does not offer "real-time" tracking, but rather allows for retro-spective visualization of biopsy needle tracks relative to MRI-defined lesion locations. As an extension of this limitation, 3D TRUS imaging must be undertaken after every needle deployment to confirm location, with the needle held in exact place for 3–5 s.

Mapping and Navigation

Mapping and navigation are integral capabilities that are offered to varying degrees by the different fusion platforms. Mapping is the process by which software electronically tracks and records the location of a biopsy core in 3D space within a prostate model utilizing pre-procedure MRI as the reference "map." This information can be stored within the system for later use. Clinical applications of mapping include, but are not limited to, targeting cancer-positive-specific sites within the prostate on repeat biopsy (i.e., for patients on AS protocols) or planning the volumetric dimensions for focal therapy. Alternatively, a positive core from systematic sextant biopsy in a location not delineated by MRI ("MR invisible") can be mapped and subsequently targeted in a precise manner in a repeat fusion biopsy [31]. Navigation is the process by which the fusion biopsy system guides the operator with real-time imaging feedback to a specific lesion location for prospective placement of a biopsy needle. This is accomplished with utilization of a TRUS probe for real-time visualization and guidance toward a target pre-identified on MRI. Thus, a combination of tracking, navigation, and mapping allows for controlled and directed biopsies, accurate targeting, and accumulation of location data for future use in follow-up.

Biopsy Approach

Prostate biopsies are typically performed via a transrectal or transperineal approach, with transrectal being the most frequently used technique in the USA. Common, but transient, complications of prostate biopsy include hematuria, hematospermia, lower urinary tract symptoms (LUTS),

and pain [41]. With respect to post-biopsy, clinical outcomes, of particular concern and importance, are rates of infection and infectious complications following a biopsy procedure. Despite antimicrobial prophylaxis, infectious complications are increasing over time and are the most common reason for hospitalization post-biopsy [41]. In recent years, there has been a noticeable rise in the rate of TRUS biopsy sepsis, thought to be due to increasing prevalence of multiresistant (particularly fluoroquinolone resistance) causative bacteria in the rectal mucosa [42, 43]. Given that during a TRUS biopsy, the needle directly traverses the rectal mucosa, an increased risk of introducing rectal flora into the urinary tract and/or bloodstream is likely. In one study in which transperineal biopsy was performed in 245 patients, the rate of hospital readmission for infection was zero [44]. In a prospective, randomized, and controlled trial in 339 patients comparing TRUS biopsy to transperineal (TP) biopsy, the CDRs were equivalent (35.3 % vs. 31.9 %, $p > 0.05$). Importantly, the major complication rate was substantially lower in the TP biopsy group relative to the TRUS biopsy group (0.6 % vs. 4.3 %, $p < 0.05$). However, TP biopsy was more time-consuming (17.51 ± 3.33 min vs. 14.73 ± 3.25 min, $p < 0.05$), more painful (visual analogue scale score, 4.0 vs. 2.0; $p < 0.05$), and more often required additional anesthesia (15.0 % vs 1.2 %, $p < 0.05$). Therefore, TP biopsy may be a viable option in patients who have a history of sepsis on prior prostate biopsies or those who are at increased risk of developing infections along with infectious complications. Urologists should become increasingly aware of this rise in infectious complications post-biopsy and should consider appropriate antibiotic prophylaxis in all cases [45].

Commercial Systems

We devote the rest of this chapter to highlight the major fusion biopsy platforms currently available, including techniques, strengths, and weaknesses of each platform, as well as patient outcomes. It is important to note that these systems have and are continually evolving, with new features and applications constantly being added to adapt to various clinical scenarios and demands.

Electromagnetic Tracking

The **UroNav** platform (Invivo Corp., Gainesville, Florida, USA), which developed through a collaborative effort between the National Institutes of Health and Philips/Invivo Healthcare, began clinical trials in 2004 and was cleared by the US Food and Drug Administration (FDA) in 2006. This system is designed to be versatile, as it can operate with several different ultrasound vendors (Philips, General Electric, and BK Ultrasound systems) and can interface with readily available MR imaging software (DynaCad, Invivo). The UroNav platform has evolved, now incorporating both mapping capability and elastic registration. Furthermore, software has been developed to allow for the transperineal biopsy approach and is currently being prospectively evaluated. In 2015, the UroNav device was FDA cleared for guidance for focal therapy.

The workflow begins with the acquisition of mpMRI sequences (T2W imaging, DCE, and DWI) to identify suspicious lesions with the prostate. The radiologist segments the prostate and marks locations of target lesions and sends the MR imaging data to the UroNav workstation (Fig. 17.2). At the start of the procedure, the patient is placed in the left lateral decubitus position similarly to standard TRUS biopsy position, and an electromagnetic field generator box (~1 ft by 1 ft) is stationed directly above the patient's pelvis to allow for tracking of the TRUS probe in 3D space in real time. After attaching a sensor to the TRUS probe, the operator performs a "sweep" of the prostate in the axial plane from base to apex or apex to base. The sweep captures consecutive small slices of the prostate, which are then automatically compounded by the software to generate a working 3D TRUS volume prostate model. The borders of this 3D prostate model are then semiautomatically segmented (with manual corrections if necessary), followed by registration with MR imaging via rigid or elastic registration.
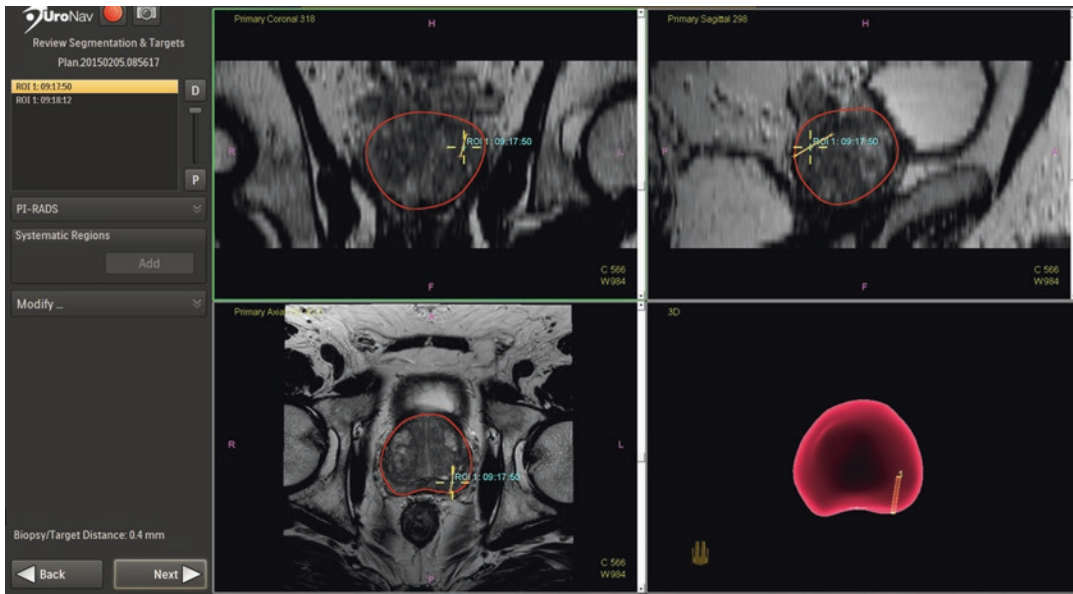
Fig. 17.2 UroNav screen capture of imported T2-weighted images demonstrating MR prostate segmentation and region of interest for targeted biopsy

Manual adjustments can be made to the registration throughout the procedure to account for patient and/or prostate motion, as well as differing degrees of prostate deformation due to variation in TRUS probe pressure applied.

After completion of registration, the operator can then proceed with targeted biopsies of the prostate utilizing a freehand TRUS approach. The UroNav system displays targets as a "bullseye" on the fused TRUS-MR image, which can appear side by side or overlaid on top of one another with a blending slider feature to adjust the relative transparencies of each image (Fig. 17.3). Through tracking of the TRUS probe, the navigation software guides the operator to the planned biopsy trajectory for each target. The TRUS probe is maneuvered until the bullseye is aligned onto a TRUS needle guide displayed on the screen; this is followed by insertion of the needle tip to the proximal edge of the lesion and spring biopsy deployment across the target, both in the axial and sagittal planes [46]. Mapping functionality documents the exact location of each core, which can be stored for later use.

Since its inception in 2006, several studies have been undertaken to test the functionality,

accuracy, and utility of the UroNav system in clinical practice. Xu et al. illustrated the accuracy of the system to be 2.4 ± 1.2 mm in phantom studies [47]. In a landmark study in 1003 patients by Siddiqui et al. comparing MR/ultrasound fusion-guided biopsy utilizing the UroNav platform with standard 12-core TRUS biopsy, it was shown that targeted biopsy diagnosed 30 % more high-risk cancers vs. standard biopsy (173 vs. 122 cases, $p < 0.001$) and 17 % fewer low-risk cancers (213 vs. 258 cases, $p < 0.001$). This finding is highly critical, as a common critique of the standard systematic 12-core approach is that it tends to overdiagnose low-risk cancers, leading to unwarranted treatments, and underdiagnose high-risk cancers, resulting in lack of treatment and poor clinical outcomes. Furthermore, Rastinehad et al. illustrated in a propensity score-matched cohort (matched on age, PSA, MRI suspicion score, and prior negative biopsies) that improved detection of clinically significant cancer with mpMRI and fusion biopsy is reproducible across institutions [48]. In addition to this work, electromagnetic needle tracking capability has been validated by showing the software can accurately document the location of prior biop-
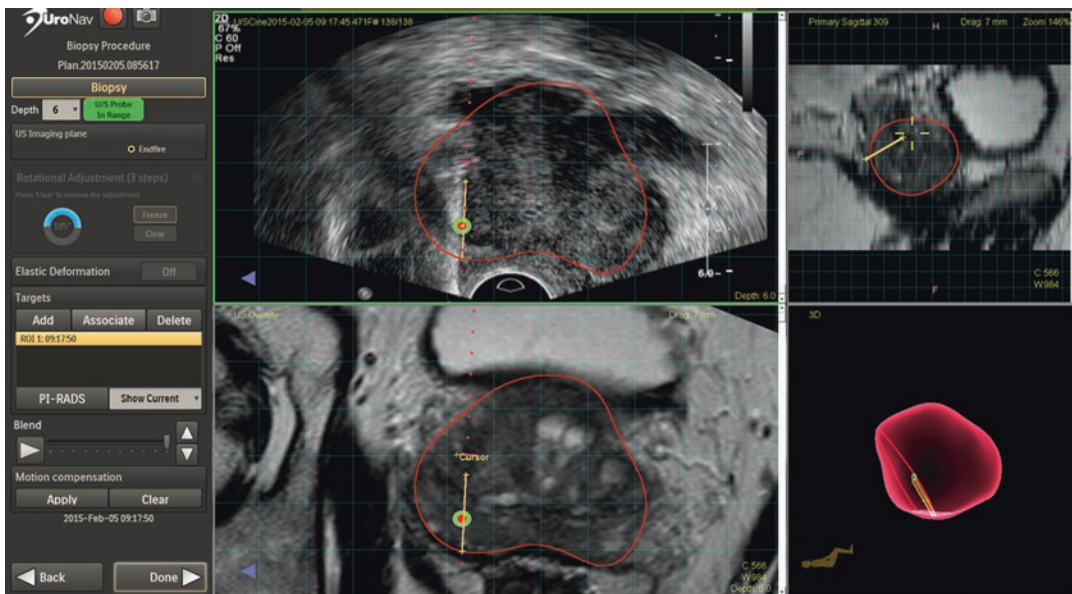
Fig. 17.3 UroNav screen capture demonstrating co-display of real-time TRUS and MR after registration. Bullseye demonstrates centroid point of a left peripheral zone lesion

sies, as well as direct subsequent biopsies to specific sites within the prostate [49].

Virtual Navigator (Esaote, Genoa, Italy) and **Real-time Virtual Sonography** (RVS) (Hitachi, Tokyo, Japan) are fusion platforms that were originally designed for percutaneous interventional guidance procedures and thereby had capabilities to fuse real-time TRUS with many different imaging modalities, such as computed tomography (CT), positron emission tomography (PET), or MRI [50–53]. The use of these systems in prostate biopsy has only recently been explored. The functionality is very similar to other fusion platforms, in which real-time TRUS imaging is fused with prior MR imaging via rigid registration. Both platforms employ electromagnetic tracking systems as well as freehand TRUS biopsy approach. Virtual Navigator primarily employs a transrectal biopsy approach, whereas RVS has capabilities for both transrectal and transperineal biopsies.

Studies with these systems with respect to prostate biopsy are limited. Puech et al. published results with the Virtual Navigator platform and found significant differences in overall cancer detection rate in favor of targeted biopsy over systematic biopsy (69 % vs. 59 %, $p = 0.033$), as well as higher detection of clinically significant prostate cancer (67 % vs. 52 %, $p = 0.0011$) [7]. However, these results must be interpreted cautiously as evaluation of targeted-core CDRs included results from combination of both cognitive targeting and targeting with the Virtual Navigator platform. A report using the Virtual Navigator platform in 78/131 (59.5 %) patients with a suspicious area found on MRI found this system to produce a significantly higher CDR relative to systematic 10–12-core biopsy ($p = 0.0065$) [8]. Targeted biopsy with this platform detected an additional 9 % (7/78) of patients missed by random biopsy with Gleason score >6, while random biopsy detected an additional 18 % (14/78) of low-risk patients with Gleason 6 disease. Miyagawa et al. evaluated transperineal biopsy with Real-time Virtual Sonography (RVS) in 85 patients with prior negative random biopsy and suspicious lesions found on MRI; overall, prostate cancer was detected in 52 patients (61 %), of which 87 % (45/52) were found via RVS-directed targeted cores [54]. On a per-core analysis, targeted cores with the RVS platform detected significantly more cancer than conventional

TRUS biopsy (32 % [62/192 cores] vs. 9 % [75/833 cores], $p < 0.01$).

Mechanical Position Encoders

The **Artemis** fusion biopsy platform (Eigen, Grass Valley, California, USA) was FDA approved in 2007, with patient recruitment and clinical trials beginning in 2009 at the University of California, Los Angeles (UCLA). As mentioned earlier, the Artemis device differs from the others in that it utilizes a robot-like self-articulating mechanical arm to sweep the prostate and perform targeted biopsies [3]. In this system, the needle and probe positions are tracked in 3D space with angle-sensing encoders built into each joint of the arm. Similar to other platforms, a high-quality MRI with T2W, DWI, and DCE sequences is obtained prior to biopsy to identify suspicious lesions within the prostate. Image registration is carried out by the Artemis software via elastic transformation algorithms. After image registration, navigation software guides the operator to the planned targets. The mechanical arm allows for 4 degrees of freedom, with biopsy limited by rotation of the arm along a fixed axis [55] (Fig. 17.4). Therefore, the learning curve with this system is more involved as users have to become acclimated to the software as well as TRUS biopsy using manual rotation of the mechanical arm as opposed to the freehand techniques commonly utilized by urologists during general TRUS biopsy.

Several studies have been carried out to test accuracy and utility of prostate biopsy with the Artemis system. Initial work showed a 33 % biopsy positive rate when suspicious lesions were targeted compared to a 7 % positivity rate for systematic nontargeted biopsy (19/57 cores vs. 9/124 cores, $p = 0.03$) [39]. MR fusion with subsequent targeted biopsy only added an additional 5 min on average to the overall biopsy procedural time. While testing the utility of the tracking mechanism, it was demonstrated that the Artemis system could return to prior biopsy sites within 1.2 ± 1.1 mm accuracy, which was independent of prostate volume or location of biopsy site. In a

study with the Artemis system in 105 men with prior negative biopsy and elevated PSA, 21/23 men (91 %) with cancer detected on targeted biopsy had clinically significant cancer compared to 15 of 28 (54 %) with systematic biopsy; therefore, fusion biopsy yielded higher rates of clinically significant cancer [24]. The ability to eliminate mechanical error (e.g., hand unsteadiness during firing of the probe) is a unique and potential advantage of this robotic platform and may very well lead to higher accuracy while performing targeted prostate biopsy.

The **BiopSee** platform (Pi Medical, Athens, Greece) is similar to Artemis, yet utilizes a custom-made mechanical stepper fixed to the operating table to manipulate the TRUS probe as opposed to a self-articulating mechanical arm. Probe and needle motion are tracked via two built-in encoders; these encoders track motion of the probe in two dimensions: depth in/out and rotation. The workflow of this platform is very similar to many of the other platforms: pre-procedural MRI is obtained, and biopsy procedure consists of performing a sweep of the prostate with the TRUS probe from cranial to caudal, registering MRI data with real-time TRUS data via rigid registration, and carrying out targeted biopsies of specific regions within the prostate considered suspicious on MRI. Uniquely, this system is only equipped to perform biopsies via the transperineal route, in which biopsy needles are guided through a grid mounted to the mechanical stepper; however, ultrasound image guidance is still performed transrectally. As a potential limitation to this platform, users must familiarize themselves with not only the software but also the mechanics in handling the TRUS probe along fixed degrees of movement and rotation while simultaneously trying to align the needle with the virtual needle guide on the screen.

Most of the work with this system has been undertaken by Hadaschik et al. in Heidelberg, Germany. In an initial study with 106 men, the CDR was 59.4 % (63/106 patients), and MRI correlated positively with histopathology in 71 of 103 patients (68.9 %) [38]. On a per-core analysis, lesion-targeted cores had a significantly higher positivity rate than nontargeted cores
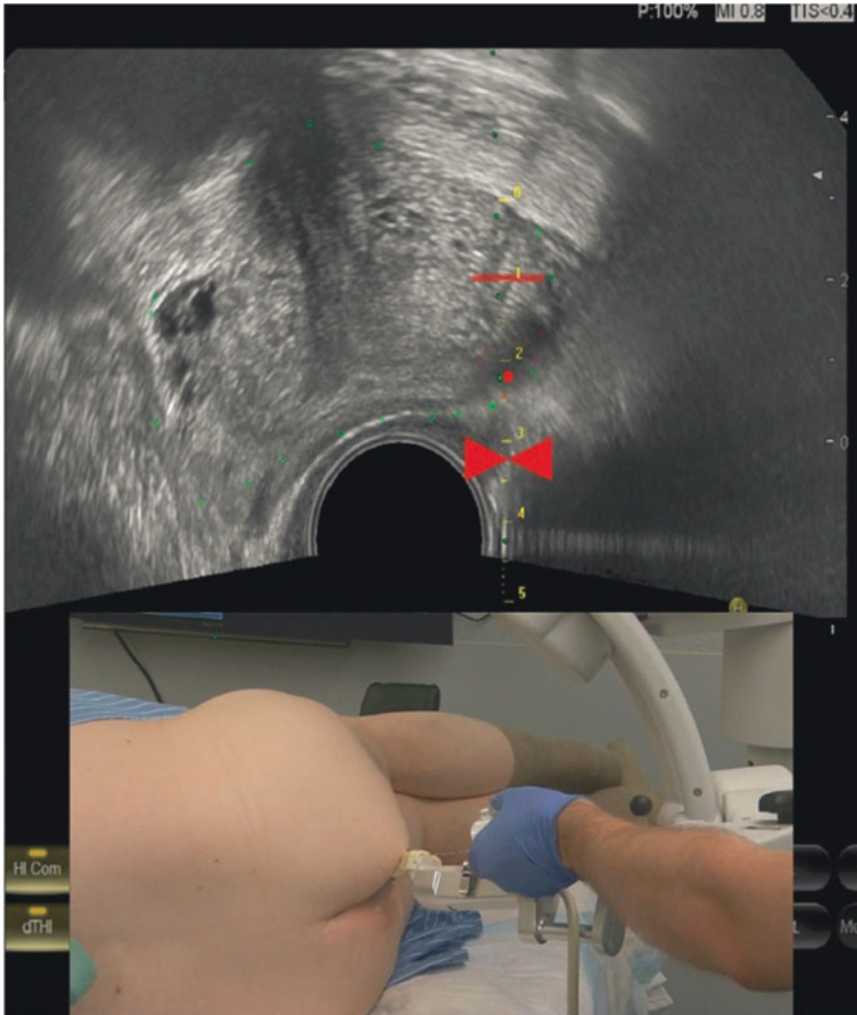
Fig. 17.4 (**a**) Artemis platform. The patient is placed in the lateral decubitus position. The US probe held securely by the robotic arm is placed transrectally to image the prostate. The needle biopsy guide is projected onto the US image to illustrate needle trajectory. The *red markings* assist in planning needle depth positioning and project the core sample to be taken. (Reprinted with permission from Eigen, Grass Valley, California, USA). (**b**) Artemis co-display of TRUS and T2W MRI of right peripheral zone lesion. Three-dimensional reconstruction demonstrates the acquired core location in the 3D volume. (Reprinted with permission from Eigen, Grass Valley, California, USA)

(101/410 [24.6 %] vs. 179/2051 [8.7 %], $p < 0.0001$). Lastly, the group reported an average procedural targeting error of 1.7 ± 1.7 mm for the first 2461 biopsy cores taken (comparing the virtually planned biopsy trajectory with the manually documented 3D needle positon of each biopsy core). Further work showed targeted biopsy CDRs of 82.6 % (86/104), 67 % (11/149), and 15 % (14/94) for patients with highly suspicious, questionably suspicious, and non-suspicious lesions detected on multiparametric 3 Tesla MRI, respectively [56]. On a core-by-core analysis, targeted cores detected significantly more cancer than systematic biopsies (386/1281 [30 %] vs. 523/6326 [8.2 %], $p < 0.01$). While initial work is promising, additional studies with this system are required to fully validate its accuracy and utility in clinical practice.

The **BioJet** platform (BK Ultrasound, Peabody, Massachusetts, USA; DK Technologies,
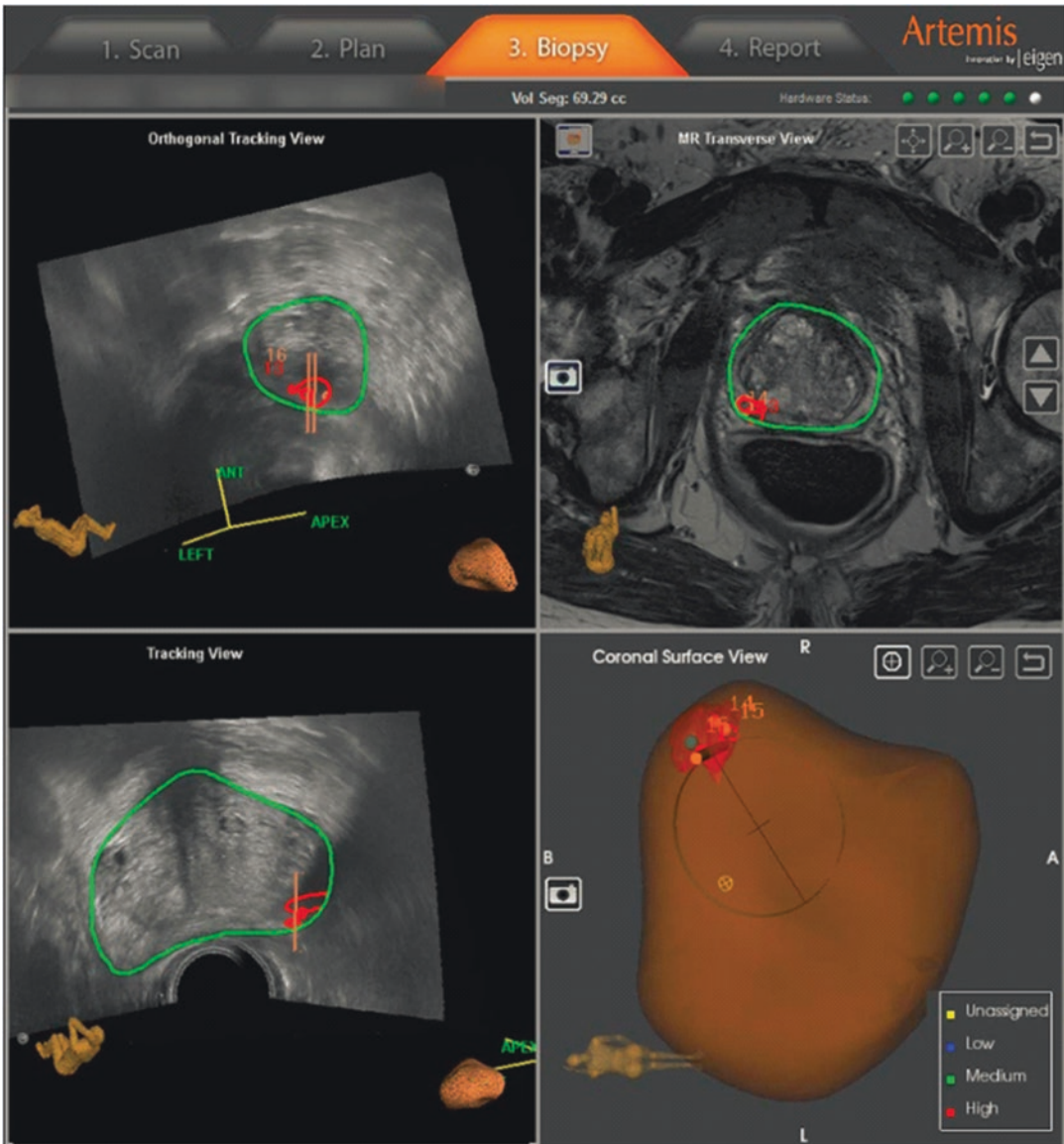
Fig. 17.4 (continued)

Barum, Germany), similar to Artemis, employs the use of a mechanical arm with angle-sensing encoders for tracking of the TRUS probe. Targeted biopsy can be performed via the transrectal or transperineal routes; however, the system is currently equipped with only rigid registration algorithms [57]. In a small proof-of-concept study consisting of 20 patients, Shoji et al. found an overall CDR of 70 % (14/20); the CDR was significantly higher for targeted biopsy cores utilizing the BioJet system relative to systematic biopsy (31.8 % vs. 6.7 %, $p < 0.0001$) [57]. However, the authors of the study pointed out that the shapes of the prostate contour on MRI and TRUS were pointedly different and contours had to be fused manually with several adjustments. In a study examining 72 total lesions in 39 men, one report found strong agreement between cancer detection via the BioJet platform and higher global Prostate Imaging Reporting

and Data System (PI-RADS) score for the dominant lesion found on mpMRI (positive cancer: 4.0 ± 1.3 vs. negative cancer: 2.6 ± 0.8, $p < 0.0006$) [58]. Using a global PI-RADS score cutoff ≥4, a sensitivity of 85 %, specificity of 82 %, and negative predictive value of 92 % were achieved. However, in a recent study in a prospective paired cohort of 50 patients with visible targets on MRI, Valerio et al. found similar CDRs on a per-patient level between cognitive fusion biopsy, directed targeted biopsies with the BioJet platform, and systematic transperineal template mapping biopsy (32 patients, 64 %; 34 patients, 68 %; and 38 patients, 76 %, respectively, $p > 0.05$) [59]. At a patient level, BioJet-based targeted biopsy did find more clinically significant disease relative to visually directed (cognitive) targeted biopsy, but this increased yield was not statistically significant (22 % vs. 14 %, $p = 0.48$). Therefore, more high-powered studies may be necessary to demonstrate significant differences in detection of clinically significant cancer with the BioJet platform relative to other biopsy methods.

Image-Based Tracking

The **Urostation** platform (Koelis, Grenoble, France), widely utilized across clinical centers in Europe, is an interesting platform in that tracking of the TRUS probe and needles is conducted with TRUS-TRUS registration. Thus, additional hardware such as an electromagnetic field generator or robotic arms is not necessary. The process begins with acquisition of prostate MRI as in other fusion platforms. At time of biopsy procedure, a 3D panorama TRUS volume is obtained via sweep of the prostate, and this model is fused to pre-procedural MRI data using elastic registration. Then, after each biopsy core is taken, a 3D TRUS image is acquired with the needle in place and registered to the original sweep TRUS volume to confirm proper needle placement. Similar to UroNav, this platform is advantageous as the biopsies are performed utilizing a standard freehand approach. However, one important drawback is that needles must be held in place without movement for 3–5 s

to allow for 3D TRUS acquisition in order to acquire an accurate needle location. As technology improves, real-time 3D US image acquisition may make the process seamless.

Initial studies with phantom models conducted by Ukimura et al. at the University of Southern California (USC) in Los Angeles, California, USA, demonstrated an accuracy of 84 % (24/27 lesions hit) with this platform and a mean procedural targeting error of 2.09 ± 1.28 mm [40]. In a study of 80 patients with 115 MRI suspicious lesions, the hit rate for the Urostation platform was 97 % (112/115 lesions with confirmed biopsy inside target), and 60/115 (52 %) targets were positive for cancer [60]. Mozer et al., in a prospective study utilizing the Urostation platform in 152 biopsy-naïve men, found that the proportion of positive cores and proportion of men with clinically significant prostate cancer were significantly higher with the targeted-core protocol relative to a systematic 12-core protocol ($p < 0.001$ and $p = 0.03$, respectively). Therefore, initial work with this platform seems promising.

Discussion

MR/TRUS fusion technology has revolutionized the way we visualize, diagnose, and manage prostate cancer. To this day, the prostate remains the only solid-organ malignancy that is biopsied "blindly." The current standard of care is to direct 10–12 cores to various regions within the prostate, with the hope of identifying cancer, if present. Though systematic in fashion, the biopsies are in essence random as they are not directed toward specific targets within the prostate. Previously, imaging for prostate cancer has been a challenge due to its deep location within the pelvis, the complexity of prostatic zonal anatomy, and its multifocal nature. However, major strides in mpMRI capabilities over the last several years have allowed for precise characterization of cancerous lesions within the prostate; when this valuable information is integrated into fusion platforms, it allows the operator to perform targeted biopsies with high accuracy in the

specific location(s) in which there are image-identified lesions. Furthermore, this information can be stored and utilized in the future for various purposes, such as re-targeting the exact same location or planning focal therapy. Thus, fusion technology sheds light on the prostate and allows urologists to actually "see" malignancy with greater confidence, as opposed to grasping for cancer in the dark.

Software-based MRI/TRUS fusion-targeted biopsy, in general, detects more clinically significant cancers with fewer cores than standard biopsy [61–64]. A major criticism of systematic biopsy is the tendency to indiscriminately identify more clinically insignificant, low-risk cancers and less clinically relevant high-risk cancers. Therefore, targeted fusion biopsy may allow for more accurate risk stratification and subsequent treatment. Additionally, the clinical utility of fusion technology in various scenarios is apparent, such as in patients with history of prior negative TRUS biopsies yet continued prostate cancer suspicion, monitoring of patients on active surveillance, and targeting of lesions in areas of the prostate that are traditionally missed via systematic biopsy. Nevertheless, additional studies are warranted to further define the specific patient population that benefits the most from fusion biopsy [65].

Despite substantial progress in such a short time, there are many questions that still remain unanswered. At this time, most who have integrated fusion platforms into their practice perform systematic biopsy in addition to targeted biopsy. This is done, in part, to compare the two forms of biopsy head-to-head in the same patient, yet also because there still remain a small proportion of patients in which systematic biopsy reveals clinically significant disease missed by targeted fusion biopsy. Therefore, it is yet to be determined if targeted biopsy can be used alone primarily, or as an adjunctive strategy with systematic biopsy [26].

With respect to the available platforms, initial evidence suggests they offer clinical utility in one form or the other. However, there has been a paucity of clinical trials comparing the different platforms head-to-head. Retrospective analyses comparing the outcomes with each platform are quite difficult, as definitions, clinical parameters, workflow, and technique vary tremendously from institution to institution and study to study (for instance, variations in patient populations, mpMRI acquisition, MR imaging interpretation, fusion biopsy technique, definition of clinically significant cancer, etc.) [66].

Conclusion

Perhaps the most important question is how novel fusion technologies can be further integrated into mainstream urological practice. Due to proven success, the use of these commercially available fusion biopsy platforms seems to have taken off substantially in the last several years both in the USA and abroad. However, it is yet to be determined exactly what role fusion biopsy will play in the future. This office-based procedure empowers the urologist to specifically target lesions in the prostate; however, the entire process, from MR imaging interpretation to registration of a 3D ultrasound with MRI to accurate targeting of a "bullseye" displayed on the screen, requires several unique skillsets and a multidisciplinary team [67]. Though it remains to be seen whether this technology provides a favorable cost/benefit ratio, changes in the prostate cancer screening paradigm have forced clinicians to be more judicious in their approach to patient selection for biopsy. Improvements in imaging have facilitated this, and fusion technology will help integrate imaging findings to improve cancer diagnosis.

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