MRI-Guided Prostate Biopsy of Native and Recurrent Prostate Cancer

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Abstract

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Prostate cancer is the most commonly diagnosed noncutaneous cancer and second-leading cause of death in men. Many patients with clinically organ-confined prostate cancer undergo definitive, curative treatment of the whole gland with either radical prostatectomy or radiation therapy. However, many men are reluctant to take the definitive step due to potential morbidity associated with either therapy. A growing interest in active surveillance or focal therapy has emerged as realistic alternatives for many patients. With each of these management strategies, it is critical to accurately quantify and stage the cancer with improved biopsy targeting and more precise imaging with magnetic resonance imaging (MRI). Furthermore, having dependable prostate imaging allows for targeted biopsies to improve the yield of clinically significant prostate cancer and decrease detection of indolent prostate cancer. MRI-guided targeted biopsy techniques include cognitive MRI/transrectal ultrasound fusion biopsy, in-bore transrectal targeted biopsy using a calibrated guidance device, and in-bore direct MR-guided transperineal biopsy with a software-based transperineal grid template. Herein we present a contemporary review of MRI-guided targeted biopsy techniques for new and recurrent cancerous foci of the prostate.

Objectives: Upon completion of this article, the reader will be able to identify the utility of MRI-guided biopsy of the prostate gland, the current commercially available units, and the advantages and drawbacks of each system.

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The American Cancer Society (ACS) estimated that in 2016, there will be 180,890 newly diagnosed cases of prostate cancer with an estimated 26,120 deaths. The risk of prostate cancer is 70% higher in blacks than in non-Hispanic white males. Prostate cancer is the most commonly diagnosed noncutaneous cancer and second-leading cause of cancer death in men.¹

Unfortunately, it is unknown at which time an aggressive prostate cancer should be detected to attain the highest chance of cure. However, it seems intuitive that very early detection may play a role in preventing the development of metastatic disease.² In view of the significant disparity on

recommendations for early detection and prostate cancer screening among various scientific organizations (i.e., American Urological Association, American Society of Clinical Oncology, National Comprehensive Cancer Network, ACS, U.S. Preventative Task Force, and the European Association of Urology) as well as the data uncertainty of the harm/benefit balance of screening, this overview will not delve into this controversy. Our focus instead will be on the current state of the art of prostate biopsy techniques once the decision has been made to obtain tissue. The significance of precise tissue collection is further amplified by level 1 evidence, supporting detection and subsequent aggressive treatment of intermediate- and high-risk prostate cancer.³ Therefore, accurate ascription of cancer risk (i.e., grade and stage) using the biopsy and imaging is critical. Advances in prostate imaging and image guidance play a crucial role in providing this information.

Historically, transrectal ultrasonography (TRUS) of the prostate has been integral to extend the capabilities of the physical exam of this organ. TRUS is most frequently performed in conjunction with needle biopsy of the prostate and was first popularized by Cooner et al.⁴ In the past, the indication for prostate TRUS was either an abnormality of the digital rectal exam (DRE) or an elevation in serum prostate-specific antigen (PSA). TRUS allows for precise direction of the biopsy needle into regional prostate anatomy and regions of interest (ROI) seen on ultrasound. However, studies have confirmed the inability of standard gray-scale TRUS alone to localize and target early prostate cancer (i.e., hypo- or hyperechoic lesions).⁵ Contemporary use of prostate TRUS has evolved from conventional gray-scale ultrasonography to the use of color and power Doppler, contrast media-enhanced ultrasound, and strain or shear wave elastography to better identify regions and targets of interest.⁶ The added benefit of these other ultrasound modalities have not been thoroughly vetted when used as multiparametric package analogous to the series of sequences used with multiparametric MRI (mpMRI).

The TRUS prostate biopsy has remained the cornerstone for prostate cancer diagnosis dating back to the systematic “sextant” biopsy protocol with three cores per side.⁷ A meta-analysis of 68 studies led to a recommendation of a more laterally directed schema with 12 cores improving prostate cancer detection rates by a factor of 1.3.⁸ Using this systematic 12-core TRUS sampling for men undergoing initial biopsy with elevated PSA yields cancer detection rates between 30 and 55%.⁹ The false-negative rate for this 12-core schema is on the order of 20 to 24%¹⁰ and repeated 12 core or saturation biopsies show detection rates of 11 to 47%.¹¹ This is particularly true for men with anteriorly located tumors.¹² To improve the accuracy of the sampling, some experts advocate the use of template, transperineal-mapping biopsies to systematically sample all quadrants of the prostate.¹³ This has been criticized for oversampling of insignificant tumors with risk of additional morbidity and need for general anesthesia.

In the past decade, increasing evidence supports the use of prebiopsy mpMRI for significant disease localization, with intent of addressing the limitations of the systematic biopsy,

reducing the detection of low-risk cancers, and improving the detection of clinically significant prostate cancer.^{13–15} A variety of approaches have evolved to capitalize on the accuracy of the multiplanar, high soft-tissue contrast, high resolution and ability to image functional and anatomic parameters with mpMRI.

In an attempt to combine the ubiquitous nature of TRUS in clinical practice of prostate disease and the superior image characteristics of mpMRI, software has been developed to fuse the MR images to the live ultrasound image. The coupling of these two technologies by either software-based techniques or cognitive/visual methods promises to increase the diagnostic accuracy and may have similar detection rates, but use fewer cores as compared with standard biopsy.¹⁶ “In-bore” direct MRI-guided prostate biopsies utilize three basic schematic layouts: transrectal needle guidance devices, transperineal needle guidance grids, or MRI compatible robot-assisted devices to exploit the superb lesion conspicuity of the MR imaging.¹⁷

The ideal prostate biopsy strategy would be to identify clinically significant prostate cancer and minimize the detection of indolent disease. Screening patients using mpMRI may avoid morbidity associated with biopsy if no lesions are seen. Restriction of biopsy to MRI concerning lesions may also reduce over diagnosis of low-risk disease.^{18,19} Thus, using MRI and targeted biopsy strategies is a promising approach. Finally, targeted biopsies have implications for active surveillance protocols with promise of improved detection of intermediate- and high-risk disease, facilitating better selection of candidates for initial biopsy and watchful waiting.²⁰ Furthermore, targeting the most concerning areas can be used with gene-based biomarkers to potentially improve risk stratification. However to date, an analysis of targeted biopsy tissue genomic signatures has not been accomplished with rigor and appropriate follow-up. Combined advancements in imaging, biopsy targeting, and genomic testing to reveal the underlying tumor biology promise a new era in personalized approach to prostate cancer management. The following sections will explore the evolution of MRI for cancer diagnosis and biopsy targeting for the diagnosis of prostate cancer.

MRI for Prostate Cancer Imaging

Prostate cancer has traditionally been diagnosed by PSA screening and DRE followed by DRE-directed biopsy. In the more contemporary period, the use of ultrasound imaging has helped direct the biopsies but has fallen short of being sensitive enough to find all prostate cancers within the gland. Furthermore, random sampling the entire organ has provided some advantage but may miss or undersample small volume but clinically significant disease. The recent introduction and maturation of mpMRI allows for imaging-based identification of prostate cancer, which may improve diagnostic accuracy for higher-risk clinically significant tumors.²¹ In 2015, a consensus panel agreed to PI-RADS v2 (an organized reporting system for mpMRI findings in the prostate), which is designed to improve detection, localization, characterization, and risk stratification in patients with suspected cancer in

treatment native prostate glands.²² Targeted biopsy of suspected cancer lesions detected by MRI is associated with increased detection of high-risk prostate cancer and decreased detection of low-risk prostate cancer, particularly with the aid of MRI/ultrasound fusion platforms.²³ The use of mpMRI has expanded beyond detection to staging, characterization, monitoring for active surveillance, and cases of suspected recurrence after failed definitive therapy.

mpMRI for recurrent prostate cancer continues to evolve and has potential to evaluate both local recurrence and distant bony and nodal metastases.²⁴ In 2013, a consensus panel chaired by Professor Michael Marberger endorsed utilization of mpMRI to identify patients for focal therapy.²⁵ mpMRI is capable of localizing small tumors for focal therapy. While mpMRI plays an established, critical role in native and recurrent prostate cancer imaging, functional, metabolic imaging for prostate cancer is in its formative years. 11C-choline positron emission tomography (PET)/CT has an advantage to reveal both local recurrent and distant metastatic prostate cancers. 11C-choline PET/CT had a sensitivity of 73%, a specificity of 88%, a positive predictive value of 92%, a negative predictive value of 61%, and an accuracy of 78% for the detection of clinically suspected recurrent prostate cancer in postsurgical patients.²⁶ In a study of post-prostatectomy patients with rising PSA, mpMRI was superior for the detec-

tion of local recurrence, 11C-choline PET/CT was superior for pelvic nodal metastasis, and both were equally excellent for pelvic bone metastasis. 11C-choline PET/CT as well as PET/MRI and mpMRI are complementary for restaging prostatectomy patients with suspected recurrent disease.^{24,27} However, 11C-choline PET/CT is not widely available.

With the limitations of ultrasound and PET/CT imaging, MRI remains preeminent for detection and staging of prostate tumors within the pelvis. MRI provides superior soft-tissue contrast resolution, high spatial resolution, direct multiplanar imaging capabilities, and a large field of view.

If the focal treatment is intended for potential curative treatment, it is very important to assure that there is no distant disease with whole-body CT/MRI, bone scan, and 11C-choline PET/CT. Unfortunately, none of these imaging modalities is perfect, and appropriate selection of image staging is unique to each patient.

MRI Targeted Prostate Biopsy Techniques

Cognitive/Visual-Directed MRI Targeted Biopsy

During TRUS-guided biopsy procedures, the operator can estimate the location of MRI suspicious lesion based on prior review of prostate MRI. However, this technique is highly dependent on the skill of the physician performing the biopsy

Fig. 1 Keolis Urostation prostate biopsy system (a) is based on image organ-based tracking which is fused to prior mpMRI (b). Work flow images for targeting biopsies are shown (c). Final biopsy core positions are also tracked and plotted by the system relative to the 3D prostate model (d). Some images have been acquired from <http://koelis.com/en/>.

to translate the MRI data into the three-dimensional (3D) realm of the ultrasound biopsy. With appropriate experience, this is straightforward and easy to implement without an upfront equipment investment. However, this cognitive fusion (or visual estimation) based targeted biopsy method is highly operator dependent. This method is prone to error in reliably mapping the MRI suspicious lesion on real-time TRUS, and the confirmation of TRUS-guided targeted biopsy needle location over the MRI suspicious lesion is not directly feasible. In a study of 555 patients by systematic biopsy as well as cognitive fusion-guided targeted biopsy, overall 54% (302/555) of patients were found to have cancer; 82% of them were clinically significant. Systematic biopsy and cognitive fusion-guided targeted biopsy detected 88 and 98% of clinically significant cancers, respectively.²⁸ Cognitive fusion targeted biopsy showed 16% more high-grade cancers and higher mean cancer core lengths than standard systematic biopsy. Cognitive targeted biopsy would only avoid 13% of insignificant tumors. Using a similar, visually directed approach for the transperineal biopsy, Valerio et al compare this to a software-based, targeted biopsy. The software-based, targeted transperineal approach found more clinically significant disease than visually directed biopsy, although this was

not statistically significant (51.9 vs. 44.3%, $p = 0.24$).²⁹ The current diagnostic ability of visually/cognitively targeted and software-based biopsies seems to be nearly comparable, but heavily dependent on the experience of the operator. Ongoing prospective trials hope to confirm these findings, albeit based on those with significant operator experience.

Cognitive/visual targeted biopsies are also critical to the localization of biopsy-proven local recurrences following radical prostatectomy. Linder et al demonstrated cognitive, MRI-directed, TRUS-guided biopsy of the prostate bed and its high level of sensitivity in detecting local recurrences even at low PSA levels, relying on endorectal coil mpMRI as a first imaging evaluation for biochemical recurrences.³⁰

Software-Based Ultrasound: MRI Fusion Targeted Biopsy

Software-based MRI/TRUS fusion-guided biopsy combines the advantages of real-time TRUS, including better temporal resolution and cost-effectiveness, with those of MRI, including better spatial resolution and more accurate cancer detection. This technique promises improved detection of clinically significant tumors and enhanced yield in patients needing rebiopsy for elevated PSA despite prior benign biopsy results.

Fig. 2 The InVivo UroNav prostate biopsy system (a) is based on a nonrigid registration algorithm which allows real-time spatial tracking of targets and needle location. Work flow images for targeting biopsies from the MRI are shown (b) with 3D reconstruction. Final biopsy core positions are also tracked and plotted by the system relative to the 3D prostate model (c). Some images have been acquired from <http://www.invivocorp.com/solutions/prostate-solutions/>.

There are three key tracking methods: (1) image organ-based tracking, (2) electromagnetic sensor-based tracking, and (3) mechanical arm, sensor-based tracking. Common to all the ultrasounds, MRI fusion platform is some form of segmentation of the prostate to develop a 3D prostate model based on a pre-acquired MRI of the prostate. Concerning ROIs are then marked on the MRI in 3D for export to the fusion workstation. This may be accomplished by CD or direct network connection. The live ultrasound is then performed and a 3D dataset is obtained with a manual or electronic sweep through the prostate. Identical segmentation of the ultrasound dataset is then accomplished. Rigid body fusion of the two datasets is accomplished with a combination of automatic and manual tools. Once satisfactory fusion is accomplished, often aided by elastic deformation and motion correction, the biopsy mode is employed to target each of the preidentified target(s) as well as any systematic regional biopsies which may be desired. All systems have a means of registering each core location in space and have some form of report generation with associated pathology.

Image organ-based tracking method fuses prior mpMRI with real-time ultrasound using a surface-based registration

and elastic organ-based deformation algorithm (Urostation, Koelis, Minogue Medical Inc., Montreal, Quebec). A proprietary, rapid acquisition, 3D end-fire endocavitary transducer allows for near real-time, organ-based tracking of the prostate. With this feature, each biopsy core is tracked with a 3D scan once the biopsy is taken. MRI suspicious lesions are brought into the aiming mechanism of the biopsy gun attached to the ultrasound probe. This is relatively inexpensive and allows systematic biopsies as well as targeted biopsies. However, confirmation of targeted needle biopsy tracts is retrospective (►Fig. 1).

Electromagnetic sensor-based tracking using nonrigid registration algorithm allows real-time spatial tracking of targets and needle location. This system is dependent on the operator having an advanced ultrasound skill set and allows for free-hand ultrasound scanning during the 3D ultrasound dataset acquisition and biopsy (UroNav, InVivo Corp., Gainesville, FL; Real-Time Virtual Sonography [RVS], Hitachi-Aloka, Wallingford, CT). The RF sensor-based tracking can be designed for any ultrasound system; however, patient movement during acquisition of the 3D ultrasound dataset or biopsy procedure can lead to errors in targeting. In

Fig. 3 The Eigen Artemis prostate biopsy system (a) is based on both RF sensor registry and organ-based tracking to register with a pre-acquired MRI. A 3D ultrasound dataset is acquired by rotating the transducer probe cradle and this image is segmented on the workstation. The mechanical arm, sensor-based tracking system, in which a mechanical tracking arm is attached to a conventional ultrasound probe, allows real-time spatial tracking of targets and needle location. Work flow images demonstrate registration of the prostate position (b). Images demonstrating projected biopsy path (c). Biopsy tracks are projected back into a 3D prostate model (d). Some images have been acquired from <http://www.eigen.com/>.

a recent prospective study of 1,003 men undergoing an MR/ultrasound fusion targeted biopsy and concurrent standard biopsy, targeted MR/ultrasound fusion biopsy was shown to diagnose 30% more high-risk prostate cancer (defined as Gleason score $\geq 4 + 3$), while a combination of standard and targeted biopsies revealed 22% more prostate cancer, mostly (83%) low-risk prostate cancer (defined as Gleason score $3 + 3$ and low volume $3 + 4$) (**►Fig. 2**).²³

As in the RF sensor-based and organ-based tracking, the Artemis system uses pre-acquired MRIs for planning of systematic and targeted biopsies. A 3D ultrasound dataset is acquired by rotating the transducer probe cradle and this image is segmented on the workstation. The mechanical arm, sensor-based tracking system, in which a mechanical tracking arm is attached to a conventional ultrasound probe, allows real-time spatial tracking of targets and needle location (Artemis; Eigen, Grass Valley, CA). This system is less operator dependent but relatively bulky and expensive. In a recent retrospective review of 601 men who underwent both MRI-ultrasound fusion targeted biopsy and systematic biopsy, targeted MRI-ultrasound fusion biopsy detected fewer Gleason score 6 prostate cancers (75 vs. 121; $p < 0.001$) and more Gleason score ≥ 7 prostate cancers (158 vs. 117; $p < 0.001$) when compared with systemic biopsy.³¹ In a review of 105

patients with prior negative biopsies and elevated PSA, MRI-ultrasound fusion mechanical arm targeted biopsy improved detection of clinically significant prostate cancer when compared with systemic biopsy (**►Fig. 3**).³²

In-Bore Direct MRI Targeted Biopsy

Direct in-bore MRI-guided biopsy allows imaging confirmation of targeting without need for sophisticated image registration and fusion with live ultrasound images. In a study of 265 patients with rising PSA despite prior negative TRUS-guided biopsies, direct in-bore MRI-guided biopsy detected cancer in 41% (108/265) of cases; 87% (94/108) were clinically significant.³³ Reporting results from a prospective clinical observational study, Penzkofer et al showed the utility of in-bore prostate biopsies with at least one MRI-detected lesion in men with¹ no prior prostate cancer,² undergoing active surveillance monitoring,³ and suspected recurrent cancer following prior treatment.¹⁷ Overall cancer was detected in 56.7% with 48.1% with no prior cancer, 72% of those under active surveillance and 72% of those in whom recurrence was expected. The accuracy of the transperineal in-bore biopsy appears good as demonstrated by analysis of biopsy and post-prostatectomy histopathology.³⁴ MRI-detected targets located in the anterior gland had the highest cancer yield (62.5%).

Fig. 4 Patient is placed on the MRI scanner table prone positioned on the DynaTRIM biopsy platform (a). After placing the transrectal needle guide in position, a sagittal T2-weighted image through the needle guide is obtained for calibration (b). The angulation and trajectory are controlled by the control dials on the holder (c). Once the needle guide coordinates are adjusted, a coronal oblique confirmation scan is performed assuring appropriate position (d).

Although these advantages are attractive, this approach is not widely used for several reasons, some of which are high upfront investment in MRI-compatible equipment, prolonged use of MRI scanner competing with diagnostic imaging, and need for collaboration with the urologist, radiologist, and anesthesiologist. All these factors contribute to increased cost of biopsy, and increased difficulty in scheduling, resulting in few institutions offering these biopsies.

MRI-Specialized Techniques

MR Guidance Technologies

Interventional MR techniques have utilized needle guidance devices which have integrated varying amounts of software interface, from robotic guidance systems to live imaging during free-hand placement. In-bore MR-guided biopsy techniques include transrectal targeted biopsy using a calibrated guidance device and in-bore direct MR-guided transperineal biopsy with a software-based transperineal grid template.

Transrectal In-Bore MRI Biopsy

InVivo Corp. has developed a biopsy system (DynaTRIM) which integrates with their prostate CAD diagnostic imaging

platform to guide transrectal biopsies. To accomplish the CAD targeted biopsies, a localization device (fiducial marker) is built into a transrectal needle guide. A sagittal localizer image through the fiducial marker is initially obtained, identifying needle-guide location and position within the MRI bore. The lesion is localized using InVivo prostate CAD biopsy software (►Fig. 4). The DynaTRIM is calibrated with the sagittal image, allowing needle trajectory graphic generation through the needle guide lumen. A cursor is then placed on the target region and the software calculates the difference between the current needle-guide tip and the target location as well as depth from an axial image.

Once the needle guide coordinates are adjusted, a coronal oblique confirmation scan is performed. An 18-gauge MRI-compatible core biopsy needle is advanced through the needle guide, and a core biopsy specimen is obtained. A follow-up scan prior to removal of the needle is performed to document the needle position. The basis for localization is mpMRI, from which findings can be identified and scored (►Fig. 5). Once the needle guide coordinates are adjusted, a coronal oblique confirmation scan is performed. An 18-gauge MRI-compatible core biopsy needle is advanced through the needle guide, and a core biopsy specimen was obtained. A

Fig. 5 Prostate imaging with 1.5T with a 16-channel dual array flexible coil (InVivo, Gainesville, FL) demonstrating a left peripheral zone tumor. (a) Axial dynamic contrast enhanced (DCE) image showing a small hyperenhancing area in the left peripheral zone; (b) The corresponding apparent diffusion coefficient map from a high b value ($b = 1,400$) diffusion-weighted imaging. (c) Axial T2-weighted image with decreased T2 signal in the same left peripheral zone area. (d) The perfusion maps corresponding to the axial image in (a).

Fig. 6 An MR-compatible perineal template was used to guide insertions of the biopsy needles into the prostate. The device is designed to be placed against the perineum. The fiducials are manually identified and biopsy tracks propagated into the MR images (a). An integrated software application provides an interface for fiducial localization within the stack of axial MR images (the fiducials are localized with a mouse click), and superimposes catheter guide trajectories onto MR images and calculates insertion depths to facilitate stereotaxic-like needle localization (Visualase, Houston, TX) (b). T2-weighted HASTE imaging with no fat saturation demonstrates the previously identified abnormality in the right peripheral zone (red arrow, c). T2-weighted TrueFISP imaging demonstrates the small artifact associated with the biopsy trough deployed through the lesion (red arrow, d).

follow-up scan prior to removal of the needle is performed to document the needle position.

Transperineal In-Bore MRI Biopsy

MRI-compatible perineal template was developed for needle guidance for biopsy and focal ablation into the prostate.³⁵ The template consisted of a $3 \times 3 \times 1$ inch Acrylite sheet (CYRO Industries, Rockaway, NJ) with a 4×6 cm array of 14-gauge diameter holes positioned at 5 mm apart. The device is designed to be placed against the perineum with the ability to attach to a standard endorectal coil (Medrad, Pittsburgh, PA). Three water-filled cavities, one positioned within the Lexan rod protruding from the top of the template and two in the opposite template corners, serve as fusion/calibration fiducial markers. Identification of these fiducials in MR images is geometrically sufficient to determine the orientation of the template with respect to the imaging volume. Given these parameterizations, it is possible to compute and draw the intersection of each grid trajectory with a currently viewed axial (or oblique) plane from the MR image volume set. An integrated software

application provides an interface for fiducial localization within the stack of axial MR images (the fiducials are localized with a mouse click), superimposes catheter guide trajectories onto MR images, and calculates insertion depths to facilitate stereotaxic-like needle localization (—Fig. 6).

Several robotic systems have been developed to guide needle placement into the prostate.^{36–38} These systems have significant promise for future clinical use, but suffer from limited adoption generally locally where they were developed.

Conclusion

As the most common cancer in men, prostate cancer diagnosis and treatment for new or recurrent disease will demand considerable resources and effort for years to come. MRI is playing a seminal role in the management of this disease. MRI and ultrasound fusion for prostate biopsy guidance appears to represent the next step in timely diagnosis and navigation to clinically significant cancers. Combining these advancements

in imaging, biopsy targeting and genomic testing to reveal the underlying tumor biology promise a new era in personalized approach to prostate cancer management. With better localization and characterization of the cancer, development of robust prospective studies using focal/regional ablative technologies will be a natural progression of these technologies.

Disclosure

There are no disclosures for Dr. Gorny and Dr. Greenwood.

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