Review Article

Co-registration of MRI and ultrasound: accuracy of targeting based on radiology-pathology correlation

Win Shun Lai[1], Jessica G. Zarzour[2], Jennifer B. Gordetsky[1,3], Soroush Rais-Bahrami[1,2]

[1]Department of Urology, [2]Department of Radiology, [3]Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, USA

Contributions: (I) Conception and design: WS Lai, S Rais-Bahrami; (II) Administrative support: S Rais-Bahrami; (III) Provision of study materials or patients: JB Gordetsky, S Rais-Bahrami; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Soroush Rais-Bahrami, MD. Department of Urology, University of Alabama at Birmingham, Faculty Office Tower 1107, 510 20th Street South, Birmingham, AL 35294, USA. Email: sraisbahrami@uabmc.edu.

Abstract: We reviewed the role of multiparametric magnetic resonance imaging (MP-MRI) and methods of MRI guided biopsy including in-bore, cognitive fusion, and software-based fusion. MP-MRI has been developed, optimized, and studied as a means of improving prostate cancer detection beyond the standard evaluation that utilizes digital rectal examinations and serum prostate specific antigen (PSA). MP-MRI has been proven to be an excellent diagnostic imaging modality that improves prostate cancer detection and risk stratification by guiding biopsy samples. The co-registration between MRI and ultrasound has allowed for software-based fusion which enables office-based biopsy procedures while still benefiting from the detailed prostate characterization of MRI. MP-MRI/ultrasound fusion guided biopsy has been studied in detail as this technology has been developed, tested, and validated in the past decade. The imaging to pathology correlation supporting the use of MP-MRI/ultrasound fusion is well documented in the literature. As the indication for the use of prostate MP-MRI becomes more widespread, it is important to continue to evaluate the correlation between imaging and pathologic findings.

Keywords: Prostate cancer; fusion biopsy; transrectal ultrasound (TRUS); imaging; histopathology; Gleason

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Introduction

Prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer-related deaths in American men (1). Classically, prostate cancer was diagnosed with age appropriate screening with the use of a digital rectal examination (DRE) and serum prostate specific antigen (PSA) assessment; elevated PSA or abnormal (DRE) findings would prompt a random biopsy of the prostate, systematically sampling sextant regions of the gland without any targeting of cancer suspicious areas. Although early investigations also demonstrated that hypoechoic lesions on transrectal ultrasound (TRUS) may correlate with cancer foci, this resulted in lower cancer detection rates than the standard 12-core approach (2).

The advent of multiparametric magnetic resonance imaging (MP-MRI), for the purposes of high-resolution anatomic and functional imaging of the prostate, has allowed for high efficiency detection of prostate cancer foci, particularly areas of higher grade disease (3). Hence, this advanced imaging has emerged as a tool in the diagnosis, risk stratification, and management of prostate cancer in men who are at risk or already diagnosed with this common cancer (4). Initially, the diagnostic power of MP-MRI for prostate cancer detection was used to allow for targeted biopsy in the setting of "in-gantry" or "in-bore" MRI guided biopsies. These techniques incurred increased costs, largely driven by the time required to perform in-bore biopsies as well as the limited armamentarium of MRI safe tools and equipment. Thus, the use of MP-MRI has evolved

into the guiding diagnostic study, which is then used for out-of-gantry biopsy techniques. Out-of-gantry biopsy techniques consist of using MP-MRI areas of suspicion and real-time ultrasound to guide needle placement at the time of the biopsy. This "fusion" of imaging modalities has been described and performed in one of two fundamental ways: 1—cognitive fusion and 2—software fusion (5). When biopsies are performed outside the MRI gantry, an added validation of the process is required to assess the accuracy and clinical impact rendered by MP-MRI fusion guided biopsies in the office setting.

Herein, we review the development and mechanisms for both cognitive fusion and software fusion between MP-MRI and ultrasound to allow for targeted biopsy of specific areas within the prostate that were identified with suspicion for harboring prostate cancer on MP-MRI. We will also discuss the correlation between the imaging characteristics and pathology supporting the fusion of MP-MRI and ultrasound imaging to allow for targeted biopsy techniques for detection and management of prostate cancer.

MRI detection of prostate cancer

The use of MRI for the management of prostate cancer initially started as a staging tool in the 1990s primarily used to evaluate for extraprostatic extension of disease beyond the capsule or into the seminal vesicles (6). At that time, detection of intraprostatic lesions correlating to areas of prostate cancer was identified as a potential tool but was limited. The development of higher field strength magnets and use of an endorectal and phased-array coils to optimize signal-to-noise ratio, specifically for optimizing images of deep pelvic structures, have improved the characterization of lesions within the prostate as well as identification of prostate cancer lesions post treatment (7,8).

Since then, the development of a MP-MRI incorporating T2-weighted (T2W) imaging, T1-weighted imaging with dynamic contrast enhancement (DCE), and diffusion weighted imaging has allowed for more definitive detection and localization of prostate cancer foci (9,10). The multiple parameters helped overcome limitations faced with each individual type of imaging sequence. It was found that cancer suspicion was heightened when multiple parameters were found to isolate the same area of concern, adding accuracy in cancer detection over the use of a solitary MRI sequence. Furthermore, the areas of imaging suspicion then could lead to the potential of improved biopsy sampling and cancer detection (11,12). The scoring of MRI visible lesions with suspicion for harboring prostate cancer has further been developed into a well-defined system, Prostate Imaging Reporting and Data System (PIRADS), which was first published in 2012 by the European Society of Urogenital Radiology (ESUR) (13). A revised version of this systematic prostate imaging scoring system, called PIRADS v2.0 has been developed and published by the PIRADS steering committee of the American College of Radiology and the ESUR prostate MRI working group in 2015 (14). Studies have shown that an increasing level in PIRADS correlate with an increased detection rate of prostate cancer, especially those of high-grade (Gleason ≥7) (15,16).

Methods of MRI guided biopsy

With the advances in MRI and specifically the implementation of MP-MRI for the aim of evaluating for the presence of prostate cancer, MRI guided prostate biopsy was the next obvious step in the diagnostic pathway. Previous biopsies were transrectal ultrasound (TRUS)-guided without specific targeting of any cancer suspicious foci in most cases. This systematic but random nature of prostate tissue sampling, which was the working standard approach, was being augmented with the goal of targeting biopsy needles into MRI visible lesions. Targeted biopsy of the prostate has been achieved by three fundamental approaches. These include direct "in-bore" MRI guidance, cognitive fusion between MRI and ultrasound, and software-based fusion between MRI and ultrasound. The goal of all three approaches is to reliably direct biopsy sampling into suspicious areas detected by MRI of the prostate.

"In-bore" MRI guided biopsy

The first MRI guided biopsies were implemented as direct targeting in the setting of the MRI, as "in-bore" biopsies. For this technique the patient had typically already undergone a diagnostic MP-MRI prior to the biopsy session in the MRI gantry. The patients would then undergo either transrectal or transperineal approaches to prostate biopsy in the gantry of the MRI magnet. The needles were introduced, targeting MRI visible lesions with intermittent scans to confirm placement of the needle into the lesions of interest (17-19). This method provided a high fidelity targeting modality to ensure needles were placed into the imaged area of suspicion as needle localization was confirmed with the same imaging modality used to identify the lesions being targeted. In turn, this could provide a

reduction of needle sampling due to accuracy. Furthermore, inherent to the MRI storing acquired images, precise documentation of needle sampling and localization was achieved using this technique. Disadvantages of "in-bore" direct MRI guidance include the cost incurred due to the amount of time needed in the gantry of the MRI magnet, the specialized biopsy equipment required which would be safe in the setting of a high field strength magnet, and the added setup for sedation and patient positioning to achieve these cumbersome "in-bore" biopsy procedures compared to routine office-based ultrasound based prostate biopsies.

Cognitive MRI to TRUS fusion biopsy

The second phase of MRI guided biopsies was to employ the diagnostic MP-MRI findings to target areas of suspicion using cognitive fusion of MRI lesion locations to real-time TRUS localization by the biopsy operator to target biopsy needles into higher suspicion areas. This is theoretically the simplest MRI guided biopsy approach as it requires no added instrumentation and a minimal alteration in workflow compared to performing systematic extended sextant biopsy with TRUS guidance. The practitioner performing the biopsy reviews the MP-MRI localization of suspicious lesions and then estimates the three-dimensional localization on the real-time TRUS exam used at the time of the biopsy procedure. The disadvantage of this technique is that it is operator dependent to accurately localize the MRI findings onto real-time ultrasound localization compounded with the distortion of the prostate gland anatomic topography between the time of the MRI study and the TRUS evaluation. Furthermore, TRUS is acquired in two-dimensions at differing oblique planes, fanning through the tissue, whether performed in the end-fire or side-fire mode of image acquisition, compared to truly parallel axial images from the diagnostic MP-MRI study. Despite these disadvantages, higher cancer detection rates have been shown in patients undergoing cognitive fusion to guide biopsy compared to systematic biopsy approaches without any MRI direction or targeting (20-22).

Software-based MRI to TRUS fusion biopsy

Software-based co-registration of MP-MRI and TRUS has allowed for three dimensional MRI segmentation and three dimensional ultrasound renderings to be fused for an overlay that allows for real-time TRUS to guide needle placement to areas of MRI suspicion. In this workflow, MRI segmentation of intraprostatic regions of interest that are outlined can be visualized during the TRUS at the time of the biopsy procedure. Hence, a high correlation between MRI findings and TRUS targeting of the same regions can be achieved while allowing for a biopsy to be done in the routine setting of an office-based procedure (23,24). The capability of performing software-based MRI/TRUS fusion biopsies in an outpatient setting under local anesthesia is similar to the cognitive fusion technique. However, studies have shown that the software-based fusion biopsy platform provides improved accuracy detection rates compared to systematic biopsy and outperforms the increased detection rendered by using the cognitive fusion approach alone (12,25-27).

Software co-registration of MRI and ultrasound

Software-based fusion biopsy systems accomplish the co-registration of diagnostic MP-MRI and ultrasound imaging via rigid and/or elastic fusion. This co-registration is the essential step in fusion whereby a predetermined three dimensionally segmented MRI prostate volume is "fused" or matched with the three-dimensionally acquired ultrasound prostate volume. Fusion is accomplished by matching for internal and external fiduciary landmarks (rigid fusion), surface rendering to compensate for tissue deformation of pliable tissues (elastic fusion), or both (combination of rigid and elastic registration). This accounts for changes in prostate volume for each case in terms of anatomic orientation and deformation between the time of the MP-MRI and the TRUS performed at the time of biopsy. Rigid transformations allow for translational and rotational variations to co-register the images matching up landmarks including points, curves, and surfaces of the figures being overlaid. Alternatively, elastic transformations account for warping or scale changes to achieve improved surface overlay matchup. Of the commercially available software-based MRI/TRUS fusion biopsy devices, some combination of rigid, elastic, or combined co-registration is employed.

Once MRI and ultrasound images are co-registered, or fused, location tracking is achieved through a number of different mechanisms depending on the commercially available technology. Some fusion biopsy devices use electromagnetic tracking while others use mechanical arms with encoded joints calculating distance and trajectory from a fixed point of reference (5). In all cases, the technology depends on motion across the volume of the prostate gland after co-registration is achieved, hence the fusion step is

the most important to have accurate biopsy targeting of the predefined regions of interest from the MP-MRI study. Furthermore, software-based fusion biopsy platforms allow for mapping of needle biopsy locations in the three dimensional field, providing documentation for cases of future confirmatory biopsies.

Pathology confirmation of MRI to ultrasound software fusion

The co-registration of MRI and ultrasound inherent to fusion biopsy has been investigated in detail during the development phase of these technologies from an engineering standpoint. Countless clinical correlates have allowed for validation of the accuracy of these techniques.

The overall ability of MP-MRI to accurately diagnose prostate malignancy has been established through various platforms. Several studies have validated MP-MRI imaging findings by comparing them directly to post radical prostatectomy specimens. Turkbey and colleagues performed a prospective study involving 70 patients with biopsy proven prostate cancer. Prostate indication MP-MRI of the prostate was performed on these patients within a mean of 86.5 days. Imaging was then followed by radical prostatectomy within 180 days. All lesions, not just index, were included for their analysis accounting for greater than 500 lesions identified on T2W MRI in this population of patients undergoing radical prostatectomy. With an analytic method used to account for errors due to potential gland distortion, this study found that sensitivity and specificity for detecting lesions using T2W MRI alone was 0.73 and 0.89 respectively. Overall 80% (56 of 70) of patients were staged correctly (28).

Another study by the same group investigated accuracy of MP-MRI in determining tumor volume. In this study, 135 patients underwent MP-MRI of the prostate followed by prostatectomy within 60 days. Results showed a strong correlation between MRI tumor volume and tumor volume on final pathology with a Pearson coefficient of 0.633 ($P<0.0001$). A receiver operating curve analysis revealed that MRI tumor volume was highly accurate in determining tumor volume on radical prostatectomy histopathology tumor volume with an area under the curve of 0.949 ($P<0.00001$) (29).

Based upon the pathologic correlation between MP-MRI and radical prostatectomy pathology, fusion biopsies were developed. One of the initial software-based fusion devices which employed electromagnetic tracking was tested in the setting of prostate phantoms as part of its development. Three-dimensional spatial accuracy was measured using CT imaging of the phantom with needles in place after MRI and TRUS fusion to target needle placement. The degree of needle placement error was less than 2.5 mm on average with a maximum error measured at 4.8 mm (30). Since this early study in the development phase of MRI to ultrasound fusion, a combination of rigid and elastic transformations as well as algorithms for motion compensation have been integrated into most commercially available fusion biopsy platforms to further enhance the accuracy and precision of needle targeting.

True validation of MRI findings can be difficult due to changes associated with the pathologic processing of radical prostatectomy specimens. Prostatectomy specimens after removal may deform due to loss of surrounding supporting tissue. In addition, the fixation process and slicing of tissue is known to cause loss of volume and specimen deformation, respectively. Also, MRI has been shown to underestimate the volume of cancer foci within the prostate gland (31,32). Despite these limitations, MRI and ultrasound image co-registration has proven to augment the yield of targeted biopsy with significant efficiency over systematic biopsy (33). Furthermore, patients who have undergone MRI/TRUS fusion guided prostate biopsy who have then proceeded to radical prostatectomy have been investigated by several groups. These studies have shown findings supporting more accurate grading and staging based upon a targeted biopsy approach after imaging co-registration (34,35).

A recent study investigated the cancer detection for using different tangential planes with TRUS to perform biopsies with an end-fire TRUS probe. No significant difference in cancer detection was demonstrated whether targeted biopsy samples were taken in the axial or sagittal approach. However, an increased prostate volume was predictive of discordance in cancer detection between the two planes of sampling (36). This suggests that lesion localization with MRI and ultrasound fusion has a greater rate of error in larger prostate glands because the focal point of interest proven to be cancerous on one needle biopsy targeted to that area had higher likelihood to not be resampled in the tangential plane approach in cases of larger prostate gland co-registrations. Despite this finding, higher concordance was seen in cases with higher MRI suspicion score, suggesting spatial inaccuracies in imaging co-registration could be overcome based upon lesion size and more defined

imaging characteristics, which together yield a higher level of imaging suspicion.

In a population of men with active surveillance criteria prostate cancer, an analysis of tumor volume on MRI was compared to linear length of tumor found on biopsy cores taken via an MRI/TRUS fusion approach compared to concurrent systematic biopsy (37). The findings demonstrated a much higher correlation of highest percentage core involvement and corresponding tumor length between the diagnostic MRI lesions and biopsy cores obtained via the co-registration of MRI and TRUS for targeted biopsy. In comparison, the standard systematic biopsies had no such significant correlation. In addition, other studies have investigated the correlation between MP-MRI with no suspicious lesions or low-suspicion lesions and MRI/US fusion guided biopsy pathology. These studies have demonstrated a high negative predictive value of MP-MRI, allowing for confidence in counseling patients to pursue active surveillance or potentially defer to a longer interval biopsy sampling protocol (38-40). In cases of MRI/US fusion guided biopsy with all benign prostate pathology, the likelihood of subsequently finding significant cancer on follow-up biopsy is very low, further supporting the accuracy of the co-registration and targeting process (41).

Numerous studies have validated the use of MP-MRI and ultrasound co-registration, allowing for superior prostate cancer localization and detection over standard sextant TRUS guided biopsy. Future directions include utilization of this fusion technology for more tailored and targeted cancer treatments. The realm of imaging for detection and accurate risk stratification is ripe for not only presurgical planning, but also a platform for focal therapies or targeted boost therapies in prostate cancer management.

Conclusions

Software-based fusion platforms have been designed with a very accurate co-registration between MRI and ultrasound imaging. This allows for accurate and precise targeted biopsy, which has been proven to outperform systematic biopsy in the detection of clinically-significant foci of prostate cancer with the use of less biopsy cores. This has been validated on both targeted biopsy pathology as well as radical prostatectomy pathology specimens.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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