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Review Article

The Role of MRI-US Fusion Techniques in Detection of Clinically Significant Prostate Cancer

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ABSTRACT

Prostate cancer is the commonest male cancer and the second leading cause of cancer-related death in men. Over many decades, prostate cancer detection represented a continuous challenge to urologists. Although all urologists and pathologists agree that tissue diagnosis is essential especially before commencing active surgical or radiation treatment, the best way to obtain the biopsy was always the big hurdle. The heterogenicity of the tumor pathology is very well seen in its radiological appearance. Ultrasound has been proven to be of limited sensitivity and specificity in detecting prostate cancer. However, it was the only available targeting technique for years and was used to guide biopsy needle passed transrectally or transperineally. Magnetic Resonance Imaging (MRI) has revolutionized the process with the advent of its multiparametric imaging (mp MRI) where the prostate is evaluated by different MRI techniques and the likelihood of the detected lesion is scored using the new prostate imaging-reporting and data system (PIRADS) scoring. Despite the improved detection of clinically significant prostate cancer by mpMRI, the ideal way to target the area of suspicion detected by mpMRI is the next level of challenge. In this review article, we will discuss the recent methods of targeting and focus on the different platforms used to integrate the mpMRI static images with the real-time US scanning in what is called (US-MRI fusion techniques).

Introduction

According to the Australian Institute of health and welfare, prostate cancer (PCa) was the most commonly diagnosed cancer in men in 2017. The number of registered cases was 16,665, and the estimated risk was 1 out of 7 before the age of 85. Moreover, it recognizes PCa as the second leading cause of cancer deaths in Australian men (3,452 deaths in 2017) with a death risk of 1 in 30 (1).

Screening and diagnosis of PCa have changed greatly over the last decades. Whereas digital rectal examination of the prostate (DRE) was the main tool for screening and guiding prostate biopsies before the 1980s, the discovery of prostate-specific antigen (PSA) and the introduction of PSA test as a screening and diagnostic aid for PCa has increased the number of patients diagnosed with the disease dramatically.

Both techniques, however, have their drawbacks.

DRE depends greatly on the clinician's experience and can detect tumors in the posterior aspect of the gland mainly. PSA, on the other hand, is organ-specific but not disease-specific. Studies showed that the use of DRE alone failed to reduce disease-specific mortality (2). Disease detection at earlier stages and disease-specific mortality was greatly improved with the use of PSA as a screening and diagnostic tool. However, a major side effect was the increased detection of clinically insignificant prostate cancer (3).

Transrectal prostate ultrasound examination (TRUS) was initially introduced and used for screening of the prostate for possible

cancerous lesions. Later, it was used to guide the biopsy needle through the prostate to sample suspicious areas. A hypoechoic area was traditionally considered an area of interest. Although this has increased the PCa detection rate by up to 66%, it was associated with high false-negative rates due to the inability of the ultrasound greyscale to differentiate between benign and malignant pathologies of the prostate (4). Aiming at improving the yield of TRUS-guided prostate biopsy, biopsies from different parts of the prostate in a systematic way were added to biopsies targeting areas of interest (5).

To improve cancer detection rates, TRUS-guided prostate biopsy has witnessed many evolutions in terms of the approach to the prostate (transrectal vs. transperineal) and the number and sites of the cores taken. Different centers adopted different schemes, but unfortunately, none is considered ideal and accepted by all clinicians, and cancer detection rates continue to range between 33% and 44%. In addition, many of these cancers are clinically insignificant (6-8). Because of the above-mentioned limitations, and for years, PCa was considered the only solid organ tumor in the body that's diagnosed by random biopsies rather than targeting the tumor mass itself.

Repetition of TRUS-guided prostate biopsy due to high clinical suspicion after a prior negative biopsy detected 10-25% more cancer cases (9,10). This fact, in combination with the finding that prostate cancers showed higher grade in prostatectomy compared to biopsy specimens in 36% of cases (11) lead to the realization of the need to improve TRUS guided biopsy techniques and find better imaging modalities.

Role of MRI in PCa

MRI was used primarily to stage PCa in patients diagnosed with the disease in terms of local (extracapsular extension and seminal vesicle involvement) and distant (lymph node and other organs involvement) staging. Its role in diagnosing primary intra-prostatic disease was limited (12,13). In 1998, D'Amico and coworkers showed that the use of endorectal coil (ERC) allowed better detection and characterization of prostate cancer in clinically localized disease (13). ERC was then showed to better detect local recurrence after radical prostatectomy (14). In addition to ERC, technical improvements in MRI resulted in the use of higher magnetic field strength (3 Tesla) and significant signal-to-noise reduction. Over the last few years, different modalities of MRI imaging were investigated for accuracy in detecting and staging PCa. The list includes but is not limited to T2 weighted (T2W) images, dynamic contrast-enhanced images (DCE), diffusion-weighted images (DWI), and magnetic spectroscopic imaging (MRSI) which detects the levels of choline and citrate in the lesion. When two or more of these parameters are used, the MRI is called multiparametric MRI (mpMRI). As each of these techniques has its strengths and weaknesses, combining more than one technique would be expected to result in better sensitivity and specificity. Over the last few years, many studies demonstrated the higher accuracy of mpMRI in detecting and staging PCa (15-19).

Of the major advantages of mpMRI is its ability to detect tumors of the anterior and central parts of the gland which are usually under-biopsied during TRUS-guided prostate biopsy (20).
Consequently, current guidelines recommend the use of mpMRI for patients with negative biopsy results and high clinical suspicion of PCa only (21).

To minimize the inter-reader discrepancy in interpreting mpMIRs, the European Society of Urogenital Radiology (ESUR) has introduced a structured reporting scheme for prostate mpMRI based on the BI-RADS system used for breast carcinomas. The prostate system is called prostate imaging-reporting and data system (PI-RADS) and was first published in 2012. A second version of which has been published recently in collaboration with the Americal College of Radiology and AdMeTech Foundation (22-24). This system relies on a Likert scale and ranges from 1 to 5 to help risk-stratify patients with suspicion of harboring prostate cancer.
Types of MRI guided prostate biopsy:

As many studies proved the accuracy of mpMRI in detecting and risk stratifying prostate cancers, a considerable effort has been made to incorporate it in the management guidelines for patients with suspicious prostate lesions, especially when some studies succeeded to relate the apparent diffusion coefficient (ADC) value measured on DWI sequence and tissue histology (19). MRI has been tested when used by itself to target the lesion or in association with TRUS.

Three different techniques of mpMRI-aided targeting of prostate lesions have been studied:

A. In-bore MRI guided prostate biopsy
B. Visual (cognitive registered) MRI-US fusion biopsy
C. MRI/US software-based fusion biopsy.

In-bore MRI guided prostate biopsy

After obtaining a diagnostic mpMRI and a suspicious lesion is found, the patient is taken back to the MRI scanner. While the patient is in a prone position, the biopsy needle is placed into the area of interest inside the prostate. Needle positioning is confirmed by repeating the MRI scan after each adjustment of the needle position until a satisfactory position inside the lesion is confirmed, biopsies are then taken from that area. In this technique, only target biopsies are taken, and it can be done through a transrectal or transperineal approach using ERC or an external coil only (25-27). This technique is considered the best in terms of confirming the needle position inside the area of interest. It, however, has many disadvantages. Time and cost of repeating scans are not the only issues, it requires special equipment that needs to be magnetically inert. In addition, systematic biopsies are not taken at the same session. Clinician experience and the slow learning curve is another issue as most of the urologists are well trained on the transrectal and the transperineal US-guided prostate biopsy which is available in most if not all teaching centers, unlike MRI-guided biopsy which is available in specialized centers only. A few studies reported on the use of in-bore MRI-guided prostate biopsy and showed a detection rate of clinically significant prostate cancer between 20% and 80% (27-30). Hambrock and colleagues compared in-bore MRI-guided with TRUS-guided biopsies and reported a significantly better detection rate in MRI-guided biopsies. They used radical prostatectomy specimens as a reference for comparison (31).

Visual (cognitive registered) MRI-US fusion prostate biopsy:

In this technique, the radiologist, after interpreting the mpMRI, draws a diagram of the prostate gland and locates lesions according to their site, size, and PI-RADS score in the diagram. Clinicians then use the mpMRI images and the diagram to register in their minds the site(s) of the lesion(s), and their personal experience to target these sites during a standard TRUS-guided prostate biopsy. Thus, it requires no more resources than the standard TRUS-guided biopsy, and it enables the clinician to sample all parts of the prostate in what's called systematic biopsies in addition to target biopsies. The major drawback of this technique is being very operator-dependent. It relies on the operator's ability to reflect the MRI images on the

actual zonal anatomy of the prostate. This in turn results in high variability and low reproducibility of the technique among urologists.

Comparing visual MRI-guided prostate biopsy to standard 12 core TRUS biopsy, both Haffner and Park and their coworkers demonstrated that more clinically significant prostate cancers (16% more Gleason 4 and 5 cancers) were detected when MRI images used to pre-plan targeting (32,33).

MRI/US software based fusion prostate biopsy:

In a trial to combine the accuracy of mpMRI images and real-time scanning of US, scientists came out with the idea of MRI/US FUSION. The main concept is to use the MRI to localize the tumor (or area of interest) in the prostate and use the TRUS to guide the biopsy needle into that area. In this way, the clinician can avoid the time and cost drawbacks of in-bore MRI-guided biopsy and take the advantages of TRUS biopsy without relying too much on personal experience in targeting areas of interest. Computer software will create a prostate model from MRI images and merge it with the model created from the US scan in a process called fusion. In this technique, the target biopsies can be taken more precisely from areas of interest inside the prostate without confounding the systematic biopsies.

This technique is of great interest to clinicians and scientists now and is rapidly evolving. The focus is put on the way the MRI and US prostate models are contoured and fused. The shape of the same prostate can differ in different patient positions and of course with the insertion of ERC or TRUS. Image registration should take into consideration this shape deformation to ensure precise fusion. Certain landmarks can help ensure adequate image fusion, these include prostate apex, base, outer curves, seminal vesicles, and even intraprostatic landmarks like cysts or calcifications. Any landmark that can be identified in both MRI and US images can help maximize the accuracy of fusion.

Two types of image fusion currently exist, rigid or elastic. In rigid fusion, the images themselves are not deformed but can be rotated around different axes to align them together. In this method, the image integrity is maintained but the images may look ugly and distorted. Inelastic fusion, on the other hand, the images themselves can be modified to account for deformations created by the positional changes or ECR and TRUS probe. The anatomy in this method is altered by the computer to find the best match between MRI and US images. In both rigid and elastic fusion, the software usually allows for operator corrections and adjustments to improve the match. This step may account for errors and depends on the operator's experience again. The extent of this operator input is another difference between various fusion platforms.

Biopsy needle driving is the other difference between available fusion platforms. In some platforms, the needle direction and depth of penetration is under the operator control, while in others it is totally under mechanical control of a robot-driven mechanical arm.
In addition to the main differences outlined above, fusion platforms also differ in motion compensation, the margin of human input, the number of steps requiring manual input to create and fuse the models, the way they display the MRI and US models (side to side or superimposed), and complexity of user interface.

UroNav platform was the first rigid fusion platform to gain USA FDA approval in 2004, while Artemis platform was the first elastic fusion platform to get approval in 2008. Since then many platforms have advertised and popularized.

The workflow for all the platforms is basically similar. It starts with interpreting the diagnostic mpMRI by an experienced uroradiologist to mark areas of interest according to the PI-RADS system, the MRI prostate model then contoured, and the areas of interest are delineated inside the model. Some platforms will just superimpose this model over the US real-time scan images or display them side to side. Other platforms will create a US model and fuse the two models before allowing biopsies to be taken. Biopsy taking is then either done totally by the operator or is controlled by an automated arm that controls the needle positioning and depth of penetration.

Lesion size on MRI remains the main limitation of MRI/US fusion biopsy platforms. Other limitations include variability in mpMRI interpretation and the accuracy of image fusion (34).
Many studies were published in relation to MRI/US fusion biopsy to assess different platforms and compare it with one or more of the other prostate biopsy techniques.

Moore et al (2013) compared the three types of targeted prostate biopsy (In-bore MRI, cognitive fusion, and MRI/US software fusion) with systematic prostate biopsy and reported that target biopsies were able to detect more than 33% more men with clinically significant prostate carcinoma (35). Logan and colleagues in their systematic review (2014) included nine studies on 6 different MRI/US fusion platforms and concluded that MRI/US fusion target biopsies detected more clinically significant cancers than systematic biopsies (34). Gayet et al. performed another systematic review and included 11 studies in relation to MRI/US fusion biopsy platforms with seven different platforms studied. They reported no better overall cancer detection rates, however, fusion target biopsy detected significantly more clinically significant cancers (36). Similar results were reported by Wegelin and his team in their recent systematic (2017) review (37).

The Biobot (iSR'obot™ Mona Lisa) system:

Is a robotic transperineal prostate biopsy system with MRI/US fusion software (Urofusion™, Biobot surgical, Singapore). It uses elastic fusion technology to fuse the MRI-based prostate model with that of the US scan. The T2 transverse MRI image series is imported into the system and used to create the MRI model of the prostate. The operator defines the prostate apex, base, and prostate outline on some of the slides, then the system will semi-automatically create the model. The operator then marks the lesions on that model. This system uses a probe sheath for the TRUS probe to move inside the rectum to obtain a smoother scanning with minimal prostate deformation during probe motion. Once the TRUS is inserted, the prostate is scanned, and a US prostate model is created with the options to do a 1mm or 0.5 mm slice thickness. The two models are then fused. A 2D and 3D views of the fusion model are created to help the operator get a better impression of what the prostate looks like in reality and enhance the biopsy plan. The system itself would then assign the number and sites of target and systematic biopsies, but this can be modified by the operator. The operator can see the details of proposed core biopsies in the prostate model and go back to modify them every time until he/she is satisfied with the biopsy plan. A dual cone approach is used by the system that uses one skin puncture to pass the biopsy needle and take all the cores of one lobe. This is hypothesized to minimize pubic arch interference and enable complete prostate coverage in addition to minimizing post-procedure pain and infection. The software itself is built to accommodate for prostate movement during the procedure to minimize errors. The

robotic arm will control the direction and depth of the biopsy needle, but the actual targeting is made by the operator.

By the end of the procedure, the system will print an automatically generated report with photos of the targeting process which is helpful for reproducibility in case of repeating the biopsy especially for patients on active surveillance.

Mona Lisa Biobot system was introduced by Ho et al. in 2011 and has obtained the FDA (USA), CE (Europe), and TGA (Australia) approvals (38,39). Although the first version of this device was designed for mapping biopsies, the current version is regarded as the first full-robotic system with control of needle direction and depth (39).

Conflict of Interest

No conflict of interest.

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