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INVITED CLINICIAN'S WORKSHOP

Prostate Cancer

Targeted prostate biopsy using magnetic resonance imaging-ultrasound fusion

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Prostate cancer is the second most common cancer among men worldwide, with an estimated 1.1 million new diagnoses and over 300,000 deaths reported in 2012 by the World Health Organization. A recent 5-year prevalence of the disease was nearly four million, far exceeding all other malignancies in men.[1] Because of these numbers, efforts to improve early detection, accurate assessment of disease burden, and appropriate treatment options are important public-health priorities. However, the basic tool for diagnosis, transrectal ultrasound (TRUS) guided biopsy, is flawed by failure to detect many serious cancers (>30% false negative rate)[2,3] and over-detection of nonserious cancers. Multiparametric magnetic resonance imaging (mpMRI) of the prostate empowers the clinician to identify tumors that would otherwise be missed by conventional techniques and to record the precise locations of positive cores through targeted biopsy using MRI-ultrasound (MRI-US) fusion. As mpMRI advances and the level of experience for the user grows, the correlation between the level of suspicion for a prostate lesion and the MRI-US fusion targeted biopsy revealing malignancy improves. Consequently, the concordance among the targeted biopsy and surgical pathology rises. This in turn, allows the patient and provider to be confident that the therapeutic plan decided upon is representative of the true disease state.

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TECHNIQUE

Various predictive tools and tests have been utilized to help urologists counsel patients regarding the need for a prostate biopsy, as well as the potential aggressiveness of their disease. Renditions of prostate-specific antigen (PSA) that help counsel a patient on forgoing or obtaining a biopsy include PSA density, PSA velocity, Free PSA %, and Prostate Health Index. Lately, genetic testing has emerged as an additional option in the urologist's armamentarium. Hologic's Prostate Cancer Gene 3, Myriad Genetic's Prolaris and Genomic Health's Oncotype Dx are genetic tests that examine the urine or prostate biopsy tissue to help delineate the potential aggressiveness of the disease. Technology has also paved the way for improved prostate imaging with the hope of defining benign or malignant changes in patients undergoing prostate cancer screening and to track the areas of concern over time. Techniques have included variations of US, computed tomography, MRI, as well as positron emission tomography imaging.[4] Regardless of imaging choice, the goal is to extend beyond the limitations of blind biopsy for those at risk, by detecting more clinically relevant cancers, identifying the location of these cancers, decreasing patient morbidity, and aiding in the development of a safe and effective treatment plan.

Multiparametric magnetic resonance imaging has become the imaging of choice by many practitioners including the urologic surgeon since the advent of the 0.35 T magnet.[5] Now, diffusion-weighted imaging (DWI), dynamic contrast-enhanced (DCE), and spectroscopic imaging have supplemented the simple T2-weighted imaging (T2-WI) to improve cancer detection as well as staging.[6] mpMRI compared to standard 12 core biopsy has been shown to increase the number of positive cores, men diagnosed with more than 1 core, and proportion of men diagnosed with clinically relevant prostate cancer.[7] Preoperative/preprocedural counseling, active surveillance (AS) monitoring, and intraoperative planning rely on the capability of mpMRI. However, biopsy remains the gold standard at diagnosing prostate cancer despite available imaging, blood and genetic testing. It is up to the provider how the tissue is obtained and how mpMRI can be incorporated into this process.

Three different methods have been described in order to perform a targeted prostate biopsy by fusing MRI: MRI-MRI fusion (also called in-bore biopsy) and MRI-US fusion which includes both device and cognitive fusion. In-bore biopsy implies the patient is physically in the MRI tube obtaining his biopsy. Despite the accuracy of utilizing real-time MRI to place the needles into the areas of concern, this method can be time-consuming as well as expensive since an additional MRI is needed at the time of biopsy. Often, systematic biopsies are avoided while only areas of concern are biopsied.[8] Although the negative predictive value for excluding Gleason grade (GG) ≥7 tumors approaches 100% in some studies, true systematic biopsies are still essential to identify smaller and lower grade tumors.[9,10] Cognitive fusion is performed by simply reviewing the location of suspicious lesions on MRI and targeting them under US. This does not enable biopsy core mapping or three-dimensional reconstruction. As an alternative, the MRI of the prostate can be stored in a device then fused with real-time US creating a three-dimensional model of the prostate permitting the aiming and tracking of core sites.[8] Device fusion generates a single

image from multiple images generated by a 3T transabdominal multiparametric T2-WI, DWI, and DCE MRI with a biplanar US, improving the selection of worrisome lesions as well as ensuring an adequate systematic biopsy (**Figure 1**). A prospective trial, though small in sample size, showed similar cancer detection rates between cognitive and device fusion target biopsy, but there remains concerns of the intraoperative user being capable of targeting small lesions without the tracking capability and digital overlay.[11]

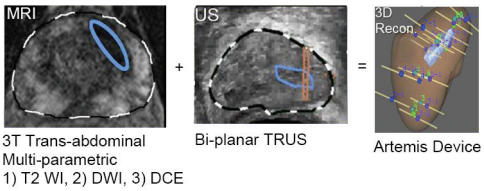

Figure 1: Targeted biopsy of the prostate using magnetic resonance imaging (MRI-US) fusion. Multiparametric MRI was performed including T2-weighted imaging, diffusion-weighted imaging, and dynamic contrast-enhanced to identify suspicious areas. The MRI can be stored in a device like Eigen's Artemis, then fused with real-time US creating a three-dimensional model allowing for biopsy mapping and tracking.

COMMENT

Controversy still exists when it comes to the treatment of localized prostate cancer. With the results of the Prostate Cancer Intervention versus Observation Trial demonstrating no overall benefit in prostate cancer-specific survival for patients who underwent radical prostatectomy compared to those who were simply observed, treatment of prostate cancer has been extensively questioned. Of note, over 65% of these patients had low-risk disease and patients were followed for almost 12 years.[12] Conversely, the survival advantage was clearly seen in patients under 65 years old who had intermediate-risk disease as shown in the Bill-Axelson "Radical prostatectomy or watchful waiting in early prostate cancer" paper. Now, the follow-up was over 23 years with an ever increasing benefit of treatment seen the longer patients were followed as supported by the difference in overall survival outcomes between 2011 and 2014 publications.[13] Granted, these patients were not diagnosed with targeted biopsies, but it does emphasize the importance of adequate grading, staging, and follow-up. As definitive treatment for low-risk prostate cancer falls out of favor as supported by recent literature, AS becomes a viable option for these patients. But, the provider as well as the patient, need to be confident that the grade and stage of prostate cancer are accurate when enrolling in an AS program. Over 100 men with low-risk prostate cancer according to Epstein criteria underwent an mpMRI guided targeted biopsy using the Artemis device (Eigen, Grass Valley, California, USA) after being enrolled in AS at the University of California Los Angeles (UCLA). Areas of suspicion on mpMRI-US fusion were graded by suspicion level and biopsied at 3 mm intervals. Patients also underwent 12 systematic cores which were tracked and mapped. Initial targeted biopsy resulted in reclassification of 36% of men, including 23% due to GG 6 or greater and 13% due to high volume Gleason 6 disease further supporting

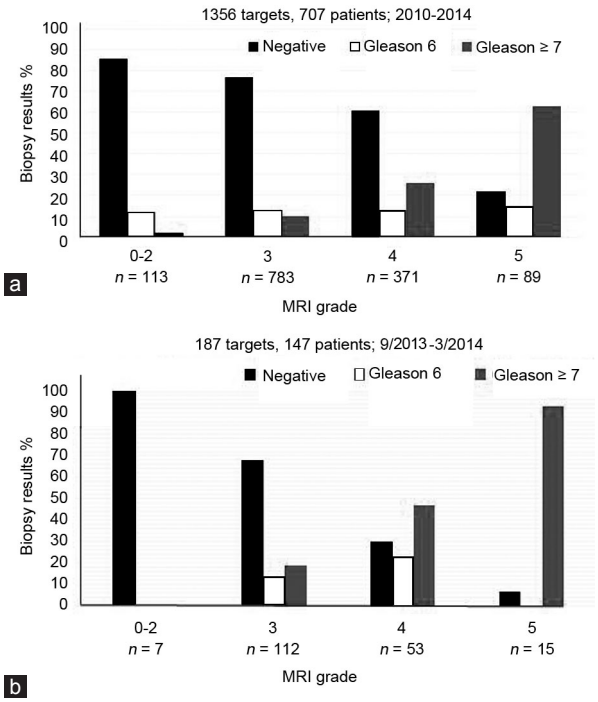

Figure 2: Targeted biopsy using magnetic resonance imaging (MRI)-ultrasound fusion correlating biopsy histology with MRI grade of suspicion, 5-year period (**a**) and a recent 6-month period (**b**). The recent data (**b**) indicate improved reliability of the grading system versus prior data (**a**). A learning curve is appreciated.

the importance of properly selecting patients for AS and identifying the ones that could benefit from definitive therapy.[14]

As many men are reclassified after their initial targeted biopsy, there are patients who have fallen victim to previous negative biopsies despite harboring clinically relevant disease. Over a 5-year period, 1097 targeted including 12 core systematic mapping biopsies were performed in 839 men using the Artemis device at UCLA. Intermediate-high grade cancers GG ≥ 7 were diagnosed in 159 patients (19%). 91 (10.8%) underwent their first biopsy but for 43 (5.1%) and 25 (3.0%) patients, they had underwent 1–2 or ≥3 biopsies. Many of these patients go on to receive definitive treatment. But, for those who are found to have low-risk disease or confirmed to have only low-risk disease by their targeted biopsies, the patients and physician can be confident when selecting AS versus definitive treatment.

Multiparametric magnetic resonance imaging has evolved over the last 30 years along with the various treatment options for prostate cancer. The addition of DWI and DCE has improved the accuracy of detecting extracapsular extension and seminal vesical invasion.[15,16] Often times, mpMRI is used for preoperative consultation, but intraoperative decision-making can be influenced as well. The use of mpMRI for intraoperatively planning during robotic assisted laparoscopic radical prostatectomy has helped decrease positive surgical margins and improve preservation of the neurovascular bundles compared to the clinical parameters alone.[17] As technology changes and clinicians become

more accustomed to a particular procedure or a certain image modality, accuracy, and outcomes will improve. This pertains to reviewing the mpMRIs. Over a 5-year period, 1356 targeted biopsies were performed on 707 men. The radiologist uses a combination of T2-WI, DCE, and DWI to create a score that signifies the overall level of suspicion for a lesion; 1–5, with 1 being normal and 5 representing a very highly suspicious lesion. For a target lesion with an overall suspicion level of 3, roughly 80% of the targeted biopsies were negative, 11% were GG 6, and 9% were GG ≥7. Now for an overall level of suspicion of 4, the biopsies that were negative, GG 6, or GG ≥7 were 60%, 15%, and 25%, respectively. To no surprise, an overall level of suspicion of 5 results in a 20% chance of a negative biopsy, while finding GG 6 and GG ≥7 is 15% and 65% (**Figure 2a**). Compare these results with a more recent 6-month period during which, 187 targets were biopsied in 147 men. For an overall suspicion level of 3, 4, and 5, the probability of having a negative biopsy, GG 6, or GG ≥7 is 65%, 15%, 20% compared to 30%, 20%, 50%, and finally 5%, 0%, and 95%, respectively (**Figure 2b**). In a relatively short amount of time, the likelihood of a very high suspicious lesion yielding intermediate- to high-risk disease improved 30%, stressing the importance of continuity and consistency within the entire urologic care team.

There are a number of benefits mpMRI offers when caring for the patient whose cancer is suspected or who has already had a diagnosis. But, there certainly are limitations underscoring the need for a true systematic mapping biopsy. When there are no areas of interest on mpMRI and targeted biopsy is not feasible, a systematic mapping biopsy can still be performed using the Artemis (Eigen, Grass Valley, California, USA). The limitations of the traditional systematic 12 core biopsy include under-detection as well as poor correlation with the prostatectomy specimen. The labeled biopsy location often differs from the tumor location on final pathology supporting the fact that US alone is unreliable.[18] Furthermore, a negative MRI does not eliminate the possibility of clinically relevant disease despite other publications claiming high negative predictive values for suspicious mpMRI lesions.[9,10] In 189 biopsies performed at UCLA (17% of patients) where no target was identified on mpMRI, 26% had GG 6 disease while 20% harbored GG ≥7. As the adoption of mpMRI of the prostate becomes more prevalent, there has been an unmerited push for imaging to replace biopsy in men on AS. At our institution, a frequent multidisciplinary conference takes place where pathology, radiology, and urology evaluate and discuss all mpMRIs as well as the corresponding whole mount prostatectomy specimens (**Figure 3**). The improved correlation between preoperative imaging and targeted biopsy is a direct result of this multidisciplinary conference. In patients that have a target lesion, the relationship between the target's pathology and the overall level of suspicion identified on mpMRI is strong. The concordance rate between the highest GG on targeted biopsy and the GG identified on whole mount pathology, the pathology that is found to be upgraded and the pathology that is downgraded, are 82%, 16%, and 2%, respectively (**Figure 4**).

CONCLUSIONS

With every new procedure, technique, or test, adoption rates lag behind unless a clear and safe advantage is evident. With the support of mpMRI, targeted biopsy using MRI-US fusion can improve detection and tracking of a patient's disease while reducing the apprehension of a negative biopsy or being on AS. Even though data show minimal benefit of prostate cancer treatment for low-grade disease and for older patients, many patients fall victim to unnecessary treatment. Technology will no doubt continue to push medicine forward, but with every incremental movement our duty is to evaluate how this will impact the patients. Targeted biopsy using MRI-US fusion increases confidence when placing a patient on AS or moving them toward definitive treatment due to accurate detection and staging, and also facilitates intraoperative planning. This technology will definitely serve as a conduit for targeted therapy and may replace conventional systematic biopsy altogether.

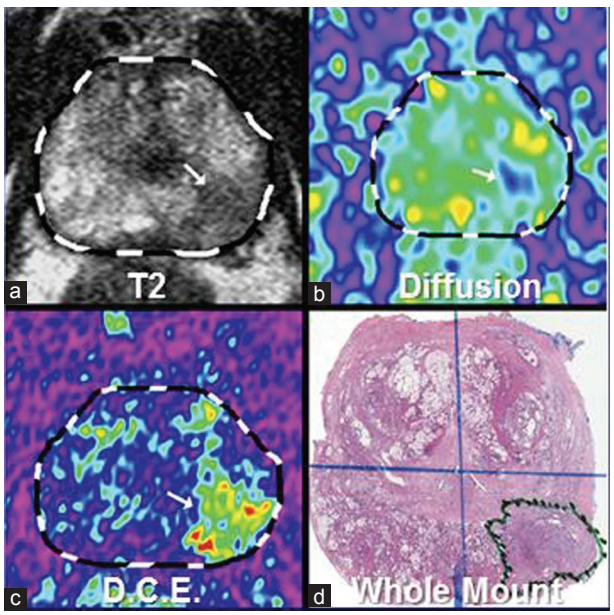

Figure 3: Multiparametric magnetic resonance imaging of a left peripheral prostate gland lesion on T2-weighted imaging (**a**), diffusion-weighted imaging (**b**), dynamic contrast-enhanced (**c**), and on whole mount pathology (**d**). Arrow directed toward lesion.

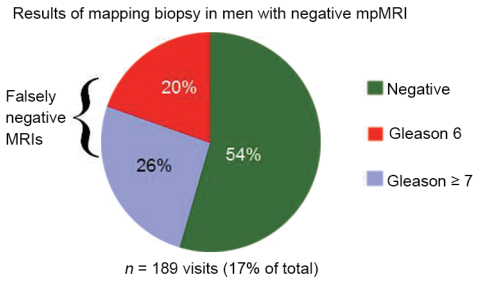

Figure 4: When biopsy is indicated clinically, the absence of a target lesion on multiparametric magnetic resonance imaging (mpMRI) should not obviate a systematic mapping biopsy. mpMRI failed to detect 20% of clinically relevant disease.

EDITORIAL COMMENT—(BY DR JOHN W DAVIS, DEPARTMENT OF UROLOGY, THE UNIVERSITY OF TEXAS, MD ANDERSON CANCER CENTER, HOUSTON, TEXAS, USA)

Many years ago, I became interested in MRI as a staging tool for planning robotic prostatectomy. Even with T2 weighted imaging you could practice reading the images yourself and training yourself to select nerve sparing with more information than just biopsy/PSA/clinical staging. However, the study interpretations were largely descriptive and inconsistent in formatting. Essentially you had to interpret report word-smithing such as "possibly suspicious," "suspicious," and "cannot exclude." My challenge to our radiology group was to make the prostate MRI similar to the Bosniak staging for cystic renal masses—on a numeric scale you could objectively communicate that a patient needed no action, follow-up imaging, or surgery. The tricky part of MRI has been coming up with a grading system that is universally validated and accepted. Today, we are much closer to this goal as Dr. Marks' team presents—high grade lesions can be treated with very high suspicion of significant cancer—over 60% in their system. Further validation of grading systems is still needed, and there remains significant barriers in this field in terms of rolling out effective technique across imaging centers, and costs. With the introduction of the multi-parametric technique, and easier access to imaging with reimbursement, patients with elevated PSA and prior negative biopsy or on active surveillance have improved options to characterize their situation better. Two further points deserve emphasis: 1) patients still need systematic biopsies as this paper demonstrates, and 2) placing a multi-parametric MRI in front of a primary biopsy remains a hotly debated topic that will no doubt evolve in the next few years.

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