REVIEW

MRI-targeted biopsy: is systematic biopsy obsolete?

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Introduction: *Although prostate cancer is the most common non-cutaneous cancer in men, it is traditionally diagnosed with a non-targeted, systematic transrectal ultrasound prostate biopsy (TRUS-Bx). This technique has been demonstrated to both under-detect clinically significant (CS) cancer and over-detect clinically insignificant cancer, and performs poorly in patients with a prior negative biopsy. With recent advances in MRI technology, most prominently the advent of multiparametric MRI, MRI-targeted prostate biopsy (MRI-TB) has been gaining favor as a more accurate alternative to TRUS-Bx. In this review, we attempt to summarize the current literature on MRI-TB and to determine if there is evidence supporting the use of MRI-TB alone.*

Materials and methods: *The literature was reviewed for articles pertaining to MRI-TB and its performance compared to systematic biopsy.*

Results: *Most studies support the increased sensitivity of MRI-TB (0.90, 95% CI 0.85-0.94) compared to TRUS-Bx (0.79, 95% CI 0.68-0.87) for the detection of CS prostate cancer, as MRI-TB can detect up to 30% more high risk and 17% fewer low risk cancers. MRI-TB also tends to perform better than TRUS-Bx in patients with prior negative biopsy, as TRUS-Bx may miss up to half of CS cancers detected by MRI-TB, and in those with lesions at atypical locations. However, as the technology for imaging and image-guided biopsies continues to develop, there is still a role for TRUS-Bx in the management of patients with prostate cancer.*

Conclusions: *Our analysis of the literature suggests that although MRI-TB is superior to TRUS-Bx, there is still a role for traditional systematic biopsy.*

Key Words: MRI-targeted biopsy, technique

Introduction

Prostate cancer is the only solid organ cancer that is traditionally diagnosed with a non-targeted biopsy technique.[1] Although transrectal ultrasound prostate biopsy (TRUS-Bx) is the standard of care, ultrasound alone is not adequate for targeting specific lesions, as 40% of these cancers are isoechoic.[2] The systematic sampling of the prostate on TRUS-Bx may only sample around 0.04% of the entire gland, and performs particularly poorly in apical and anterior regions.[3,4] Systematic biopsy results are upgraded 21%-54% of the time on final pathology after prostatectomy.[5] The overdiagnosis of low risk cancers also presents an issue, as TRUS-Bx has a tendency to detect higher rates of clinically insignificant cancer.[6] The limited diagnostic capability of TRUS-Bx has led to a search for alternative approaches to prostate biopsy.

Multiparametric MRI (mpMRI) is an upcoming modality for the diagnosis and staging of prostate cancer. As the use of mpMRI and MRI-targeted biopsies (MRI-TB) becomes more widely accepted,[7] a wealth of data has emerged supporting the benefits of a targeted biopsy approach, both for increasing detection of clinically significant (CS) cancers, and for decreasing the detection of clinically insignificant cancers. Further emphasis has been placed on mpMRI and MRI-TB due to the recent alterations in guidelines, which no longer recommend annual prostate-specific antigen (PSA) screening tests, prompting a search for alternative diagnostic approaches.[8,9] As imaging technology develops, prostate cancer diagnosis will continue to become more reliant on prostate MRI, and therefore MRI-TB.

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With the greater use of MRI-TB, the question arises- is there still a need for TRUS-Bx? In this review, we aim to analyze the available literature in order to determine whether MRI-TB alone is sufficient to adequately detect CS prostate cancer.

MpMRI

mpMRI of the prostate has been shown to be more accurate than standard imaging techniques not only for the detection of prostate cancers but also for the ability to identify higher grade cancers.[10] mpMRI generally consists of several modalities, including T2 weighted imaging, diffusion weighted imaging (DWI), dynamic contrast enhanced (DCE) MRI, and sometimes MR spectroscopy. Each of these modalities has its own strengths and weaknesses; however, combined, they produce sensitivity and specificity of 90% and 88% in the detection of tumor foci > 0.5cc, compared to histopathology after radical prostatectomy (RP).[11] When RP specimens were analyzed in patient-specific molds based on mpMRI images, the positive predictive value was as high as 98%.[12] In the recent PROMIS randomized control trial, the sensitivity of mpMRI was 93% in the detection of CS prostate cancer, compared to 48% for TRUS-Bx, although specificity was 41% and 96%, respectively.[13] In addition, in a series of patients with negative mpMRI, TRUS-Bx found CS cancer in 0% of biopsy naïve patients and 4% of prior negative biopsy patients.[14] The excellent diagnostic capacity of mpMRI forms the basis for the improved accuracy observed on MRI-TB.

MRI-TB

Techniques

MRI-TB involves the use of MR images to guide biopsy of specific areas in the prostate and can be accomplished in three ways: software fusion of MRI and ultrasound images (MRI-TRUS fusion biopsy), direct "in-bore" MRI biopsy, and cognitive fusion. MRI-US fusion biopsy is now the most widely used MRI-TB technique. This technique was designed as an office-based alternative to in-bore MRI-guided biopsy, and various platforms have been developed which will register a prior MR image to the ultrasound image visualized during the procedure.[15] Tumors that are found to be suspicious on mpMRI can be directly overlaid in-vivo, allowing for accurate targeting and concurrent confirmation of needle placement. In-bore MRI biopsy involves performing prostate biopsy in the MRI gantry itself. As with software fusion, biopsy needles can be visualized in real time. However, this procedure is time consuming and costly, and often necessitates general anesthesia. Cognitive fusion is the third form of MRI-TB in which the operator uses prior knowledge of prostate tumor locations on MRI to direct an ultrasound-guided biopsy. Although this technique does not incur the cost of a software fusion device, it requires significant proficiency on the part of the operator, resulting in a great deal of variability in performance.[10,15]

Cancer detection rates

One difficulty in the analysis of the literature on MRI-TB is the heterogeneous nature of studies, which vary

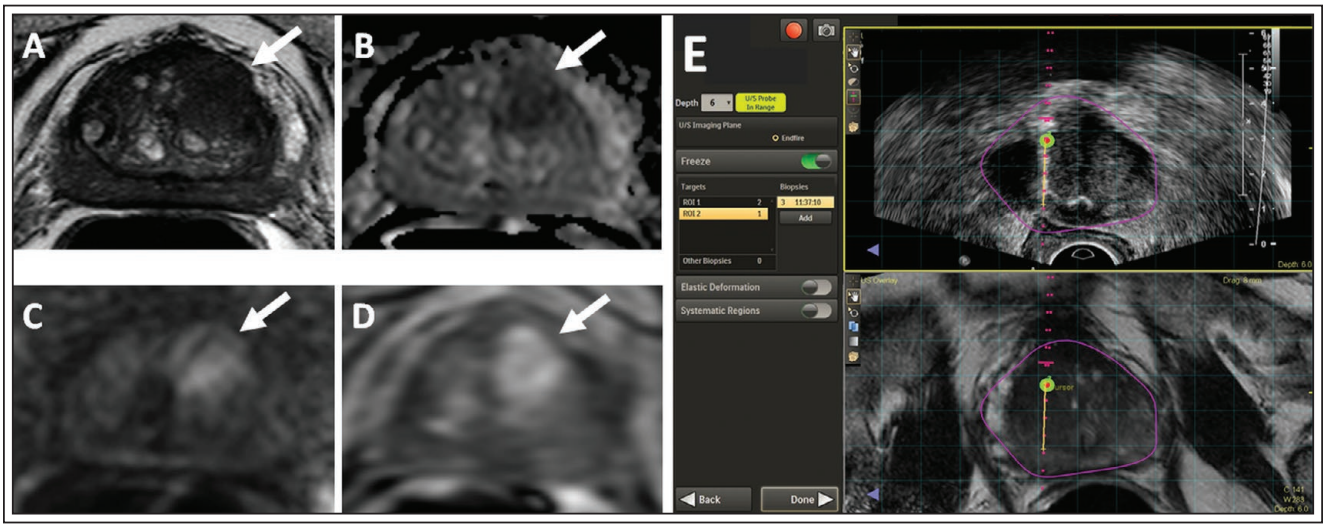

Figure 1. A 70-year-old man with serum PSA = 10.26 ng/mL and prior negative TRUS-guided biopsy. PIRADS 5 lesion seen on T2W MRI **(A)**, ADC map **(B)**, DWI **(C)**, and DCE **(D)** (arrows). Lesion was sampled via MRI-ultrasound fusion biopsy **(E)**, revealing Gleason 3 + 4 prostate cancer.

greatly in aspects ranging from patient population to the definition of "clinical significance." However, multiple systematic reviews, including a recent meta-analysis by Wegelin et al, have found that despite the wide range in the cancer detection rate (CDR) and CS CDR, both fusion biopsy and in-bore biopsy detected more CS cancers and tended to detect fewer clinically insignificant cancers compared to TRUS-Bx,[6,16-18] Figure 1. In addition to this overall improved performance, MRI-TB has also been found to have superior cancer detection in enlarged prostates, where standard biopsy has a higher risk of under-sampling the gland,[4,19] and in locations which are traditionally difficult to sample, such as anterior and midline regions.[20-22] Siddiqui et al were the first to demonstrate that MRI-US fusion biopsy had a similar CDRs to standard biopsy (46.0% versus 46.8%), but detected 30% more high risk and 17% fewer low risk cancers.[23] They concluded that MRI-US fusion was more accurate than TRUS-Bx or combined biopsy (MRI-US fusion + TRUS-Bx) for intermediate to high risk cancers, and that the supplementation of targeted biopsy with TRUS-Bx provided little additional benefit. In their 2015 study, Salami et al found comparable results, with similar CDRs for MRI-US fusion and TRUS-Bx, and a significantly higher CS CDR in fusion biopsy.[3] Although fusion biopsy performed remarkably well in their cohort, the investigators continued to recommend a combination of targeted and systematic biopsy. As with MRI-US fusion biopsy, Pokorny et al found that in-bore biopsy detected almost twice as many intermediate/high risk cancers compared to TRUS-Bx, and considerably fewer low risk cancers.[24] It is not surprising, considering the relatively poor performance of TRUS-Bx, that the majority of the literature suggests that MRI-TB is superior to TRUS-Bx in the detection of CS cancer, while simultaneously avoiding the overdiagnosis of clinically insignificant cancer.

False negative rates

It has been established that MRI-TB provides increased diagnostic accuracy, but is it accurate enough to stand on its own? What is the risk of forgoing standard TRUS-Bx? A 2015 study by Delongchamps et al concluded that only 4% of CS cancers would be under-detected by MRI-US fusion alone,[1] and several other reports have found similar rates of missed or misclassified CS cancer.[3,25,26] Furthermore, Siddiqui et al found that the addition of TRUS-Bx to MRI-US fusion only resulted in a 2% upgrade in risk category from benign or low/intermediate risk to high risk.[23] They calculated that the number needed to biopsy in order to detect one additional case of high risk prostate cancer on systematic biopsy was 200 patients, and that for every additional case of CS cancer detected, 17 cases of clinically insignificant cancer would also be detected. However, other studies have found higher false negative rates for fusion biopsy. In an analysis from Filson et al, TRUS-Bx revealed CS cancer in 16% of men with negative MRI, and in patients with positive MRI, fusion biopsy missed 18% of cases (compared to 21% TRUS-Bx).[27] Overall, however, the false negative rates of MRI-TB were relatively low, and tended to include a larger proportion of clinically insignificant cancers.

Randomized control trials

Most studies on the efficacy of MRI-TB are not randomized, and many are retrospective in nature. However, a recent randomized control trial by Baco et al of 175 patients compared an mpMRI positive cohort which received a combination of MRI-US fusion and TRUS-Bx, to an mpMRI negative cohort which received only TRUS-Bx.[28] The CS CDR for MRI-US fusion alone in the MRI positive cohort was not significantly different than the CS CDR of standard biopsy in the MRI negative cohort (38% versus 49%). In the positive MRI cohort, although MRI-US fusion missed 10% of CS cancers, it detected all cancers missed by TRUS-Bx, further demonstrating the unreliability of TRUS-Bx. This study was limited by a low sample size, use of a 1.5T magnet rather than a 3T, and lack of DCE on mpMRI. Although MRI-US fusion was not found to have significantly higher CS cancer detection compared to TRUS-Bx, it was able to detect CS cancers missed by TRUS-Bx.

A larger, randomized prospective study by Panebianco et al compared standard of care TRUS-Bx to a combination of TRUS-Bx and MRI-TB, with "targeted biopsy" defined as ultrasound targeting of the sextant containing the index lesion previously identified on mpMRI[2]. They enrolled 1140 men randomized in two cohorts: the first cohort underwent TRUS-Bx and the second cohort underwent prostate mpMRI followed by targeted and random biopsy. The CDR was much lower in the TRUS-Bx cohort compared to the targeted cohort (37% versus 73%). In addition, none of the patients with negative MRI and negative first biopsy were found to have CS disease on subsequent saturation biopsy (45 cores). Unfortunately, the data on MRI-TB was analyzed in combination with TRUS-Bx so it is impossible to assess the efficacy of MRI-TB alone. However, the substantial increase in cancer detection observed with the addition of MRI-TB speaks to its diagnostic benefit.

A third study by Arsov et al is unique in that it directly compared two types of MRI-TB in patients with prior negative biopsy.[29] The investigators found that in-bore biopsy alone was comparable to MRI-US

fusion biopsy alone (CS CDR 29% versus 26%). They calculated that the number of cores needed to detect one CS tumor was 19 for in-bore biopsy, 21 for MRI-US fusion, and 48 for TRUS-Bx. The study concluded that in patients with suspicious lesions on mpMRI, the addition of TRUS-Bx added minimal benefit to in-bore biopsy. Unfortunately, this study was limited by small sample size secondary to early cessation and did not meet the primary endpoint (CDR ≥ 60% in the MRI-TRUS cohort and ≥ 40% in the in-bore cohort). However, the results suggest that both in-bore biopsy alone and MRI-US fusion alone are superior to TRUS-Bx, and that both techniques yield a relatively high proportion of CS cancer in a cohort with traditionally low levels of cancer detection.

There is a need for further randomized control trials to determine if and when MRI-TB alone will be sufficient for the diagnosis of prostate cancer. One such study is the PRECISION trial, a multi-institutional randomized control trial currently in progress. The PRECISION trial will compare MRI-TB to systematic TRUS-Bx in biopsy-naïve men for the diagnosis of CS and clinically insignificant cancer, and its results may provide further insight into the possibility of a diagnostic pathway involving exclusively MRI-TB. However, current studies suggest that although MRI-TB has comparable or superior cancer detection when compared to TRUS-Bx, there is still a small proportion of significant cancers that are detected on standard biopsy alone.

Prior negative biopsy

The use of MRI-TB has long been of interest in patients with one or more prior negative biopsies. Vourganti et al found that in patients with prior negative biopsy, TRUS-Bx missed half of all high grade cancers detected by MRI-TRUS fusion biopsy.[30] In the case of multiple negative biopsies, a multi-institutional analysis by Sidana et al found that with each additional biopsy, the CDR on TRUS-Bx decreased while the CDR on MRI-TRUS fusion remained constant.[31] An interesting study by Hong et al looking at patients specifically with prior negative fusion biopsy found that fusion biopsy was particularly useful in detecting smaller lesions which had been missed on initial biopsy.[32,33] When compared to other tools used to stratify patients with prior negative biopsy, such as prostate health index and prostate cancer antigen 3, mpMRI has also been shown to be superior. On decision curve analysis for predictors of prostate cancer, mpMRI provided the most significant increase in predictive ability, when added to the researchers' base model, with an area under the curve of 0.936.[34] In light of the data supporting targeted biopsies in the prior negative cohort, a recent consensus statement was released by the American Urological Association and the Society of Abdominal Radiology recommending prostate MRI and MRI-TB for patients with prior negative TRUS-Bx.[35]

Correlation with post prostatectomy pathology

Much of the literature concerning MRI-TB compares targeted biopsy to standard biopsy, and not to whole gland prostate specimens, which can be considered the "gold standard" for histologic diagnosis. When compared to whole-gland pathology, MRI-US fusion has upgrade rates of 44%-54%, with a combined biopsy concordance of 82% and 81%.[36,37] Siddiqui et al calculated that the sensitivity of fusion biopsy versus standard biopsy for predicting whole-gland pathology was 77% versus 53%, and that the AUC for mpMRI-US fusion was significantly greater than the AUC of TRUS-Bx or combined biopsy. In their randomized control study, Panebianco et al found that mpMRI had a sensitivity and specificity of 86% and 94% compared to RP results.[2] As with fusion biopsy, only a small proportion of studies compare the performance of in-bore biopsy to final pathology after prostatectomy. One study by Hambrock et al demonstrated the concordance between in-bore biopsy and whole gland prostate specimens obtained after RP to be 81% as compared to 55% on 10-core TRUS-Bx, and the authors concluded strongly in favor for the use of MRI-TB.[38] Although MRI-TB appears to have the potential for good predictive ability of whole-gland pathology, the concordance rate for combined biopsy remains higher than that of MRI-TB alone.

Comparison with saturation biopsy

How does MRI-TB compare to the other alternative to standard biopsy: saturation biopsy? Radtke et al compared fusion biopsy to saturation biopsy of the whole prostate, with a median of 24 cores/gland. They found no difference in the detection rates of CS cancer between fusion biopsy and saturation biopsy, but found that fusion biopsy avoided the over-diagnosis of 43.8% of low grade tumors.[39] They also found that fusion biopsy missed 0% of CS cancers in patients with a prior negative biopsy, concluding that fusion biopsy alone was comparable to saturation biopsy, while taking fewer cores. Kaufmann et al compared in-bore biopsy to saturation biopsy and found that, similar to fusion biopsy, in-bore biopsy had a comparable CDR to saturation biopsy in prior negative patients while taking fewer cores per patient.[40] In addition, they found CS cancer in all positive biopsies taken with the in-bore technique, indicating that it had a tendency towards diagnosing higher risk cancers. These results indicate that MRI-TB is either superior or comparable to saturation biopsy, while requiring far fewer biopsy cores.

Learning curve

Although MRI-TB has been found overall to have superior diagnostic capability when compared to TRUS-Bx, many studies continue to recommend the use of combined systematic and targeted biopsy, citing lower accuracies of MRI-TB when compared to combined biopsy.[18,27,36,41] One factor contributing to the variability in reported results on MRI-TB is the operator skill necessary to perform a targeted biopsy. Although requiring less expertise than cognitive fusion, both MRI-US fusion and in-bore MRI biopsy require the experience necessary to identify suspicious lesions on MRI and target them in real time. Recent research by Calio et al demonstrated a significant increase in MRI-US fusion biopsy detection of age/PSA-controlled CS cancer detection, as well as a significant decrease in clinically insignificant cancer detection, over a period of 10 years.[42] These results demonstrate the learning curve required to successfully utilize MRI-TB.

Complications

Many studies have documented a rise in complication rates after prostate biopsy, largely due to infections, as well as an increase in fluoroquinolone-resistant strains.[43,44] Analysis of the English National Cancer Registry showed a significant increase (20%) in the rate of hospitalization after prostate biopsy in the study period alone.[43] Although complications of prostate biopsy are typically minor (pain, bleeding), rarely, septic shock and Fournier's gangrene may occur.[43,45] Therefore, any measure which may reduce these complications is a welcome one. A review by Loeb et al found higher rates of infection and post-biopsy pain with increased biopsy cores.[45] An analysis of the SEER database found a 1.7-fold increase in the rate of both hospitalizations and serious infectious complications for each additional prostate biopsy performed. The correlation between both number of biopsy cores and additional biopsies, and post-biopsy complications serves as a reminder that performing both TRUS-Bx and MRI-TB, although increasing accuracy, does not come without risk.

It is difficult to compare complication rates between MRI-TB and TRUS-Bx, as the former is rarely performed without the latter. A review by Borghesi et al found that MRI-TB had lower complication rates than either transrectal or transperineal TRUS-Bx, although they did not differentiate between MRI-TB alone and MRI-TB + TRUS-Bx. They found that rates of hematuria and urinary retention were far lower for MRI-TB compared to TRUS-Bx, and that the hospitalization rate for MRI-TB was as low as 0%.[44] Furthermore, a recent study by Egbers et al found that pain duration and intensity were lower for in-bore biopsy alone than for TRUS-Bx performed a median of 13 months earlier.[46] As the literature suggests that MRI-TB tends to have lower rates of complications post-biopsy, performing MRI-TB alone may prove to be a safer alternative to combined targeted and random biopsy. Using MRI-TB biopsy, a more accurate diagnosis can be made using fewer cores, theoretically decreasing complications from prostate biopsy.

Cost

A common practical concern is the cost of the MRI-TB diagnostic pathway. True long term cost effectiveness of mpMRI and subsequent MRI-TB in comparison to standard TRUS-Bx is difficult to accurately calculate. One must consider the initial system acquisition cost, the cost of each diagnostic pathway, as well as the cost of the treatment, or lack thereof, in addition to life years gained and/or lost.

Initial investment in new technology is always required and is not insignificant. In the U.S., the initial acquisition cost of the MRI-TB system ranges from $200,000-$300,000. However, when analyzing the cost savings of the MRI-TB pathway, the data suggests that true long term savings lies in the prospect of fewer prostate biopsies required, and additionally, the possible decrease in definitive treatment performed in cases indolent disease.[23,24]

Approximately 1 million prostate biopsies are performed in the U.S. per year, with each having a total procedural cost ranging from $500-$4000.[47] The vast majority of these are TRUS-Bx. The complication rates of TRUS-Bx have increased over the years,[45,48] with reports of fever after 4.2% of prostate biopsies, and 0.8% of patients requiring hospitalization.[49] These complications are, as stated above, related to the number of biopsies performed as well as the number of cores taken at the time of biopsy. With MRI-TB, there is potential for a decrease in the number of overall prostate biopsy procedures as well as the number of cores required during each procedure. This cost savings was demonstrated by Lotan et al in a model for men with a prior negative biopsy reported.[50] In this study, the overall cost for 100 men was $90,400 and $87,700 for standard TRUS-Bx and MRI-TB arms, respectively. Irrespective of cost, MRI-TB has been demonstrated, in several studies, to result in higher quality-adjusted life years for patients.[51,52]

Although MRI-TB may require higher up-front expense, it may be demonstrated to become an essential screening tool which may allow patients to follow a pathway that ultimately treats patients effectively and safely is a far less invasive way than our current standard of care. In addition, MRI-TB has been shown to be a more cost effective pathway.

Conclusions

MRI-TB, in particular software fusion and in-bore biopsy, has been shown in numerous studies to accurately detect the majority of CS prostate cancers, many of which are missed on TRUS-Bx. In contrast, TRUS-Bx has a low diagnostic yield and adds to a great deal of the overdiagnosis of clinically insignificant cancers. The treatment of these low risk cancers is a burden, not a benefit, and adds to both healthcare costs and complication rates. In addition, the inconclusive nature of a negative TRUS-Bx, particularly in patients with prior negative TRUS-Bx, leads to a great deal of unnecessary anxiety and concern for both patients and providers. Although most of the literature suggests that MRI-TB is more accurate, TRUS-Bx is valuable in that it captures a small proportion of CS cancers missed by MRI-TB. Therefore, we conclude that the current literature supports the recommendation of combining targeted and standard biopsy rather than performing either alone. There is a need to further develop current technology, particularly MRI-US fusion software, in order for MRI-TB to be sufficient as a stand-alone procedure. Improvements in lesion registration, targeting, and user interface will help to mediate the significant learning curve required to master what is still a difficult procedure. However, as prostate imaging and biopsy technology continues to improve, MRI-TB will likely outpace standard biopsy and perhaps, in the future, replace it altogether. □

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