Role of pre-biopsy multiparametric MRI in prostate cancer diagnosis: Evidence from the literature

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ABSTRACT

As the conventional workup for diagnosing prostate cancer, transrectal systematic biopsy carries the risk of sepsis and overdiagnosis of insignificant prostate cancer. In recent years, multiparametric MRI (mpMRI) has revolutionized the diagnostic approach to prostate cancer. With widespread use of the prostate imaging and data system (PIRADS), MRI reporting has been more standardized. Several landmark papers have indicated that mpMRI in combination with targeted or combined biopsy can confidently diagnose more clinically significant prostate cancer while reducing diagnoses of insignificant disease. In this review, we aim to discuss the advantages of pre-biopsy MRI based on the current literature and to address its reliability in ruling out prostate cancer, reproducibility, and cost-effectiveness.

Keywords: Magnetic resonance imaging; prostate biopsy; prostate cancer.

Introduction

Prostate biopsy is the standard workup for patients with clinical suspicion of prostate cancer. Conventionally, systematic prostate biopsies are taken under transrectal ultrasound guidance. However, by nature, ‘blind’ biopsy is prone to sampling error and clinically significant prostate cancer (csPCa) may be easily missed. Such problems cannot be resolved by increasing the number of biopsy cores, as this may in turn lead to over-detection of clinically insignificant prostate cancer and increase the risk of post-biopsy sepsis. We need better ways to visualize the location of the tumor to optimize prostate cancer diagnosis by biopsy. The recent advent of multiparametric magnetic resonance imaging (mpMRI) has revolutionized the diagnostic approach of prostate cancer. In this review article, we discuss the role of pre-biopsy MRI in prostate cancer diagnosis and summarize the evidence we have so far.

Introduction of MpMRI and PIRADS

MpMRI comprises four sequences: T1-weighted, T2-weighted (T2W), diffusion-weighted (DWI), and dynamic contrast-enhanced imaging (DCE). This imaging modality has an increasingly important role in the diagnosis of prostate cancer.

Prostate imaging reporting and data system (PIRADS version 2.1) is a validated scoring system for predicting the risk of prostate cancer based on MRI features.[1] Adherence to PIRADS guidelines is recommended for standardization. MRI-guided targeted biopsy (TB) should be offered to patients with PIRADS 3–5 lesions.[2] In the study by Stabile et al.[3], TB was performed for all PIRADS ≥2 lesions on mpMRI for 343 patients. The detection rates for csPCa at TRUS-Bx were 8% for PIRADS 2, 15% for PIRADS 3, 36% for PIRADS 4, and 58% for PIRADS 5 lesions (p=0.03).

There are three types of MRI TB. MRI-ultrasound fusion TB (FUS-TB) refers to co-registration of MRI images with real-time transrectal ultrasound images using computer software. Cognitive-registration TB (COG-TB) is when suspicious lesions are identified on mpMRI by a radiologist and then targeted using transrectal ultrasound guidance by the
operating surgeon. In-bore MRI TB (MRI-TB) is performed in the MRI suite where previous diagnostic images are registered with real-time interventional images. The FUTURE trial showed no significant differences among these three techniques in detection rates for overall prostate cancer (FUS-TB 49%, COG-TB 44%, MRI-TB 55%, p=0.4) and csPCa (FUS-TB 34%, COG-TB 33%, MRI-TB 33%, p>0.9) in patients with prior negative biopsy and persistent suspicion.[4]

Biparametric MRI without DCE has been suggested to generalize its use in prostate cancer diagnosis. In a retrospective study of 236 patients, omitting DCE did not lead to any significant change in the diagnostic accuracy [area under curve (AUC) 0.914 vs. 0.917 in receiver operating characteristic (ROC) analysis].[5] Biparametric MRI with no DCE reduces cost, time and gadolinium contrast side effects. In this regard, a multi-institutional prospective study, known as the PRIME study, has been designed to prove the noninferiority of biparametric MRI (T2W and DWI) to mpMRI (T2W, DWI, and DCE) in the diagnosis of csPCa.

**MRI-TB vs. systematic biopsy for prostate cancer diagnosis**

There are three landmark studies evaluating the role of MRI in diagnosing prostate cancer in biopsy-naïve men. Please refer to table 1 for a summary of these studies.

In the PRECISION trial, 500 biopsy-naïve patients were randomized to either MRI-TB only or systematic biopsy only. The detection rate of International Society of Urological Society grade (ISUP) grade ≥2 cancers was significantly higher in the MRI-targeted biopsy group (38%) than in the systematic biopsy group [26%, p=0.005, detection ratio (DR) 1.46]. The detection rate of clinically insignificant cancer was lower in the MRI-TB group than in the systematic biopsy group (9% vs. 22%; p<0.001). Participant-reported complications at 30 days were less frequent in the MRI-TB group than in the standard-biopsy group, including hematuria (30% vs. 63%), hematospermia (32% vs. 60%), pain (13% vs. 23%), rectal bleeding (14% vs. 22%), and erectile dysfunction (11% vs. 16%). These findings reflected the lower percentage of men undergoing biopsy and fewer biopsy cores obtained in the MRI-TB group than in the standard-biopsy group.[6]

In the MRI-FIRST trial, 251 biopsy-naïve patients underwent systematic biopsy by an operator who was blinded to mpMRI findings and MRI-targeted biopsy by another operator. MRI-TB detected significantly more ISUP grade ≥3 cancers than systematic biopsy (19.9% vs. 15.1%, p=0.0095; DR: 1.32). There was no significant difference in detection rates for ISUP grade ≥2 cancers (32.3% vs. 29.9%, p=0.38; DR: 1.08). MRI-TB detected fewer cases with clinically insignificant prostate cancer than systematic biopsy (5.8% vs. 20%, p<0.0001).[7]

The 4M study included 626 biopsy-naïve patients, all of whom received systematic biopsy. Those with positive mpMRI (PIRADS 3–5, 51%) underwent additional in-bore MRI-TB. The detection rate for ISUP grade ≥2 cancers still favored MRI-TB over systematic biopsy (25% vs. 23%; DR: 1.09, p=0.17). However, MRI-TB and systematic biopsy detected ISUP grade ≥3 cancers at similar rates (11% vs. 12%; DR: 0.92, p=0.46). MRI-TB detected significantly fewer cases of clinically insignificant prostate cancer than systematic biopsy (14% vs. 25%; DR: 0.57, p<0.0001).[8]

According to a meta-analysis, MRI-TB detected more clinically significant cancers than systematic biopsy (DR 1.16 [95% confidence interval (CI) 1.09–1.24], p<0.0001). In the subgroup analyses, the superiority of MRI-TB relative to systematic biopsy in detecting csPCa was not dependent on prior biopsy status biopsy-naïve DR 1.18 [95% CI 1.06–1.31], prior biopsy-negative DR 1.22 [95% CI 1.05–1.42], prior biopsy-positive DR 1.09 [95% CI 0.92–1.30], p=0.71). Moreover, MRI-TB detected fewer clinically insignificant cancers than systematic biopsy [DR 0.66 (95% CI 0.57–0.76), p<0.0001]. And this effect did not differ by systematic biopsy type, prior biopsy status or registration choice in the subgroup analyses.[9]

MRI pathway refers to the approach of performing MRI-TB only for MRI-suspicious lesions. According to a Cochrane review by Drost et al.[10], the MRI pathway missed less csPCa than systematic biopsy by 12% (95% CI 2%–23%) for mixed groups, 5% (95% CI -5% to 16%) for the biopsy-naïve group and 44% (95% CI 19%–75%) for prior negative biopsy group respectively. Furthermore, when compared to systematic biopsy for all patients, MRI pathway avoided more overdiagnosis of clinically insignificant prostate cancer (DR: 0.61 for mixed, 0.63 for biopsy naïve, 0.62 for prior negative biopsy) and 29% biopsy procedures in MRI-negative patients. The false-negative rate of MRI in detecting csPCa was merely 2.8%, as compared to 11% for systematic biopsy.

**Main Points:**

- Multiparametric MRI detects more clinically significant prostate cancers and less insignificant disease than systematic biopsy.
- In combination with prostate specific antigen density or other markers, MRI-negative patients can safely avoid prostate biopsy.
- Standardization of MRI reporting and targeted biopsy is essential to reproducing satisfactory outcomes.
Recently, a prospective study with a sample size of 2,103 patients compared the respective detection rates of clinically significant and insignificant prostate cancer by MRI-targeted, systematic and combined biopsy. The operators who took systematic biopsies were blinded to MRI information. Compared to systematic biopsy, the cancer detection rates of MRI-TB were significantly lower for grade group 1 cancers and significantly higher for grade groups 3–5 (p<0.01). Combined biopsy led to 9.9% more cancer diagnoses than with either method alone and 21.8% upgrading to a higher grade group. On the contrary, MRI-targeted biopsies underdiagnosed 8.8% of clinically significant cancers (grade group ≥3). Among the 404 men who underwent subsequent radical prostatectomy, combined biopsy was associated with merely 3.5% upgrades to grade group 3 or above on histopathological analysis, outperforming MRI-TB (8.7%) and systematic biopsy (16.8%).

The European Association of Urology Guideline recommends mpMRI before prostate biopsy in both biopsy-naïve and prior negative biopsy settings. It also suggests combined biopsy for PIRADS ≥3 lesions in biopsy-naïve patients, and TB for PIRADS ≥3 lesions in patients with prior negative biopsy.

In the transrectal ultrasound prostate biopsy (TRUS) era, there was concern of infection because of the increased number of cores. In the transperineal (TP) era, however, this worry is much reduced. Also, the current fusion platforms have made TP TB feasible. As of now, combined biopsy represents the most effective way to minimize the chance of missing csPCa or pathological upstaging. Therefore, pre-biopsy MRI enables TB and combined biopsy which would optimize patient selection for active surveillance.

Can MRI-negative patients safely omit prostate biopsy?

The PROMIS study evaluated the use of mpMRI as a triage test before prostate biopsy. In this study, 576 men with clinical suspicion of prostate cancer underwent mpMRI followed by TRUS systematic biopsy and template mapping prostate biopsy every 5mm (which represented the reference test). Up to 27% patients with negative MRI could avoid prostate biopsy. The negative predictive value of mpMRI in ruling out Gleason ≥4 + 3 prostate cancers was 89% (95% CI 83%–94%). Recently, a systematic review also showed that the negative predictive value of mpMRI was 91% in the detection of csPCa. However, the negative predictive value of an investigation decreases when the disease prevalence increases, and thus may not apply to patients with individualized risk profiles. In addition, the 4M and MRI-FIRST studies indicated that up to 3%–11% csPCa could be missed if biopsy was not performed in MRI-negative (PIRADS 1–2) patients. This calls for better risk stratification for MRI-negative patients to determine whether they need prostate biopsy or not.

Prostate specific antigen (PSAD) has been supported by various retrospective studies for stratifying the risk of prostate cancer in MRI-negative patients. In the MRI-negative population, the risk of finding csPCa at subsequent systematic biopsy is <10% if the PSAD is <0.15 ng/mL/cc. The risk can be up to 27%–40% if the PSAD is > 0.15–0.20 ng/mL/cc. Norris et al. performed post hoc analysis on the PROMIS data and found that application of a PSAD threshold of 0.15 mg/mL/cc to MRI-negative patients reduced the proportion of undetected
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The combination of MRI and European Randomized Study of Screening for Prostate Cancer Risk Calculators was found to avoid prostate biopsy in 36% patients with previous negative biopsy, missing only 4% csPca.[18] Hsieh et al.[19] showed that in the Asian population, the combination of mpMRI and prostate health index (PHI) gave a better AUC for detecting csPca, compared to PHI alone (0.873 vs. 0.735, p=0.002) and mpMRI alone (0.873 vs. 0.830, p=0.035). In a retrospective study by Perlis et al.[20], no csPca was found in the group with negative results in both mpMRI and PCA3 score.

There are wide variations in the incidence of prostate cancer across different ethnicities,[21-24] and therefore, variable predictive values for each diagnostic test. There is a need for more data to streamline the diagnostic pathway for individual regions or ethnic groups.

Reproducibility of MRI reporting and MRI-TB

Reporting failure and targeting failure represent two big hurdles in the success of MRI-TB. In this regard, the inter-reader reproducibility of mpMRI reporting and accuracy of MRI-TB lie at its root.

Despite the widespread use of the PIRADS, the quality of mpMRI reporting may be variable. The positive predictive value of PIRADS four lesions was 49% (95% CI 40%–58%) among 26 centers according to a retrospective series.[25] Hansen et al.[26] conducted a prospective study comparing 158 initial and second-opinion reports by experienced uroradiologists in a tertiary center. Disagreement was noted in 54% of the reports. Expert re-reporting yielded a higher positive predictive value (NPV) for csPca compared to initial reports (0.89±0.08 vs. 0.72±0.16; p=0.04), and a higher positive predictive value (PPV) in the target area for all cancer (0.61±0.12 vs. 0.28±0.10; p=0.01) and csPca (0.43±0.12 vs. 0.23±0.09; p=0.02).

The optimal MRI-TB method remains to be determined. Although the FUTURE trial showed similar csPca detection rates among all three methods of TB, it should be acknowledged that each method necessitates adequate equipment and expertise to reproduce satisfactory results. Cognitive fusion is more operator-dependent than software-based fusion, and potentially more challenging in smaller MRI lesions.

It is suggested that urologists should learn from high-volume centers, adhere to familiar targeting methods and machines, and collaborate with radiologists by providing regular feedback of pathology reports, and take every measure to standardize MRI reporting and MRI-TB.

Cost-effectiveness of MRI and MRI-TB

Faria et al.[27] analyzed PROMIS data to identify the most cost-effective way to detect csPca in terms of testing costs, and incremental cost-effectiveness ratios in quality-adjusted life years). The use of mpMRI first and then up to two MRI-targeted TRUS biopsies detects more csPca per pound spent than a strategy using TRUS biopsy first [sensitivity=0.95 (95% CI 0.92–0.98) vs. 0.91 (95% CI 0.86–0.94)] and is cost-effective [ICER = £7,076 (€8350/QALY gained)].

The use of MRI enables accurate detection of predominantly csPca by targeted or combined biopsy. Under the assumption of accurate TB, it obviates the need for repeated systematic biopsy. Furthermore, resources can be more focused on patients suited for receiving active surveillance or radical treatment. By avoiding overdiagnosis of insignificant cancer, it also minimizes the cost, procedural risk and morbidities of unnecessary biopsies and treatment.

Overall, the use of mpMRI and MRI-TB can be cost-effective, given reliable reporting, accurate biopsy and effective treatment.

In conclusion, the advent of mpMRI has revolutionized the diagnostic approach to prostate cancer. Standardized MRI reporting and MRI-TB can improve detection of csPca, reduce overdiagnosis of insignificant disease, and concentrate medical resources on treating patients in need. More data are needed to define their clinical roles in different ethnic groups with different cancer prevalence.

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