The Use of Magnetic Resonance Imaging in the Prostate Cancer Primary Diagnostic Pathway: Is It Ready for Primetime?

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Multiparametric magnetic resonance imaging (mpMRI) has been increasingly utilized in the prostate cancer diagnostic landscape over the last five years. The majority of the literature has focused on its use in men with a previous negative biopsy. However, over time, clinicians have begun using mpMRI in the work-up of men being considered for primary biopsy and subsequently data characterizing its diagnostic performance in this setting is emerging. This review comprehensively assesses the utility of mpMRI in the primary biopsy setting.

Keywords: Biopsy; Diagnosis; Magnetic resonance imaging; Prostate cancer; Prostatic neoplasms

INTRODUCTION

Prostate cancer is the most commonly diagnosed solid-organ malignancy amongst men in the USA [1]. Despite recommendations to the contrary, men still most commonly present to clinicians for evaluation following an elevated prostate specific antigen (PSA) test. PSA has poor specificity for aggressive cancer and subsequently, the current practice of performing transrectal ultrasound-guided biopsy (TRUSB) on men with an elevated PSA has resulted in the over-diagnosis and overtreatment of indolent disease [2,3]. In an attempt to curb these latter two issues there have been extensive efforts to improve patient selection. The use of biomarkers such as PHI, 4Kscore, and SelectMDx has demonstrated the potential to aid risk-stratification of patients but these are not yet widely adopted in routine clinical practice and the latter two have not received USA Food and Drug Administration clearance to date [4]. Similarly, risk calculators have also been used as a risk-stratification tool to improve patient selection [5]. In addition to biomarkers and risk calculators, there has been considerable progress in the landscape of prostate imaging. Multiparametric magnetic resonance imaging (mpMRI) has come to the forefront of local tumor imaging over the last decade. This has most commonly been used in the setting of previous negative TRUSB but the observed utility has prompted clinicians to also adopt it in primary diagnostic pathway [6]. In keeping with this, the evidence for the use of mpMRI is primarily for the population of men with a previous negative TRUSB. Therefore,
this paper will provide a comprehensive review of the evidence for utilizing mpMRI in men being primarily evaluated for prostate cancer to determine whether its use in this manner is justified.

**LEVEL 1 EVIDENCE**

A multicentre, paired-cohort, confirmatory study performed in the United Kingdom and published in The Lancet (PROMIS) is one of the highest quality studies for using MRI to assist in the diagnosis of prostate cancer [7]. This study enrolled men who had not undergone previous prostate biopsy but had an elevated PSA and underwent an MRI followed by both transperineal mapping biopsy (cores obtained at 5 mm intervals) and TRUSB. Using a definition of Gleason score ≥4+3 or cancer core length ≥6 mm for clinically significant disease, the reported sensitivity of mpMRI in this cohort was 93% (95% confidence interval [CI], 88%–96%). This was significantly greater than the sensitivity for TRUSB (48%; 95% CI, 42%–55%). However, there is ongoing debate regarding the amount of pattern 4 disease required for cancer to be considered clinically significant [8,9]. Hence, when the definition includes the presence of any pattern 4 disease, the sensitivity of mpMRI decreases to 88% (95% CI, 84%–91%) which still significantly outperforms TRUSB. Importantly, this study demonstrates that mpMRI has a high negative predictive value (NPV) of 89% (95% CI, 83%–94%) if using the former definition for significant disease or 76% (95% CI, 69%–82%) if any Gleason score ≥3+4 cancer is considered significant. Although this data is somewhat reassuring that a negative mpMRI can rule out the presence of significant cancer, relying on it solely as a triage test would lead to aggressive cancer being missed in a quarter of the cases. There are further concerns regarding the generalizability of these results to routine clinical practice. This study was performed in a centre of clinical excellence where radiologists and biopsy operators were highly trained and experienced and thus this level of expertise may not be present across all institutions which would impact the diagnostic performance of the test.

The results of PROMIS are supported by a study of 388 Australian men who underwent mpMRI and transperineal template-guided mapping biopsy in addition to targeted biopsy if any suspicious lesions were identified [10]. A Prostate Imaging Reporting and Data System (PIRADS) 3 to 5 lesion was identified in 77% cases and mpMRI demonstrated a sensitivity of 95.8% in the detection of clinically significant disease. Two-thirds of the missed cancers were either Gleason score 6 or had no more than 10% of pattern 4 disease. Additionally, an anatomic concordance analysis performed between mpMRI and mapping biopsy demonstrated 97% agreement. The concerns surrounding the generalizability of PROMIS are also relevant in this study as the two radiologists that interpreted the mpMRIs both were experienced having reported over 1,000 scans each and radiologist experience has been demonstrated to effect detection rates [11]. Although the applicability of the results from these two studies to the wider community have been questioned due to the expertise of clinicians in these centres, we can be reassured by the early performance of the PROMIS group. Their early experience which enrolled patients up to five years preceding the commencement of PROMIS reported a sensitivity and NPV of 90% and 70% for cancer of any grade [12]. For different definitions of clinically significant disease the ranges of sensitivity and NPV were 94% to 100% and 89% to 100%. These estimates are based on a cut-off of radiological suspicion score (analogous to PIRADS) 3 to indicate positive mpMRI. If the cut-off was increased to a score of 4, specificity and positive predictive value improve while lowering sensitivity and NPV. The similarity of these results to the recent PROMIS publication suggest that a high level of diagnostic performance for mpMRI in the pre-biopsy setting is still possible without vast institutional experience.

**FACILITATING TARGETED BIOPSY**

Aside from utilizing mpMRI as a triage test to improve patient selection of those undergoing biopsy, one of the core benefits is that it permits clear identification of suspicious areas of the prostate. Until recently, transrectal ultrasound was the primary radiological modality for imaging of local prostate lesions. However, its ability to accurately predict the true disease state is low with an estimated 30% to 40% of cancers being isoechoic ‘invisible’ [13]. Furthermore, it is challenging to delineate central gland tumors in the presence of benign prostatic hyperplasia because of its associated mixed pattern of tumor echogenicity [14]. Moreover, the nature of transrectal ultrasound means that it is
challenging to identify anterior tumors [15]. These issues are further compounded by the multifocal nature of prostate cancer which requires extensive evaluation to accurately characterise the disease state [16,17]. This inability to define lesions designates TRUSB as a ‘blind’ biopsy technique. This random sampling also contributes to the observed overdiagnosis of low-grade disease.

mpMRI addresses many of these shortcomings by delineating suspicious areas that can then be directly sampled by magnetic resonance-guided biopsy (MRGB). A randomized trial performed in the biopsy-naïve population have reported that the addition of mpMRI into the diagnostic pathway of men with an elevated PSA who have not undergone prevous biopsy can improve the detection of clinically significant cancer [18]. This study demonstrated a 97% accuracy for mpMRI in the diagnosis of prostate cancer. The recently published PRECISION trial which performed an mpMRI on all participants and then randomized those with positive imaging to either targeted biopsy only or standard biopsy found that detection of clinically significant disease was higher in targeted biopsy only group (38% vs. 26%; adjusted difference, 12%; 95% CI, 4%–20%) [19]. This provides level one evidence that MRI and targeted biopsy should be included in the work-up of patients being considered for primary biopsy. However, it is not clear whether these results can be replicated in non-specialist settings because all radiologists involved in this trial were highly experienced, reporting on a median 300 mpMRIs per year. It will be important to describe the outcomes of the men from this trial which had negative imaging and did not receive biopsy. In direct contrast, two other randomized studies found no additional benefit of performing mpMRI and targeted biopsy if the MRI was positive compared to systematic biopsy in all patients [20,21]. In light of these conflicting results, further studies are required to characterise whether mpMRI and subsequent targeted biopsy provides additional benefit in this population. The results from non-randomized studies have demonstrated that 89% fewer low-risk cancers were diagnosed with MRGB compared to TRUSB [22]. The NPV for intermediate/high-grade disease in this study for MRI followed by MRGB was 97%. Similarly, a large heterogeneous population of 1,003 men reported that targeted biopsy diagnosed 30% more high-risk cancers and reduced the number of low-risk cancers diagnosed by 17% [23]. However, negative MRI cases were not subject to biopsy in this study and thus it is not possible to estimate the number of missed cases. Generally, these results are promising for the benefit of mpMRI and targeted biopsy to improve the diagnosis of significant cancer.

Some studies have also suggested that targeted biopsy alone could be accurate. A randomized study of biopsy-naïve men found comparable significant cancer detection rates between those who underwent two-core targeted biopsy and cases which underwent 12-core systematic biopsy [20]. Not only does this improve diagnostic efficiency [24], but there is theoretically a lower risk of biopsy complications as fewer cores are obtained and thus, fewer occurrences of a needle passing from a dirty to clean space. Considering that most institutions are yet to overcome the learning curve of mpMRI and subsequent MRGB, there is a considerable risk of missing significant cancer by omitting systematic biopsy and this is not recommended, nor is it widely practiced [25].

SHORTCOMINGS OF MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING IN THE PRIMARY SETTING

Despite the improved diagnostic ability gained by incorporating mpMRI into the work-up of an elevated PSA, it is still not a perfect test. A recent analysis of 223 biopsy-naïve men reviewed cases where mpMRI results were discordant with systematic biopsy to potentially identify scenarios in which mpMRI may not be accurate [15]. In this cohort, mpMRI missed 26% of clinically significant cancers. Reassuringly, the maximum cancer core length and total cancer core length of missed cancers was significantly lower in cases missed by MRGB compared to TRUSB. The study did report that mpMRI was liable to missing lesions located in the dorsolateral segments (58%) and the apex (37%). On the other hand, it did demonstrate improved diagnosis of anterior lesions. Overall this study found that reading failure was more likely to be responsible for missed lesions than sampling failure; that is, the most common scenario in these cases was a negative mpMRI and positive TRUSB rather than positive mpMRI and TRUSB with negative MRGB. This data lays the platform for further research to identify the underlying factors contributing to reading errors so that it can be
addressed. Furthermore, this highlights the importance of each institution auditing their own experience so that areas for improvement can be identified.

SELECTING PATIENTS FOR MAGNETIC RESONANCE IMAGING

A potential approach to limit the number of mpMRI scans performed is to select patients appropriately. There are currently no evaluations of risk-stratification tools in the primary biopsy setting but there have been possible approaches to improving patient selection in the population of men with a previous negative TRUSB. The recommendations on whether to proceed to biopsy after mpMRI has been largely clear-cut except in those with a PIRADS score of 3. The yield of clinically significant cancers amongst PIRADS 3 lesions have varied across the literature. Employing additional tests, including biomarkers, may assist with differentiating ‘high-risk’ PIRADS 3 lesions from ‘low-risk’. A single study in the re-biopsy setting reported that using PCA3 with a cut-off of 35 can alleviate the uncertainty of PIRADS 3 lesions as all the lesions that did not harbour prostate cancer fell under this cut-off value [26]. The use of risk indices such as the Rotterdam Prostate Cancer Risk Calculator may also be used to inform the need for mpMRI. Using this risk calculator in a Dutch cohort of men with previous negative biopsy would have avoided 51% of mpMRI scans and decreased the number of low-grade cancers diagnosed by 25% at the expense of missing 10% of significant cancers. Whether these results are applicable in the biopsy-naïve population needs confirmation [27].

COST

In a time of limited healthcare resources, it is important to determine whether the additional cost of mpMRI is outweighed by the health benefits it provides. Data from cost-effectiveness analyses suggest that the savings from reduction in biopsies and subsequent complications help counterbalance the cost of MRI. Although there have been no such studies performed from a USA health sector perspective, a European study demonstrated that the use of mpMRI to triage men with an elevated PSA increases both costs and quality-adjusted life years with an incremental cost-effectiveness ratio of €323 (euro) compared to the current standard of biopsying all patients [28]. This result is supported by another European modelling study which tested the impact of performing systematic TRUSB in hypothetical men with a negative mpMRI compared to omitting biopsy completely in this group [29]. While either strategy dominated current clinical practice, skipping biopsy in MRI-negative cases was likely the most cost-effective. This study further suggested that performing MRGB using visual registration or in-bore was likely to be more cost-effective than using software-based image registration methods. Undertaking similar studies with a local perspective will be imperative to ensure generalizability and optimal use of healthcare resources due to the substantial variation in the cost of these tests in different healthcare systems.

CURRENT GUIDELINE RECOMMENDATIONS

Due to the paucity of data on mpMRI in the work-up of biopsy-naïve men, leading urological societies such as the American Urologic Association (AUA), National Comprehensive Cancer Network (NCCN) and the European Association of Urology (EAU) have not supported the adoption of mpMRI prior to initial biopsy. The NCCN guidelines do acknowledge that although mpMRI prior to initial biopsy is not routinely recommended, there is a growing body of evidence outlining its possible benefit and hint that a formal recommendation is imminent [30]. The EAU guidelines panel recently published a meta-analysis examining the NPV of mpMRI prior to initial biopsy and concluded that although there is potential for the test to be used as a triage for biopsy, it is still not sufficiently accurate at the present [31]. The AUA Early Detection guidelines describe mpMRI as a “secondary test with potential utility for determining the need for a prostate biopsy, but with unproven benefit” and devoid of evidence that it will increase the ratio of benefits to harm [32]. It should be noted that this guideline was first published in 2013 and revised in 2015 when the use of mpMRI and its evidence was still in its infancy.

FUTURE DIRECTION

Not atypical for new technologies, the adoption of mpMRI prior to initial biopsy has outpaced the evidence to support this practice. Despite the majority of
evidence being of low-quality, the results of PROMIS provides high-quality data to justify the use of mpMRI to triage patients for biopsy. However, this study is a standalone and there are concerns surrounding the generalizability of its results to the wider community. Therefore, it is imperative that further, well-designed trials are conducted to inform the safety of relying on mpMRI to determine the need for biopsy and rule out clinically significant disease. The major oversight of many of the published papers in this domain is the lack of an appropriate reference standard. TRUSB cannot accurately characterise true disease state and relying on whole-mount prostatectomy specimens introduce selection bias, therefore the most appropriate reference standard is a template mapping or saturation biopsy.

Although mpMRI has been demonstrated to be a potentially cost-effective strategy pre-biopsy, benefits would be amplified by improving patient selection. This could be achieved by developing nomograms or by attempting to correlate biomarker results to mpMRI findings.

CONCLUSIONS

The body of evidence supporting the use of mpMRI prior to initial biopsy is growing and it appears only a matter of time before this is reflected in the guidelines. The main benefit appears that it improves diagnostic accuracy by delineating lesions that can be targeted by MRGB. Not only does this aid the diagnosis of high-grade cancer, but also decreases the incidence of indolent disease. The data is currently not clear whether mpMRI can be relied upon as a triage test to determine the need for biopsy as the published studies report that there is a considerable risk of missing significant disease if the scans are utilized in such a manner. This concern may be mitigated by improving risk stratification, potentially by using biomarkers, or it may resolve itself with increasing operator experience.

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Author Contribution

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