Review Article

pISSN: 2287-4208 / eISSN: 2287-4690
World J Mens Health 2018 September 36(3): 223-229
https://doi.org/10.5534/wjmh.180025

The World Journal of Men's Health

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

Niranjan J. Sathianathen, Christopher A. Warlick

Department of Urology, University of Minnesota Medical School, Minneapolis, MN, USA

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,

Received: Apr 9, 2018 **Revised:** May 27, 2018 **Accepted:** May 31, 2018
Correspondence to: Niranjan J. Sathianathen https://orcid.org/0000-0002-3710-014X
Department of Urology, University of Minnesota Medical School, 420 Delaware, St. SE, MMC 394, Minneapolis, MN 55455, USA.
Tel: +1-660-334-0774, **Fax:** +1-612-626-0428, **E-mail:** nsathian@umn.edu

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 previous 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.

ACKNOWLEDGEMENTS

Niranjan J. Sathianathen has received support from the Cloverfields Foundation and The Institute for Prostate and Urologic Cancers (University of Minnesota). But this has made no influence on this work.

Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contribution

Conceptualization: all authors. Data curations: NA. Funding acquisition: NA. Investigation: NA. Methodology: NA. Project administration: NA. Resources: NA. Software: NA. Supervision: Warlick CA. Validation: NA. Visualization: NA. Writing (original draft): all authors. Writing (review & editing): all authors.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017;67:7-30.
2. Holmström B, Johansson M, Bergh A, Stenman UH, Hallmans G, Stattin P. Prostate specific antigen for early detection of prostate cancer: longitudinal study. BMJ 2009;339:b3537.
3. Loeb S, Bjurlin MA, Nicholson J, Tammela TL, Penson DF, Carter HB, et al. Overdiagnosis and overtreatment of prostate cancer. Eur Urol 2014;65:1046-55.
4. McGrath S, Christidis D, Perera M, Hong SK, Manning T, Vela I, et al. Prostate cancer biomarkers: are we hitting the mark? Prostate Int 2016;4:130-5.
5. Ankerst DP, Boeck A, Freedland SJ, Thompson IM, Cronin AM, Roobol MJ, et al. Evaluating the PCPT risk calculator in ten international biopsy cohorts: results from the Prostate Biopsy Collaborative Group. World J Urol 2012;30:181-7.
6. Fütterer JJ, Briganti A, De Visschere P, Emberton M, Giannarini G, Kirkham A, et al. Can clinically significant prostate cancer be detected with multiparametric magnetic resonance imaging? A Systematic Review of the Literature. Eur Urol 2015;68:1045-53.
7. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017;389:815-22.
8. Kır G, Seneldir H, Gumus E. Outcomes of Gleason score 3 + 4 = 7 prostate cancer with minimal amounts (<6%) vs ≥6% of Gleason pattern 4 tissue in needle biopsy specimens. Ann Diagn Pathol 2016;20:48-51.
9. Sathianathen NJ, Murphy DG, van den Bergh RC, Lawrentschuk N. Gleason pattern 4: active surveillance no more. BJU Int 2016;117:856-7.
10. Thompson JE, van Leeuwen PJ, Moses D, Shnier R, Brenner P, Delprado W, et al. The diagnostic performance of multiparametric magnetic resonance imaging to detect significant

prostate cancer. J Urol 2016;195:1428-35.
11. Zhang L, Tang M, Chen S, Lei X, Zhang X, Huan Y. A meta-analysis of use of Prostate Imaging Reporting and Data System Version 2 (PI-RADS V2) with multiparametric MR imaging for the detection of prostate cancer. Eur Radiol 2017;27:5204-14.
12. Abd-Alazeez M, Kirkham A, Ahmed HU, Arya M, Anastasiadis E, Charman SC, et al. Performance of multiparametric MRI in men at risk of prostate cancer before the first biopsy: a paired validating cohort study using template prostate mapping biopsies as the reference standard. Prostate Cancer Prostatic Dis 2014;17:40-6.
13. Harvey CJ, Pilcher J, Richenberg J, Patel U, Frauscher F. Applications of transrectal ultrasound in prostate cancer. Br J Radiol 2012;85 Spec No 1:S3-17.
14. Purohit RS, Shinohara K, Meng MV, Carroll PR. Imaging clinically localized prostate cancer. Urol Clin North Am 2003;30:279-93.
15. Schouten MG, van der Leest M, Pokorny M, Hoogenboom M, Barentsz JO, Thompson LC, et al. Why and where do we miss significant prostate cancer with multi-parametric magnetic resonance imaging followed by magnetic resonance-guided and transrectal ultrasound-guided biopsy in biopsy-naïve men? Eur Urol 2017;71:896-903.
16. Andreoiu M, Cheng L. Multifocal prostate cancer: biologic, prognostic, and therapeutic implications. Hum Pathol 2010;41:781-93.
17. Djavan B, Susani M, Bursa B, Basharkhah A, Simak R, Marberger M. Predictability and significance of multifocal prostate cancer in the radical prostatectomy specimen. Tech Urol 1999;5:139-42.
18. Panebianco V, Barchetti F, Sciarra A, Ciardi A, Indino EL, Papalia R, et al. Multiparametric magnetic resonance imaging vs. standard care in men being evaluated for prostate cancer: a randomized study. Urol Oncol 2015;33:17.e1-17.e7.
19. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med 2018;378:1767-77.
20. Baco E, Rud E, Eri LM, Moen G, Vlatkovic L, Svindland A, et al. A randomized controlled trial to assess and compare the outcomes of two-core prostate biopsy guided by fused magnetic resonance and transrectal ultrasound images and traditional 12-core systematic biopsy. Eur Urol 2016;69:149-56.
21. Tonttila PP, Lantto J, Pääkkö E, Piippo U, Kauppila S, Lammentausta E, et al. Prebiopsy multiparametric magnetic resonance imaging for prostate cancer diagnosis in biopsy-naive men with suspected prostate cancer based on elevated prostate-specific antigen values: results from a randomized prospective blinded controlled trial. Eur Urol 2016;69:419-25.
22. Pokorny MR, de Rooij M, Duncan E, Schröder FH, Parkinson R, Barentsz JO, et al. Prospective study of diagnostic accuracy comparing prostate cancer detection by transrectal ultrasound-guided biopsy versus magnetic resonance (MR) imaging with subsequent MR-guided biopsy in men without previous prostate biopsies. Eur Urol 2014;66:22-9.
23. Siddiqui MM, Rais-Bahrami S, Turkbey B, George AK, Rothwax J, Shakir N, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. JAMA 2015;313:390-7.
24. Siddiqui MM, George AK, Rubin R, Rais-Bahrami S, Parnes HL, Merino MJ, et al. Efficiency of prostate cancer diagnosis by MR/ultrasound fusion-guided biopsy vs standard extended-sextant biopsy for MR-visible lesions. J Natl Cancer Inst 2016;108:djw039. doi: 10.1093/jnci/djw039.
25. Filson CP, Natarajan S, Margolis DJ, Huang J, Lieu P, Dorey FJ, et al. Prostate cancer detection with magnetic resonance-ultrasound fusion biopsy: the role of systematic and targeted biopsies. Cancer 2016;122:884-92.
26. Kaufmann S, Bedke J, Gatidis S, Hennenlotter J, Kramer U, Notohamiprodjo M, et al. Prostate cancer gene 3 (PCA3) is of additional predictive value in patients with PI-RADS grade III (intermediate) lesions in the MR-guided re-biopsy setting for prostate cancer. World J Urol 2016;34:509-15.
27. Alberts AR, Schoots IG, Bokhorst LP, van Leenders GJ, Bangma CH, Roobol MJ. Risk-based patient selection for magnetic resonance imaging-targeted prostate biopsy after negative transrectal ultrasound-guided random biopsy avoids unnecessary magnetic resonance imaging scans. Eur Urol 2016;69:1129-34.
28. de Rooij M, Crienen S, Witjes JA, Barentsz JO, Rovers MM, Grutters JP. Cost-effectiveness of magnetic resonance (MR) imaging and MR-guided targeted biopsy versus systematic transrectal ultrasound-guided biopsy in diagnosing prostate cancer: a modelling study from a health care perspective. Eur Urol 2014;66:430-6.
29. Pahwa S, Schiltz NK, Ponsky LE, Lu Z, Griswold MA, Gulani V. Cost-effectiveness of MR imaging-guided strategies for detection of prostate cancer in biopsy-naive men. Radiology 2017;285:157-66.
30. Carroll PR, Parsons JK, Andriole G, Bahnson RR, Castle EP, Catalona WJ, et al. NCCN Guidelines Insights: Prostate Cancer Early Detection, Version 2.2016. J Natl Compr Canc Netw 2016;14:509-19.
31. Moldovan PC, Van den Broeck T, Sylvester R, Marconi L, Bellmunt J, van den Bergh RCN, et al. What is the negative

predictive value of multiparametric magnetic resonance imaging in excluding prostate cancer at biopsy? A systematic review and meta-analysis from the European Association of Urology Prostate Cancer guidelines panel. Eur Urol 2017;72:250-66.
32. Carter HB, Albertsen PC, Barry MJ, Etzioni R, Freedland SJ, Greene KL, et al. Early detection of prostate cancer: AUA guideline. J Urol 2013;190:419-26.