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PROSTATE CANCER (S PRASAD, SECTION EDITOR)

The Use of Multiparametric Magnetic Resonance Imaging (mpMRI) in the Detection, Evaluation, and Surveillance of Clinically Significant Prostate Cancer (csPCa)

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Abstract

Purpose of Review With the long-standing controversy surrounding the use of prostate-specific antigen (PSA) for the detection, evaluation, and surveillance of prostate cancer, there is a need for a minimally invasive technique to identify and risk-stratify these patients. Additionally, in an effort to reduce the number of unnecessary biopsies and identify clinically significant prostate cancer (csPCa), there has been a shift in practice towards the use of multiparametric magnetic resonance imaging (mpMRI) in conjunction with decision-making regarding prostate cancer diagnosis and management. In the current review, we summarize the data regarding the use of mpMRI in the detection, evaluation, and surveillance of csPCa.

Recent Findings Recent prospective clinical trials have determined that a pre-biopsy mpMRI may rule out insignificant prostate cancers, thereby reducing the number of patients who require a biopsy. The anatomic information gathered from these pre-biopsy mpMRI performed during MRI fusion biopsy in csPCa increases the accuracy of pathologic staging in terms of Gleason scores. In regard to active surveillance, prospective trials suggest little to no clinical utility for mpMRI and fusion biopsy in the surveillance of prostate cancer despite conflicting findings from retrospective studies.

Summary Recent trials suggest that mpMRI can play an important role in the detection and evaluation of csPCa. The ideal role for mpMRI in active surveillance remains limited.

Keywords Prostate cancer · mpMRI · Fusion biopsy · Targeted biopsy · Pre-biopsy MRI

Introduction

Prostate cancer is the second most common cancer in men and the fourth most common cancer overall. It is the second leading cause of cancer death in men in the USA, with estimates of 31,620 deaths from the disease this year [1]. However, the majority of men diagnosed with prostate cancer will die of other causes which have led to increased use of active surveillance. The use of multiparametric MRI (mpMRI) for the detection, evaluation, risk stratification, and surveillance of prostate cancer has been steadily increasing over the past few years [2, 3]. mpMRI provides anatomic information of prostate cancer, identifying potential locations, extracapsular extension, seminal vesical invasion, and lymph node invasion [4].

Historically, T2W MRI imaging was used for staging in patients with prostate cancer, focusing on the assessment of extraprostatic involvement. With the development of diffusion-weighted imaging (DWI) and dynamic contrast enhanced (DCE) MRI, the clinical utility of this study has improved and urologists have been using mpMRI more frequently with one survey indicating up to 67% increased use for the detection of prostate cancer over the past 5 years [5]. Additionally, with the standardization of protocols and reporting (PIRADS v2), mpMRI has become increasingly integrated in the diagnostic workup for prostate cancer [2, 3].

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This review reviews the existing literature regarding the use of mpMRI in the detection, evaluation, and surveillance of prostate cancer.

Detection

Recent studies have evaluated the ability of mpMRI to accurately identify clinically significant prostate cancer (csPCa) that could be targeted on biopsy. In particular, mpMRI has shown promise in the detection and exclusion of cancer in men who have elevated prostate-specific antigen (PSA) levels leading to suspicion of prostate cancer [6]. Pre-biopsy mpMRI has not traditionally been the standard of care and is often not covered by insurance; however, with recent studies suggesting that pre-biopsy mpMRI may reduce the number of unnecessary biopsies, the potential impact of including mpMRI in the initial diagnostic workup for prostate cancer is under study. Furthermore, mpMRI provides useful information for targeted biopsies, potentially reducing the number of required sampling cores for confirmation [7–9]. For all of the studies included in this section, csPCa was defined as Gleason ≥ 7 and a positive mpMRI result was any radiologic score (PIRADS or Likert) ≥ 3 or a moderate/high suspicion level.

Early Studies

In 2013, Numao et al. prospectively evaluated 351 men with elevated PSA or an abnormal digital rectal exam (DRE) for clinically suspicious cancer. The cohort was then segregated as low-risk (PSA< 10 ng/ml and normal DRE) and high-risk (PSA ≥ 10 ng/ml and/or abnormal DRE) groups. They evaluated each patient with a transrectal ultrasound (TRUS) biopsy followed by an mpMRI [10]. The reported sensitivity of mpMRI was 71% with a negative predictive value (NPV) of 82%. Furthermore, in 151 men with negative mpMRI results (score < 3), in the low-risk group, prostate volume was the only significant predictor of prostate cancer. The NPV of mpMRI and lower prostate volume (<33 ml) for significant cancer ranged from 95.1 to 97.5%, indicating that 33% of men could have avoided biopsies [10]. That same year, Rais-Bahrami et al. prospectively studied 583 men evaluating the ability of mpMRI to detect csPCa. They assessed the concordance of mpMRI to TRUS biopsy as well as correlations between other clinical factors and the detection of prostate cancer. The group reported a sensitivity of 94% with an NPV of 91% [11]. Additionally, they found a significant correlation between a combination of age, PSA, prostate volume, and mpMRI suspicion score with the presence of prostate cancer (odds ratio [OR] 2.2). The OR increased with incremental increases in the mpMRI suspicion score, demonstrating even stronger correlations in the detection of Gleason ≥ 7 disease (OR 3.3) and Gleason ≥ 8 disease (OR 4.2) [11].

In 2014, Abd-Alazeez et al. evaluated 54 men with elevated PSA and at least 1 prior negative TRUS biopsy to undergo an mpMRI followed by template prostate mapping (TPM) biopsy. Each prostate was divided into 2 sectors, right and left, which were independently studied to obtain an $n = 108$; the study reported a sensitivity of 87% with an NPV of 92% [12]. mpMRI performed well based on sensitivity when the definition of significant disease did not include small tumors or those with small amounts of Gleason 4 disease. mpMRI was shown to be a poor confirmatory test with a specificity of 42% with a positive predictive value (PPV) of 29%, suggesting that it is not a reliable method to guide decisions for definitive treatment. In 2014, the same group evaluated 129 patients with suspected prostate cancer defined by a high PSA, positive family history, and/or abnormal DRE, who were biopsy-naïve—a different cohort from their previous study. Each patient underwent an mpMRI and those with positive mpMRI scores underwent TPM biopsy. Again, the group evaluated each man's prostate into two unique study subjects, establishing an $n = 258$. The study reported a sensitivity of 93% and NPV of 91% [13]. However, for varying classifications of csPCa, the sensitivity ranged from 94 to 100% with the NPV ranging from 89 to 100% [13, 14]. Using the same delineating criteria (mpMRI score ≥ 3 and Gleason ≥ 7), however, the specificity of mpMRI was reported as 21% with a PPV of 24%. These two studies in conjunction suggest mpMRI to be an accurate method to rule out csPCa in men with elevated PSA who were biopsy-naïve; however, mpMRI alone (in the absence of biopsy) is not a good csPCa confirmatory test for these individuals.

In 2014, a group in Australia prospectively evaluated 150 men over the age of 40 with elevated PSA or abnormal DRE to undergo mpMRI followed by transperineal grid-directed 30-core biopsies. Furthermore, biopsies outside the templates were performed based on tracking information from the mpMRI directed at regions of interest (ROIs). The reported sensitivity of mpMRI was 100% with an NPV of 100%. Again, mpMRI performed well as a "rule-out" test but proved to be a poor confirmatory test with a specificity of 38% and PPV of 15% [15]. Thompson et al. noted that many ROIs were classified as PIRADS 3 but were benign on mpMRI-guided biopsy. The group suggested that these men could have benefited from a follow-up mpMRI rather than immediate biopsy, generating a new PIRADS 2F category analogous to Bosniak 2F for renal cystic disease. Follow-up mpMRI within 6–12 months with PIRADS 2F classification could differentiate between malignancy and abnormalities that are typically seen in prostatitis or hyperplastic nodules in BPH, thereby increasing the PPV without affecting NPV [15]. In 2016, the same group evaluated 388 men who underwent mpMRI followed by TPM biopsy. Each imaged prostate was sampled using TPM biopsies of 18 regions which were later compared with anatomical findings on the mpMRI. Additionally, 117

men underwent a prostatectomy, which was also correlated to the mpMRI positive imaging regions. Based on the TPM biopsy results, the reported sensitivity of mpMRI for csPCa was 96% with an NPV of 93%. Additionally, only 5 prostate cancers (all Gleason 7) were missed on mpMRI which had PIRADS scores of 2. No prostate cancers were missed in MRI with a PIRADS score of 1. When assessing the 117 radical prostatectomy specimens, the group reported that 109 of the 117 men (93%) had positive mpMRI scores, and 95 (87%) of the men had csPCa [16]. Lastly, the group evaluated concordance of the mpMRI findings and the anatomical findings based on the 18-region TPM biopsy. Overall, there was a 97% concordance between the findings on mpMRI and men having a true positive biopsy in the ROI on the images. The remaining 3% had positive biopsies, but there was an anatomical mismatch between findings on the 18-region TPM biopsy and the mpMRI. The study concluded that when compared with TPM biopsy, mpMRI presents two benefits: first, it provides an excellent NPV providing a valuable tool in ruling out prostate cancer; and secondly, given the high concordance rate, mpMRI provides guidance for the anatomic location of possible cancers at biopsy [16].

UK PROMIS and Recent Trials

The most prominent multicenter trial to date evaluating the diagnostic accuracy of mpMRI with concordance to gold standard TRUS biopsies was the 2017 PROstate MRI Imaging Study (PROMIS). The trial evaluated 576 men over a 3-year period who underwent a mpMRI followed by both a TRUS biopsy and TPM biopsy. They found that mpMRI had a better sensitivity and negative predictive value than TRUS biopsy and estimated that by using mpMRI as a triage test, 25% of men at risk could avoid biopsies. However, given the lower specificity and PPV, they recommended that suspicious mpMRI results should result in a biopsy prior to any definitive treatment [17]. By utilizing the model described in this study, mpMRI could replace biopsy as a more accurate and less invasive modality for detection of prostate cancer, while biopsy could serve as a confirmatory test prior to definitive treatment. The UK PROMIS trial reported a sensitivity of 88% with an NPV of 76% for mpMRI. This performed much better compared with TRUS biopsy which was 48% sensitive with an NPV of 63%. However, mpMRI provides a very little confirmatory value to the diagnosis of prostate cancer with a reported specificity of 45% and a PPV of 65% which performs much poorly than the 99% specificity and PPV of TRUS biopsy [17].

More recently, in 2018, Otti et al. retrospectively evaluated 792 men who underwent mpMRI followed by a biopsy (106 transperineal and 686 transrectal). The study reported a sensitivity of 82% with an NPV of 85%. Additionally, the detection rate of csPCa in the PIRADS < 3 groups equaled 15%; however, it rose to 86% in the PIRADS 5 group; the current standard practice, TRUS biopsy, offers a 37% detection rate. Additionally, mpMRI performed well in detecting aggressive cancers, offering a detection rate of > 90% for Gleason ≥ 8 prostate cancers. Lastly, the study also reported a possible association between PSAD levels ≥ 15 ng/ml/ml, mpMRI scores, and csPCa, meriting further investigation [18].

Overall, when evaluating mpMRI as a tool to provide accurate diagnostic information regarding prostate cancer, it performed very well as a "rule-out" test. When looking at the overall combined data as presented in Table 1 and the forest plots in Fig. 1 ($N = 3225$), mpMRI has a sensitivity of 86.9% (95% CI 85–89%). Using data from the PROMIS trial, TRUS biopsy offers a 48% (95% CI 42–55%) sensitivity when compared with TPM biopsy as gold standard. It is difficult to directly compare the overall sensitivity from the studies discussed in this section since some of the trials compared mpMRI findings directly with TRUS biopsy as gold standard. However, when looking at just the PROMIS trial findings, mpMRI performed much better as a triage test with a sensitivity of 93% (95% CI 88–96%). Furthermore, the hierarchical summary receiver-operating curve (HSROC) shown in Fig. 1 is a collection of the studies from Table 1 with a summary point and an extrapolated HSROC. The area under the curve (AUC) in Fig. 1 is 81% suggesting that mpMRI is a well-performing diagnostic test.

An important factor to consider with mpMRI is misdiagnosis of both false positives and negatives. Overall, the number needed to misdiagnose (NNM) for mpMRI is 3 patients. This number treats false positive (FP) and false negative (FN) as equal misdiagnoses; however, it is clear that FN carries a worse outcome than FP since it would result in a patient with csPCa not receiving a biopsy. Out of 3225 patients, there were 1146 FP and 150 FN suggesting that majority of the misdiagnoses would result in unnecessary biopsies for healthy patients rather than no biopsy for patients with csPCa. Furthermore, in a patient population of 3225 patients who would have undergone mpMRI as a triage test, 931 true negative (TN) patients would avoid unnecessary biopsies. That is to say, mpMRI could result in a 28.8% (931/3225) reduction in unnecessary biopsies.

Evaluation

Conventional random biopsies possess limitations regarding concordance of Gleason score with final surgical pathology. In a meta-analysis of 15,000 patients, Cohen et al. found a biopsy concordance rate of 63% with a 36% upgrade rate and 7% downgrade rate for TRUS biopsy. Additionally, the PPV for moderate (GS 7) and high grade (GS > 7) was 70% and 50%, respectively [20]. Recently, Yu et al. reported a 47% concordance for systematic biopsy (SB) and an upgrade rate of 44% for SB [21]. With pre-biopsy mpMRI becoming a more

Table 1 Summary of the critical literature on diagnostic accuracy of mpMRI for detecting csPCa

Author	Year	*n*	TP	FN	FP	TN	NPV (%)	PPV (%)	Sens (%)	Spec (%)	Weight Spec	Weight Sens	Accuracy (%)	Youden (%)	NNM	NND
Numao et al. [10]	2013	351	85	35	72	159	82.0	54.1	70.8	68.8	9.812	9.991	69.5	39.6	3.280	2.525
Rais-Bahrami et al. [11]	2013	583	175	11	286	111	91.0	38.0	94.1	28.0	9.355	10.270	49.1	22.1	1.963	4.525
Abd-Alazeez et al. [13]	2014	258	50	4	161	43	91.5	23.7	92.6	21.1	8.196	8.738	36.0	13.7	1.564	7.299
Abd-Alazeez et al. [12]	2014	108	20	3	49	36	92.3	29.0	87.0	42.4	8.035	7.676	51.9	29.4	2.077	3.401
Thompson et al. [15]	2014	150	15	0	84	51	100.0	15.2	100.0	37.8	8.488	6.508	44.0	37.8	1.786	2.646
Bergdahl et al. [19]	2015	63	7	2	13	41	95.3	35.0	77.8	75.9	8.456	4.824	76.2	53.7	4.200	1.862
Thompson et al. [16]	2016	344	137	6	129	72	92.3	51.5	95.8	35.8	8.863	10.162	60.8	31.6	2.548	3.165
Ahmed et al. [17]	2017	576	271	37	146	122	76.7	65.0	88.0	45.5	9.529	10.589	68.2	33.5	3.148	2.985
Otti et al. [18]	2018	792	238	52	206	296	85.1	53.6	82.1	59.0	10.020	10.562	67.4	41.1	3.070	2.433
Overall	2013–2018	3225	998	150	1146	931	86.1	46.5	86.9	44.8	100	100	*59.8*	31.7	2.488	3.155

common option in the workup for prostate cancer, fusion biopsies can offer a higher accuracy while also decreasing the number of biopsy samples needed.

Fusion Biopsy Diagnostic Accuracy Compared with Final Surgical Histopathology

In 2014, Le et al. prospectively assessed the diagnostic accuracy of fusion prostate biopsies to final surgical pathology found on radical prostatectomy (RP) in 54 men. Fusion biopsies were obtained from a 12-point systematic grid as is typical of TPM biopsies, along with additional fusion biopsy (FB) cores from ROIs detected by mpMRI under US guidance. When evaluating FB technique as a binary result with Gleason < 7 being a negative test result and Gleason ≥ 7 considered a positive test result, the study reported a specificity of 100% with a PPV of 100% and accuracy of 96% for FB compared against gold standard surgical pathology after RP. Interestingly, combining TPM biopsy with FB detected the highest Gleason pattern found on RP in 81% of cases, compared with 54% for TPM biopsy and 54% for FB alone. FB results were upgraded in 17% of cases (4% GS 6 to 7 and 13% GS 7 to 8) and downgraded in 2% of cases (GS 4 + 5 to 4 + 3). Overall, the group concluded that combining SB with FB resulted in the best predictive accuracy [22].

Siddiqui et al. in 2015 prospectively studied 1003 men who underwent fusion and TRUS biopsies over a 7-year period. All patients were referred for elevated levels of PSA or abnormal DRE and most were biopsy-naïve. In total, 170 men underwent a RP allowing a comparison of the diagnostic accuracy of FB and TRUS biopsy to final surgical pathology. The study assessed the diagnostic accuracies of TRUS, fusion, and combined biopsies as a binary result where Gleason ≥ 7 with ≥ 50% of any core positive for cancer or ≥ 33% of TRUS biopsy cores is considered a positive result and Gleason 6 or low-volume Gleason 3 + 4 is considered a negative result to surgical pathology after RP. FB offered a specificity of 68% with a PPV of 75%, and TRUS biopsy was found to have a 66% specificity and PPV. Using a decision curve analysis, however, the study reported that between threshold probabilities of 30–75%, fusion MR/US biopsy offered a higher net benefit compared with standard/combined biopsies or treat-all/treat-none approaches [23].

A study from Norway in 2015 retrospectively analyzed 135 patients who underwent MR/US FB followed by RP between 2010 and 2013. Furthermore, the study focused on identification of the "index tumor (IT)" on FB. The IT was defined as the lesion with either the highest Gleason score, largest volume, or any extraprostatic involvement. These IT lesions were then analyzed on serial sections on RP specimens. Overall, the study reported FB to be 92% specific with a PPV of 98% at detecting Gleason ≥ 7 prostate cancer along with a sensitivity of 90% and an NPV of 70%. Furthermore, FB was 91%

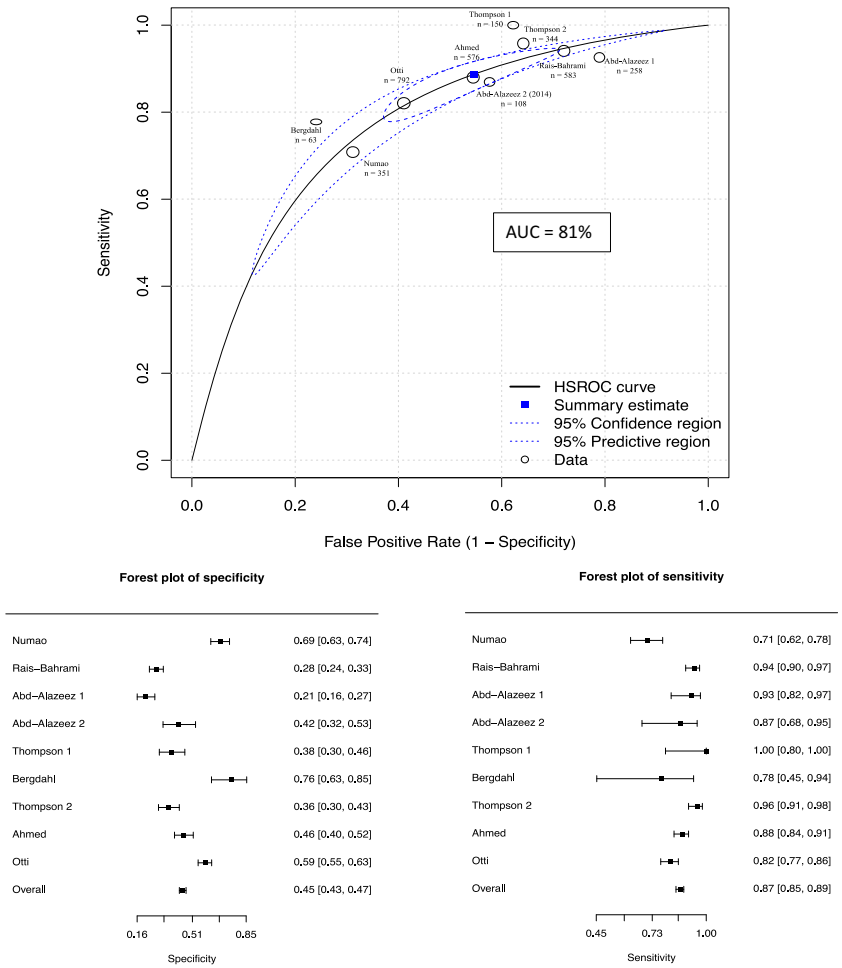

Fig. 1 Hierarchical summary receiver-operating curve (HSROC) for diagnostic performance of pre-biopsy mpMRI in detecting csPCa. This figure depicts the progressive relationship between sensitivity and specificity for mpMRI along with a summary point. As is seen on the graph and forest plots below, the pooled overall sensitivity for mpMRI is 87% (95% CI 85–89%) with an overall specificity of 45% (95% CI 43–47%). Furthermore, the area under the curve (AUC) is 81%. Graphs are generated using MetaDTA (https://crsu.shinyapps.io/dta_ma_1_43/)

accurate at detecting Gleason ≥ 7 prostate cancer when compared with final surgical pathology specimens from RP. When looking specifically at IT lesions, FB overall was 95% (128/135) concordant with RP and the primary Gleason pattern within the IT lesion was 90% (115/128) concordant between FB and RP specimens. The study concluded that FB could allow urologists to reliably locate the most significant lesions in prostate cancer and accurately determine its aggressiveness [24].

Two studies out of Germany in 2016 evaluated the accuracy of FB against RP specimens. Radtke et al. retrospectively evaluated 120 patients who underwent FB and saturation biopsy followed by RP. FB was reported to be 80% specific with a PPV of 99% at detecting Gleason ≥ 7 prostate cancer. Furthermore, mpMRI detected 92% (110/120) of IT lesions on imaging alone while FB accurately diagnosed 80% (96/120) of IT lesions. Saturation biopsy detected 92% (110/120) of IT lesions and combined saturation/FB detected 96% (115/120) of IT lesions. However, saturation biopsy required on average 24 cores compared with four cores for FB. The study concluded that mpMRI alone accurately detected 92% of IT lesions with FB only missing a small number of significant IT lesions. Combined mpMRI, fusion, and saturation biopsy offered the most accurate method for detecting significant cancers but also increased the number of false positives as it led to the detection of low-risk cancers [25]. Borkowetz et al. retrospectively analyzed 105 patients with confirmed prostate cancer by combined FB/SB who underwent RP. The study reported a 100% specificity and PPV for FB alone at detecting Gleason ≥ 7 prostate cancer when compared with RP specimens. Additionally, FB detected 90% (94/105) of prostate cancer compared with 68% (72/105) for SB alone. FB alone would have missed seven Gleason ≥ 7 tumors (false negatives) while SB would have missed 23 Gleason ≥ 7 tumors (false negatives). The reported concordance for GS between biopsy and RP was 63%, 54%, and 75% for fusion, systematic, and combined biopsies, respectively. Again, the study concluded that FB was an excellent modality at detecting csPCa while also allowing for better tumor prediction on final pathology compared with SB. Combined biopsy, however, outperformed either FB or SB alone and provided the most accurate prediction for the final Gleason score (GS) [26].

More recently, a group from Memorial Sloan Kettering retrospectively studied 73 men who underwent fusion biopsies and 93 men who underwent TRUS biopsy followed by

RP to assess the rate of GS upgrade on final pathology. They reported a 100% specificity and PPV for FB with a 92% diagnostic accuracy on final pathology for Gleason ≥ 7 tumors. The Gleason upgrading (GU) rate was higher (31.5%) with TRUS biopsy compared with FB (16.4%). Overall, the study concluded that FB offered a higher concordance between biopsy and final pathology compared with TRUS biopsy, allowing for more accurate clinical decision-making [27].

Another recent study from Mount Sinai retrospectively analyzed 93 patients who underwent FB and 443 patients who had standard 12-core biopsies followed by RP to evaluate the number of patients downgraded from International Society of Urology Pathology (ISUP) grade group (GG) ≥ 3 to GG < 3. The study reported a 63% specificity with a 90% PPV for FB for GG ≥ 3 tumors when compared with final RP pathology. Overall, 76 patients were downgraded with a higher rate in FB (23.7%) compared with 12.2% in standard biopsy. However, the group concluded that downgrading did not have any impact on surgical outcome [28].

PRECISION (2018) and MRI-FIRST (2019)

The PRECISION trial in 2018 was a prospective, randomized, multicenter trial comparing a standard diagnostic pathway with an mpMRI-driven diagnostic pathway. The study enrolled 500 patients with elevated PSA, abnormal DRE, or family history of prostate cancer to receive either the standard diagnostic investigation or a study protocol incorporating mpMRI. In the mpMRI pathway, if the patient had an abnormal (PIRADS ≥ 3) mpMRI (72% of men), they underwent a FB of the suspicious lesion without a SB; subjects with a normal mpMRI were placed on routine PSA surveillance. In the standard diagnostic pathway, all patients underwent a 10–12-core TRUS biopsy. In the mpMRI diagnostic pathway, the detection rate for csPCa (GG ≥ 2, Gleason ≥ 7) was 38% compared with 26% for the standard of care (SOC) pathway. More importantly, the detection rate for clinically insignificant cancer (GG < 2, Gleason < 7) was 9% for the mpMRI diagnostic pathway compared with 22% for the SOC pathway. The study concluded the mpMRI pathway provided a higher PPV and NPV by decreasing both the number of false positives and false negatives [29].

The MRI-FIRST trial is a 2019 multicenter prospective trial out of France that evaluated 251 patients with a PSA level ≤ 20 ng/ml and stage ≤ T2c prostate cancer. Each patient underwent a mpMRI prior to both 12-core SB and mpMRI biopsy with up to 2 cores targeting hypoechoic lesions. Each patient then underwent biopsies targeting up to 2 lesions with a PIRADS score ≥ 3. Overall, 94 patients were found to have csPCa (GG ≥ 2) of which 14% (13/94) were diagnosed by SB alone, 20% (19/94) by FB alone, and 66% (62/94) by both approaches. The study found that the detection of csPCa did not differ significantly ($p = 0.38$) between SB and FB (29.9% vs. 32.3%, respectively). The detection rate of non-csPCa cancer, however, was significantly higher by SB (19.5%) than FB (5.6%), suggesting a higher PPV for FB [30].

The observed difference in the detection rate between SB and FB in the MRI-FIRST trial is significantly smaller than what was reported by the PRECISION trial (2.4% vs. 12%, respectively). Both trials suggest that though the addition of SB to FB improved the detection of csPCa as well as the detection of low-volume and low-grade (non-csPCa) tumors. Together, PRECISION and MRI-FIRST indicate that mpMRI and FB improve the detection of csPCa in biopsy-naïve patients; however, the benefit of combined SB and FB warrants further investigation.

Overall, as shown in Table 2, the overall PPV of FB is 94% confirming its role as an excellent confirmatory tool. The average number of cores needed in fusion biopsy alone was around 4.48. However, combining SB with FB provides the best concordance for GS on final pathology. On an extrapolated HSROC bivariate analysis from the collective data, the AUC is 90% indicating that FB is an excellent diagnostic tool for csPCa confirmed on radical prostatectomy.

Surveillance

Retrospective Studies

A 2013 study retrospectively reviewed men who had received a mpMRI with FB at the time of diagnosis and were selected as potential active surveillance (AS) patients according to Johns Hopkins criteria (PSA ≤ 0.15, ≤ 2 positive cores, ≤ 50% tumor in any core, GS ≤ 6, and stage T1c) [31]. The group reassessed mpMRI findings, focusing on number of lesions, total lesion volume, dominant lesion diameter, lesion density, and lesion suspicion score based on an NCI evaluation score chart. Of the 85 patients who qualified for AS, 25 patients (29%) were reclassified on confirmatory biopsy. The study found that number of lesions, lesion density, and highest mpMRI suspicion were predictive of reclassification. The study concluded that mpMRI may contribute to the decision-making process for clinicians with respect to AS [32].

In 2015, Diaz et al. performed a similar retrospective analysis in men who underwent mpMRI and FB at the time of diagnosis and who were placed on AS according to Johns Hopkins criteria. On confirmatory SB/FB, 22.4% (34/152) of patients had GS ≥ 7 disease. The PPV and NPV of mpMRI for disease progression were 53% (95% CI 28–77%) and 80% (95% CI 65–91%), respectively, with a sensitivity and specificity of 53% and 80%, respectively. To detect one man with Gleason progression, the number needed to biopsy was 8.74 for SB and 2.9 for FB. The study concluded that stable findings on mpMRI were predictive of stable GS resulting in fewer biopsies needed for patients on AS [33].

Table 2 Summary of critical literature on diagnostic accuracy of FB for csPCa

Author	Year	*n*	TP	FN	FP	TN	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Accuracy (%)	No. of cores	Youden (%)	NNM	NND
Le et al. [22]	2014	54	50	2	0	2	96	100	100	50	96	5.900	96	27.000	1.040
Siddiqui et al. [23]	2015	170	72	22	24	52	77	68	75	70	73	6.200	45	3.696	2.221
Baco et al. [24]	2015	128	93	10	2	23	90	92	98	70	91	2.000	82	10.667	1.215
Radtke et al. [25]	2016	120	95	20	1	4	83	80	99	17	83	3.500	63	5.714	1.597
Borkowetz et al. [26]	2016	104	69	28	0	7	71	100	100	20	73	5.300	71	3.714	1.406
Kayano et al. [27]	2018	73	65	6	0	2	92	100	100	25	92	4.000	92	12.167	1.092
Beksac et al. [28]	2019	93	61	13	7	12	82	63	90	48	78	NR	46	4.650	2.193
Overall	2014–2018	742	505	101	34	102	83	75	94	50	82	4.483	58	5.496	1.714

Another 2015 study retrospectively studied 49 men with GS 6 disease who underwent mpMRI at diagnosis and again 6 months later. In evaluating the predictive value of mpMRI for progression of disease, the group found that mpMRI added a significant value alongside PSA density and baseline core length for patients on AS. The reported sensitivity, specificity, PPV, and NPV of repeat mpMRI was 37%, 90%, 69%, and 70%, respectively [34].

Prospective ASIST Trial

The 2018 Active Surveillance magnetic resonance Imaging STudy (ASIST) was a prospective, randomized, multicenter trial that aimed to assess whether mpMRI and FB affected the upgrade rate for patients on AS. Overall, 273 men with GG1 cancer diagnosed within 1 year of the study were randomized, with 136 placed in the TRUS biopsy arm and 137 placed in the FB arm. No difference was observed in the rate of GG ≥ 2 upgrade in each arm with a 27% upgrade rate in the SB arm and 33% upgrade rate in the FB arm ($p = 0.03$). Of note, FB missed 7.9% of GG ≥ 2 cancers found on SB while SB missed 6.5% of csPCa found on FB. The reported PPV and NPV of MRI for csPCa for patients on AS were 23% and 85%, respectively. In the end, the group determined that adding FB to SB did not significantly increase the upgrade rate compared with SB alone, the current SOC [35].

ASIST is the first prospective, randomized trial to evaluate the efficacy of mpMRI and FB in AS. Interestingly, the likelihood of detecting GG ≥ 2 disease was higher in men with MRI ROIs ≥ 3 even if FB was negative. The authors attribute this discordance to either poor fusion technology resulting in missing the target with biopsy, mpMRI inaccuracy, or field effect. Additionally, the study was designed prior to the adoption of PIRADS, which could have impacted identifying target lesions [36]. Further trials may be needed as fusion technology continues to improve and mpMRI becomes more integrated into AS protocols.

Conclusion

In recent years, there has been a shift towards using mpMRI and FB early and more often in the diagnostic workup for prostate cancer. With the complications associated with biopsy alongside a generalized desire by patients and providers to reduce unnecessary biopsies, mpMRI is a promising diagnostic test to incorporate into prostate cancer detection and management.

PRECISION and MRI-FIRST show that mpMRI prior to prostate biopsy can decrease overdiagnosis of prostate cancer; however, there are still men with negative mpMRI who will have csPCa. As presented in Table 1, the overall NPV of mpMRI is 86%, suggesting that 1 in 6 men with negative mpMRI results could have Gleason pattern ≥ 4 cancer

[10–13, 15–19]. Further studies are required to assess whether a significant majority of patients with false negative results present with PIRADS 2 imaging or both PIRADS 1 and 2 imaging. If this is the case, a PIRADS 2F category could be created, similar to what was suggested by Thompson et al., to increase NPV while also avoiding unnecessary biopsies. Furthermore, whether PIRADS ≥ 3 patients should undergo combined biopsies given its higher accuracy and concordance with final pathology as suggested by MRI-FIRST should also be further investigated. In the end, however, mpMRI has a significant role to play in the detection and evaluation of prostate cancer and could serve as a first-line, pre-biopsy test in patients with clinical suspicion for PCa. Using mpMRI to detect csPCa offered an AUC of 81% while FB offers an AUC of 90%. These suggest that both diagnostic tools are valuable tests to include in the workup for prostate cancer.

The studies above provide the groundwork towards larger trials, like PRECISION, that can modify and improve the current standard of care. For the surveillance of prostate cancer, it is unclear whether mpMRI provides additional utility given the results from limited data. Though initial retrospective reports suggested utility for mpMRI, the results from the ASIST trial indicate no added benefit from mpMRI. As we look towards the future, our hope is that upcoming trials will provide a clearer answer to when and how mpMRI should be utilized in the detection, evaluation, and surveillance of prostate cancer.

Compliance with Ethical Standards

Conflict of Interest Parth Patel, Shu Wang, and Mohummad Minhaj Siddiqui each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Abbreviations *mpMRI,* multiparametric magnetic resonance imaging; *csPCa,* clinically significant prostate cancer; *FB,* fusion biopsy; *SB,* systematic biopsy; *GS,* Gleason score; *OR,* odds ratio; *HSROC,* hierarchical summary receiver-operating curve; *AUC,* area under the curve; *GG,* Gleason grade; *TP,* true positive; *FP,* false positive; *TN,* true negative; *FN,* false negative; *PPV,* positive predictive value; *NPV,* negative predictive value; *ROI,* regions of interest; *CI,* confidence interval; *IT,* index tumor; *TRUS,* transrectal ultrasound; *DRE,* digital rectal exam; *PSA,* prostate-specific antigen; *NND,* number needed to diagnose; *NNM,* number needed to misdiagnose

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