

# Multi-parametric magnetic resonance imaging as a management decision tool

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**Abstract:** The ability to image the prostate accurately and better characterize cancerous lesions makes multiparametric magnetic resonance imaging (mpMRI) an invaluable tool to improve management of localized prostate cancer (PCa). Improved risk stratification is warranted given the evidence of significant overtreatment of indolent PCa. mpMRI can more accurately rule out clinically significant PCa in men deciding between surveillance and definitive treatment to reduce overtreatment. mpMRI improves detection of clinically significant PCa, which helps minimize sampling error, a major limitation of the traditional diagnostic paradigm. Aside from helping determine candidacy for initial surveillance *vs.* treatment, mpMRI is a useful tool for following men on active surveillance (AS) with the potential to reduce the need for serial biopsies. When definitive treatment is warranted, mpMRI can be used to determine the local extent of disease. This provides information that is useful in the treatment decision, counseling about outcomes, and surgical planning. While mpMRI is a significant step forward in PCa management, it is necessary to understand its limitations. mpMRI and MRI-guided fusion biopsy techniques still do not detect all clinically significant tumors. The utility of current mpMRI techniques is limited by the multifocal nature of PCa with poor detection of non-index lesions, inaccurate estimation of tumor size and geometry, and the need for interpretation by specialized radiologists. The role of mpMRI will continue to expand as improvements in technology and experience help overcome these limitations.

**Keywords:** Multi-parametric magnetic resonance imaging (mpMRI); prostate cancer (PCa); treatment decisions

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The poor specificity of prostate specific antigen (PSA) and the digital rectal exam (DRE) and the significant sampling error of systematic transrectal ultrasound (TRUS)-guided prostate biopsy (PB) has limited the precision of the conventional diagnostic paradigm for prostate cancer (PCa). With the maturation of magnetic resonance imaging (MRI) technology and experience, the potential for this imaging modality to address these conventional limitations and refine our approach to PCa treatment decisions has emerged as one of the major advances in the diagnosis and

management of this disease, despite lingering limitations. Multiparametric MRI has transitioned out of its limited role in staging to become perhaps the predominant tool for nuanced disease detection, localization and risk stratification.

The appropriate treatment for localized PCa relies on the accurate assessment of the primary disease site. mpMRI is a potentially useful tool in diagnostic strategies aimed at simultaneously reducing overtreatment of indolent disease while avoiding undertreatment of potentially more

aggressive cancer. As such, investigators and clinicians are interested in mpMRI's utility in a variety of scenarios throughout the diagnostic continuum. This review presents the evidence for mpMRI in the following clinical scenarios: (I) assessing candidacy for active surveillance (AS) in a patient with newly diagnosed PCa; (II) incorporating mpMRI into the AS paradigm; (III) detecting locally advanced disease for treatment decision making and surgical planning; (IV) identifying index tumors; and (V) estimating tumor size and geometry.

### **mpMRI to assess candidacy for AS vs. definitive treatment**

The appropriateness of AS in men with very low or low-risk PCa hinges on the accuracy of this risk assessment. Unfortunately, the aforementioned limitations of conventional TRUS PB in detecting clinically significant PCa adds considerable uncertainty to this assessment. A significant body of work demonstrates that incorporating mpMRI into the initial diagnosis of PCa is superior to TRUS PB when using MRI-ultrasound fusion biopsy (MUFb) and radical prostatectomy (RP) specimens as reference standards. The ability of a negative mpMRI to help rule out clinically significant sPCa, reported as the negative predictive value (NPV), increases confidence in the decision to pursue AS candidates. On the other hand, mpMRI aids in the detection of sPCa in patients who were initially candidates for AS based on TRUS PB alone, which corresponds to the positive predictive value (PPV). These patients may benefit from definitive treatment.

Numerous factors affect the accuracy of detecting sPCa using mpMRI, which must be taken into account when interpreting study results. These variables include the definition of clinically significant disease, baseline clinical-pathologic factors and biopsy status (biopsy-naïve or prior negative biopsy), heterogeneity of reference standards used to calculate mpMRI test characteristics (i.e., 12-core TRUS PB, targeted TRUS PB, saturation TRUS PB, transperineal template mapping (TMP) PB, cognitive or in-bore MUFb, and whole mount pathology from RP specimens), experience and blinding of the radiologists, and MRI technique [magnetic field strength, use of functional phases, use of endorectal coil (ERC)]. Finally, the predominantly retrospective, single-institution nature of existing studies introduces the risk for patient selection bias among other systemic biases.

### *Accuracy of mpMRI to assess candidacy for AS using MUFb as reference standard*

The impact of reference standards, biopsy technique, patient selection and variations in radiology performance on assessment of mpMRI performance in detection of sPCa is apparent in a 2016 systematic review that consisted of 12 studies including nearly 2,000 patients (1). Due to the aforementioned heterogeneity, studies in this review report a wide range in overall accuracy (44-87%), sensitivity (58-96%) and specificity (23-87%) for detection of sPCa. NPV varied from 63-98% and PPV of detecting sPCa ranged from 34-93%. The primary limitation of this review is that 11 of 12 studies compared detection by mpMRI against various biopsy techniques rather than whole mount RP specimens (the gold standard) as the reference standard.

Two recent studies that quantify the utility of mpMRI in the decision to pursue AS *vs.* definitive treatment are worth highlighting. Both studies utilize 3.0 Tesla (3T) MRI magnets, functional imaging sequences, and MUFb as the reference standard, which is most consistent with current practice at institutions with specialized experience in prostate mpMRI for diagnosis (2,3).

Hoeks and colleagues prospectively enrolled 64 patients with newly diagnosed low-risk PCa based on TRUS PB who were candidates for AS to receive mpMRI followed by MUFb at 3 and 12 months after initial diagnosis. After 3- and 12-month follow up, 14% (9/64) and 10% (3/30) of the patients were no longer AS candidates. Notably, the NPV for detection of any Gleason 4 or 5 cancer was 100% (45/45) in patients without a Prostate Imaging Reporting and Data System (PI-RADS) 3 or higher lesion. Conversely, the sensitivity of detecting Gleason 4 or 5 cancer in patients with a PI-RADS 4 or 5 lesion was 92% (11/12) (2).

In a retrospective evaluation of 281 men undergoing pre-biopsy mpMRI followed by systematic TRUS PB and concurrent MUFb who qualified for AS based on systematic TRUS PB results, 10% (28 men) were ineligible for AS based on MUFb upgrading to Gleason score 4 or 5 (n=8) or tumor core length (n=20). Nine men were no longer candidates due to both criteria. This study suggests that mpMRI with MUFb is more likely to disqualify older men with smaller prostates from AS (3).

### *Accuracy of mpMRI to assess candidacy for AS using whole mount pathology as reference standard*

Evaluating the test characteristics of mpMRI against whole

mount RP specimens is preferable to using MUFB as the reference standard. Four relevant studies inform the utility of mpMRI to distinguish the appropriateness of AS *vs.* definitive treatment (4-7).

Chamie and colleagues report the incremental benefit of diffusion-weighted imaging (DWI), a functional MRI parameter of molecular diffusion that helps discriminate between indolent and higher grade tumors, over clinical (Epstein) criteria (no Gleason pattern 4 or 5, PSA density  $<0.15$  ng/mL/cm<sup>3</sup>,  $<3$  positive biopsy cores, and none with  $>50\%$  involvement) in predicting the absence of sPCa on final whole mount pathology. Compared to clinical criteria alone, the addition of mpMRI improves the NPV from 68% to 84% for sPCa (pT3 or Gleason  $>6$  of any size) on final pathology, and from 73% to 92% for adverse pathology (pT3, or Gleason  $\geq 4+3$ , or Gleason  $3+4 >1.3$  cc). These results demonstrate that a negative mpMRI provides greater reassurance to low-risk patients that they are truly appropriate AS candidates (4).

Two studies characterize mpMRI findings that predicted pathologic upgrading and/or adverse pathology on RP, thus disqualifying them for AS (5,6). Song and colleagues found that among RP specimens of 382 patients with D'Amico low-risk disease (clinical stage T1 to T2a, biopsy Gleason score 6 and serum PSA  $\leq 10$  ng/mL) on TRUS PB, 55.5% revealed upgrading to Gleason  $\geq 7$  in (44.8% to Gleason  $3+4$  and 10.7% to Gleason  $\geq 4+3$ ) and 29.6% harbored unfavorable pathology ( $\geq$ pT3, Gleason  $3+4$  and tumor volume  $>15\%$  of core, or Gleason  $\geq 4+3$ ). In this series, 65.1% of patients found to have disease unsuitable for AS had PCa identified on mpMRI and 43% of tumors were located in the anterior zone. On multivariate analysis, anterior tumor on MRI (OR =2.48), older age (OR =1.06) and percent of core positive (OR =1.02) are significant predictors of tumor upgrading, while only the presence of an anterior tumor on MRI predicts unfavorable pathology (OR =2.12). NPV for sPCa in the anterior prostate if no anterior index tumor seen on mpMRI is 82.1% compared to a NPV of 61.2% for posterior sPCa if no posterior index tumor seen on mpMRI. This discrepancy reflects the difficulty in anterior tumor detection with TRUS BP and the benefit of whole gland imaging to detect these tumors in particular. This study does not evaluate test characteristics of clinical parameters so is unable to determine the incremental benefit of mpMRI in predicting upgrading and unfavorable pathology (5).

Park and colleagues evaluated 298 patients eligible for AS based on Prostate Cancer Research International Active

Surveillance (PRIAS) criteria [clinical stage T1c or T2, PSA  $\leq 10$  ng/mL, Gleason score of  $\leq 6$ , PSA density (PSAd)  $<0.2$  ng/mL<sup>2</sup>, and  $\leq 3$  positive biopsy cores] who underwent a preoperative 3T non-ERC mpMRI followed by RP. Despite a low-risk cohort (100% Gleason 6, 70.1% with 1 core positive, 80.5% clinical T1c, mean PSA level 4.1), mpMRI identified visible tumor in 88.3% of patients, defined by a 5-point Likert scale of suspicion ( $\geq 3$  was considered visible). Visible tumor on mpMRI predicts upgrading to Gleason  $\geq 7$  (49.8% *vs.* 14.3%) and unfavorable pathology (52.1% *vs.* 14.3%), defined as Gleason  $\geq 7$  and/or pathologic stage  $\geq$  pT3, on final RP pathology, corresponding to a NPV of 85.7%. On multivariate analysis, age  $\geq 65$  (OR =1.95, P=0.008), PSA density  $> 0.08$  ng/mL<sup>2</sup> (OR =2.41, P=0.004), and visible MRI lesion (OR =6.4, P<0.001) predict unfavorable disease. This study is limited by the use of a Likert scale of suspicion rather than a PI-RADS scores and the lack of correlation between visible mpMRI lesions and final pathology (6).

Against the backdrop of mounting evidence that AS is a reasonable treatment option in appropriately selected men with intermediate-risk PCa (8,9). Gondo and colleagues evaluated the utility of mpMRI in identifying a subgroup of patients with biopsy-proven Gleason  $3+4$  PCa who are downgraded to Gleason 6 on final RP pathology. The investigators retrospectively reviewed 304 cases of men diagnosed with Gleason  $3+4$  PCa on TRUS PB who underwent preoperative 3T mpMRI with ERC and RP within 6 months of biopsy. The only relevant clinical-pathologic factor that differed significantly between patients who were downgraded and those who were not is maximum percentage of core involvement with Gleason 4 (mean 22.5% *vs.* 43.3%, P=0.005). Two experienced independent radiologists interpreted different mpMRI combinations (T2WI, DWI, DCE) to determine the added value of a negative mpMRI (absence of visible tumor) for predicting pathologic downgrading compared to the clinical model alone. This study concludes that the addition of T2WI + DWI (AUC reader 1/reader 2: 0.92/0.88) performs significantly better than the clinical model alone (AUC 0.73) and the clinical model plus T2WI only (AUC 0.83 for both readers). However, the addition of anatomical T2WI only without the functional parameters does not significantly improve the predictive ability for downgrading. Similarly, adding DCE to a predictive model consisting of clinical parameters, T2WI, and DWI does not confer any additional benefit (7).

This study builds on prior work by Lee and colleagues

who conclude that the absence of a lesion on mpMRI predicts Gleason 6 pathology in low-risk men who do not meet PRIAS criteria for AS due to the number of biopsy cores positive and/or PSA density. Among these patients, those with no visible tumor on 3T non-ERC mpMRI are more than twice as likely to have favorable final RP pathology as those with a visible tumor (OR =0.43, P=0.007). Visible tumor is the only independent preoperative predictor of favorable pathology when also considering clinical-pathologic parameters (10).

While patients and physicians continue to rely on imperfect information to make PCa treatment decisions, mpMRI may aid in the decision-making process when applied to the appropriate clinical situation. It is important for clinicians to understand the ability for mpMRI to capture missed sPCa in men likely to benefit from active treatment as well as the capability to more definitively rule out sPCa in men who are better served by initial AS.

### Utility of mpMRI in men on AS

More than 1 in 3 men on AS demonstrate pathologic progression during follow up, largely owing to the sampling error inherent to conventional AS protocols highlighted in the previous section (11,12). Traditional AS protocols utilize the DRE, PSA and PSA kinetics to monitor for disease progression; however due to the poor reliability of these methods as triggers for intervention, serial PB are also recommended to identify pathologic progression (13-15). The National Comprehensive Cancer Network, in particular, acknowledges the utility of mpMRI and MUFb as an adjunct to conventional AS protocols in certain situations due to the improved detection of sPCa (14). Considering the non-trivial morbidity and quality of life detriments associated with serial PB (16-20) there is significant interest in incorporating non-invasive mpMRI testing into AS protocols to improve patient selection, safety, quality of life, and satisfaction of men on AS.

Investigators have evaluated whether mpMRI progression predicts pathologic progression in men on AS. In a retrospective study of 49 men with Gleason 6 PCa diagnosed by TRUS BP who selected AS and underwent baseline mpMRI with confirmatory MUFb followed by at least one subsequent mpMRI and MUFb more than six months later, Felker and colleagues evaluate the diagnostic performance of mpMRI with and without clinical data to determine whether mpMRI progression [increase in index lesion PI-RADS score, increased index lesion volume, or decreased index

lesion apparent diffusion coefficient (ADC)] predicts pathologic progression on subsequent biopsy (21). After a mean interval between baseline and follow up mpMRI of 28.3 months, 11 patients (39%) demonstrated pathologic progression in subsequent MUFb, defined as  $\geq$  Gleason 3+4 in any biopsy core. The sensitivity, specificity, PPV, and NPV for predicting pathologic changes was 37%, 90%, 69%, and 70% for mpMRI alone. The AUC of mpMRI alone (0.63) was inferior to that of clinical parameters alone, including PSA<sub>d</sub> and maximum core length (0.87). The combination of mpMRI and clinical parameters significantly improves the predictive model for pathologic progression (AUC 0.91, P=0.044) and demonstrates the importance of evaluating imaging findings in the context of clinical data.

In a retrospective review of 166 men with visible lesions followed on AS for a mean of 25.5 months with  $\geq 2$  MUFb, 29.5% demonstrated pathologic progression. Targeted MUFb identified 26% more cases of pathologic progression than systematic 12-core PB (44.9% vs. 30.6%, P=0.03) and progression on mpMRI was the sole predictor of pathologic progression on subsequent biopsy. mpMRI progression had an NPV of 81%, PPV of 35%, sensitivity of 77.6% and specificity of 40.5%. These results provide additional evidence that men with stable mpMRI findings on AS have a low likelihood of pathologic progression (22).

A recently published prospective AS study reports intermediate-term results of 86 men with a visible tumor on pre-enrollment mpMRI (23). After median follow up of 9.5 years, baseline ADC level below the median is a significant independent predictor of adverse histology (HR =2.13) and radical treatment (HR =2.54). Median time to radical treatment for men with low baseline ADC is 2.40 years compared to 9.33 years in men with baseline ADC above the median. This study suggests that ADC may be a useful tool to risk-stratify men entering into AS protocols, consistent with the findings of Chamie *et al.* described above. This research group is currently conducting a prospective evaluation of an AS protocol consisting of mpMRI at baseline, 12 and 24 months without mandatory repeat biopsy in patients with stable ADC measurements.

### *mpMRI to reduce the intensity of biopsy during AS*

mpMRI is a potentially useful strategy to determine which patients on AS may safely forego or delay serial PB in an attempt to minimize morbidity. A negative mpMRI in this population generates a high NPV for sPCa due to the strong specificity of mpMRI and moderate pretest

probability for sPCa in AS cohorts.

Investigators from the National Cancer Institute sought to evaluate the ability of mpMRI and MUFb to confirm AS candidacy upon entry and predict continued AS eligibility in order to reduce the number of unnecessary confirmatory biopsies (24,25). Through retrospective review of 85 very low-risk patients qualifying for AS based on Johns Hopkins criteria (PSA density <0.15 ng/mL,  $\leq 2$  positive cores,  $\leq 50\%$  tumor in any core,  $\leq$  Gleason 6, stage T1c) who underwent baseline mpMRI with at least one suspicious lesion and subsequently underwent confirmatory mpMRI, investigators found that 25 (29%) patients no longer met AS criteria after MUFb. The authors then characterized mpMRI findings that predicted the probability of disqualification from AS to create a clinically useful nomogram. The number of lesions, maximum lesion suspicion, and lesion density were significant predictors included in the model. Using this nomogram, the authors concluded that a substantial proportion of men may safely choose to forego confirmatory biopsy based on the NPV corresponding to their individual nomogram probability of AS disqualification and degree of risk tolerance (24).

Using this same nomogram for the likelihood of AS disqualification, the authors modeled the number of biopsies avoided using different thresholds to trigger repeat biopsy. They found that 27–68% of repeat biopsies could be avoided with cutoff probabilities of AS disqualification between 19–32%. The tradeoff of fewer biopsies at higher cutoffs is the greater chance of skipping a biopsy that would have revealed sPCa (26). The clinical significance of this potential delay in reclassification and time to definitive treatment remains unclear and requires additional prospective study.

Fifty-eight patients in this same cohort who were not reclassified on initial confirmatory MUFb and chose AS as their initial treatment were followed with subsequent mpMRI and MUFb (27). With a median follow up of 16.1 months, 17 men (29%) progressed to Gleason 3+4. mpMRI in this setting demonstrated a PPV of 53% and NPV of 80%. While a negative mpMRI should be reassuring, the 20% chance of sPCa despite negative mpMRI remains too high to recommend completely replacing pathologic evaluation with imaging at this point in time. Of note, this 20% “miss rate” is equivalent to the false negative rate of mpMRI for the detection of sPCa found in a number of mpMRI-whole mount correlation studies (see below).

Mullins *et al.* calculated the NPV of mpMRI for pathologic index lesions, defined as cancer present in a given

sexant on two separate TRUS PBs, through retrospective review of 50 patients followed on an established AS protocol with identical criteria as the above studies (28).

Pathologic index lesions identified on repeat biopsy are predictive of index lesions on RP and are a surrogate for sPCa (29). After a median follow up of 47.5 months, median time from initial diagnosis to initial mpMRI of 45.5 months, and a total of 215 person-years of follow up, 91% of patients with a negative mpMRI had no pathologic index lesions. The increased NPV in this study compared to the prior two studies is due to the difference in the definition of pathologic index lesion compared to other criteria for disease reclassification and because serial biopsies were performed using TRUS PB rather than MUFb as in the preceding two studies. Despite the low sensitivity (19%) and PPV (55%), patients with an mpMRI index lesion were significantly more likely to have biopsy reclassification than those without (40% *vs.* 12.5%,  $P=0.04$ ), most commonly due to volume criteria (88.9%). While this study suggests that a negative mpMRI in very low-risk men on AS is reassuring and argues for less frequent PB in some men, the presence of sPCa even in this very low-risk cohort in men with negative mpMRI reinforces the notion that mpMRI is not perfect and serial pathologic sampling is still necessary. The optimal interval for repeat biopsy in the setting of negative mpMRI is yet to be determined and warrants prospective evaluation.

### mpMRI for clinical staging and surgical planning

Clinical stage plays an important role in treatment decisions for men with localized PCa. Oncologic outcomes are significantly better in pathologic stage 1 or 2 organ-confined disease (OCD) compared to locally advanced (pT3–pT4) cancer, as defined by extracapsular extension (ECE) (pT3a), seminal vesicle invasion (SVI) (pT3b), or direct invasion into the bladder, external sphincter, or rectum (pT4). The side effects of surgical therapy differ from radiation, particularly the degree of early erectile dysfunction and urinary incontinence (30–32). Aggressive nerve sparing may help mitigate these side effects; however, overly aggressive nerve preservation must not marginalize cancer control. Therefore, in men with ECE, SVI, and/or direct invasion into the neurovascular bundle (NVB), wider surgical margins are necessary to ensure adequate resection of the primary cancer.

Physical exam and TRUS imaging understages up to 25–30% of patients preoperatively (33,34). Nomograms

aim to predict the likelihood of organ confined disease, ECE and SVI and inform treatment decisions and surgical planning by synthesizing clinical factors including PSA, Gleason score, biopsy results, and clinical staging (35,36). Improved visualization of prostate anatomy, including the prostatic capsule, seminal vesicles, and the NVB in addition to functional parameters that help differentiate benign from malignant tissue make mpMRI a potentially useful tool for preoperative planning to enhance the accuracy of clinical staging and aid in treatment decision-making.

A 2016 meta-analysis highlights the heterogeneity of studies evaluating mpMRI for local staging (37). The authors pooled data from 75 studies meeting inclusion criteria published between 2000 and 2014. These studies differ in their use of magnetic field strength, ERCs and combinations of anatomical and functional techniques, which results in significant heterogeneity in the results. Study characteristics are as follows: The majority use a 1.5T magnet (3T, n=21; 1.5T, n=47; 1.0T, n=1), 63% used an ERC (n=47), the majority utilize anatomical T2WI only (T2WI, 55%; one additional function technique, 28%; two-three additional functional techniques, 4%), and 56% are retrospective. Radiologists are blinded to clinical data in only 35 studies (unblinded in 14, partially blinded in 1, and not reported in 25) and pathologists are blinded to the MRI in only 18 studies (unblinded in 2 and not reported in 55). Subgroup analyses demonstrate functional imaging in addition to anatomical T2WI and higher field strength (3T) improves sensitivity and specificity for ECE and SVI. ERC use does not improve ECE sensitivity. Pooled data for detection of ECE, SVI and overall pathologic T3 disease are included below:

Investigators have demonstrated that mpMRI performs favorably compared to the standard clinical nomograms for local staging. 3T mpMRI outperforms Partin tables in a small (n=60), predominantly low to intermediate-risk cohort (AUC 0.82 *vs.* 0.62,  $P=0.04$ ). mpMRI test characteristics are high for OCD (sensitivity 81.6%, specificity 86.4%, PPV 91.2%, NPV 73.1%) and ECE (sensitivity 77.8%, specificity 83.4%, PPV 66.7%, NPV 89.7%) (38).

The additive benefit of mpMRI to clinical predictive models is more clinically useful than direct comparison since patients and providers make treatment decisions based on the combination of data. mpMRI consistently improves the performance of clinical models [Partin tables, Cancer of the Prostate Risk Assessment (CAPRA) score, and Memorial Sloan Kettering Cancer Center (MSKCC) nomogram] for ECE and SVI and these studies

demonstrate that combining clinical with radiographic data results in the optimal diagnostic accuracy (39,40); Feng and colleagues reported the AUC for ECE detection increases when 3T mpMRI is added to Partin tables (AUC 0.93 *vs.* 0.85,  $P=0.017$ ) and MSKCC nomogram alone (AUC 0.94 *vs.* 0.85,  $P=0.023$ ) (39). Morlacco and colleagues show that even with a 1.5T magnet, the detection of ECE improves when mpMRI is added to the CAPRA score alone (AUC 0.77 *vs.* 0.69) and the Partin table alone (AUC 0.73 *vs.* 0.61). Adding mpMRI to the CAPRA score and the Partin table alone similarly improved the predictive model (AUC 0.83 *vs.* 0.75 and AUC 0.82 *vs.* 0.75, respectively) (40).

The clinical utility of mpMRI for preoperative staging changes based on the baseline risk of disease. With different pretest probabilities for locally advanced disease, the test characteristics and therefore the PPV and NPV are variable. Somford *et al.* nicely demonstrate this principle in 183 patients undergoing a preoperative 3T ERC mpMRI and arrive at several clinically applicable conclusions. (I) In low-risk patients, the high NPV is sufficient to rule out ECE owing to the low pretest probability of these pathologic findings and aggressive nerve spare (or AS) would be appropriate. (II) The relatively high proportion of false-negative mpMRI results in intermediate-risk patients suggests that even with no ECE on mpMRI, there is a substantial risk (nearly 40%) of ECE on final path. Therefore, the NPV of 57.7% is not sufficiently reassuring for absence of ECE and the impetus is on the surgeon to avoid positive surgical margins during the resection. (III) The high specificity for ECE results in a PPV of nearly 90% for both intermediate-risk and high-risk disease. Therefore, the decision to perform non-nerve sparing prostatectomy is much clearer in these patients (41).

Additional studies demonstrate that the suspicion for ECE and definitive ECE on mpMRI are reliable indicators of “established ECE”, defined as multifocal ECE or >5 extracapsular glands. However, mpMRI is unable to detect focal ECE, though focal ECE is associated with good prognosis and is unlikely to be of clinical significance (42,43). This study also determined that mpMRI accurately localized established ECE to the specific prostate zone on final pathology, however the sensitivity for detection is lowest at the apex (30%) compared to the base (70.4%) owing to the anatomical ambiguity and the loss of fat planes at the apex (44).

Baco and colleagues investigated the relationship between tumor contact length (TCL) with the prostate capsule on mpMRI and ECE. They determined that

pathologic MRI and pathologic TCL are highly correlated ( $r=0.84$ ). Since pathologic TCL is more closely associated with microscopic ECE (mECE) than pathologic tumor volume, the authors postulate that MRI TCL would be highly predictive of mECE. They were in fact able to show that MRI TCL is a better predictor of mECE (AUC 0.88), than tumor volume on MUFB (AUC 0.70) and Partin tables (AUC 0.63). Finally, the authors suggest that  $TCL > 20$  mm is superior at predicting mECE than conventional MRI parameters used to predict ECE (bulging or disruption of the capsule, fatty tissue invasion, rectoprostatic angle obliteration, asymmetry or direct involvement of the NVB). They surmise that tumors exhibiting mECE are likely to be more involved with the capsule without necessarily causing the findings typically used to determine extensive ECE (45).

Finally, Tay and colleagues elegantly demonstrate the importance of having specialized, expert radiologists interpreting preoperative mpMRI. The authors compare test characteristics of mpMRI to predict pathologic ECE between a standard MRI interpretation and a blinded specialist read. The sensitivity and specificity of the standard read (77% and 44%) are significantly inferior to that of the specialist read (86% and 81%). The addition of the standard read minimally improves the predictive model (0.69 to 0.72) while the specialist read improves it significantly (0.91). The positive likelihood ratio using clinical parameters only, adding the standard read, and adding the specialist read are 1.7, 1.7, and 6.5. The negative likelihood ratio changes from 0.6 to 0.5 with the addition of the standard read, but decreases to 0.1 with the specialist read (46).

Finally, to determine the clinical impact of mpMRI on surgical planning, McClure and colleagues performed a prospective study of 105 consecutive men undergoing robotic RP (47). For each case, a single expert surgeon documented a preliminary surgical plan based on clinical factors alone. The surgeon then reviewed the mpMRI results and formulated a new surgical plan that incorporated the imaging findings. The surgical plan changed in 27% of the cases after mpMRI review. 57% of cases with a change in plan went from non-nerve sparing to nerve sparing, while 41% with an initial plan to preserve nerves ultimately were slated for non-nerve sparing. Positive surgical margins, a potential drawback of a false-negative mpMRI, were found in only one case that was changed from non-nerve sparing to nerve sparing based on the mpMRI findings. mpMRI findings did not alter the preoperative plans of the remaining six cases with positive margins. The authors conclude that mpMRI read by an expert radiologist may

reduce the morbidity of robotic RP by identifying more candidates for nerve sparing while preserving oncologic outcomes and low surgical margin rates.

## Limitations of pretreatment mpMRI

### *Detection of index tumor*

Due to the significant side effects associated with radical treatment for PCa, considerable interest in focal therapy has emerged in recent years. Successful focal therapy relies on the premise that accurately identifying and treating an index tumor sufficiently eradicates the potential for progression and lethal metastasis (48). Several retrospective reports of single and multi-institutional case series suggest mpMRI detection rates for index tumors are in the range of 80-95% (45,49-51). While these results are encouraging, a substantial proportion of index lesions and sPCa are missed by mpMRI, supporting the continued need for systematic biopsy in addition to mpMRI and targeted MUFB. Investigators have found that tumor detection improves with index status (index > non-index), larger size, higher pathologic grade, and location in the prostate (base/midgland > apex) (49,52). Tumor multifocality, however does not adversely affect the detection of the index tumor (49). However, these retrospective studies are subject to selection bias by design, as the reference standard to index tumor detection requires RP, and results may not be valid in patients who do not undergo RP.

### *Multifocality and characteristics of missed tumors*

The multifocal nature of PCa is well established yet multifocality does not necessarily portend worse outcomes (53-55). However, further evaluation into the pathologic characteristics of missed non-index lesions raises additional concerns about the current limitations of mpMRI in assessing candidacy for focal therapy. According to Le et al, RP specimens harbor multifocal disease in 64% of patients with an overall mpMRI detection rate of only 21%. While the majority of the missed multifocal tumors are small and low grade, mpMRI misses 28% of  $\geq$  Gleason 3+4 tumors and 28% of tumors  $>1$  cm in diameter. One in five men ( $n=25$ ) harbor a non-index lesion with  $\geq$  Gleason 3+4 pathology, 72% of which are missed on mpMRI. Additionally, 14% of tumors harboring the most aggressive pathology were not located in the largest tumor focus, suggesting that size should not be the sole criteria for

selection of candidate lesions for focal therapy (49). These findings are corroborated by Radtke *et al.*, who report that 56% of all mpMRI-missed lesions were small Gleason 3+4 tumors with a median volume of 0.6 mL (50).

The clinical significance of MRI-invisible lesions is still uncertain. Reassuringly, nearly 75% of missed Gleason 3+4 lesions contain less than 10% of pattern 4 tumor (50). De Visschere *et al.* reported on 391 patients with elevated PSA and negative mpMRI, 124 (31.7%) of whom were subsequently diagnosed with PCa within 2 years. The majority of cases are Gleason 3+3 (67.7%), 17.7% Gleason 3+4, and 14.5% primary Gleason  $\geq 4$ . Missed high-grade tumors (primary Gleason  $\geq 4$ ) are predominantly small (66.6% of 18 tumors  $< 1$  cm). About 96% of all missed tumors and 83.3% of missed Gleason 4 or greater tumors are organ confined (56).

The authors identify several factors associated with missed significant lesions on MRI upon retrospective re-review. Radtke *et al.* reported that the DWI or DCE functional sequences were technically insufficient in half of the cases of missed significant tumors (50). De Visschere *et al.* found that 52.4% of mpMRIs initially read as negative were retrospectively reinterpreted to have visible tumor in 17.7% and suspicious for tumor in 34.7%. In the 18 patients subsequently found to have high-grade tumors, retrospective re-review found only five of the initial mpMRIs were actually negative (56).

### ***Underestimation of tumor volume and geometry***

In addition to accurately detecting and localizing target lesions, mpMRI must accurately depict tumor volume and geometry in order to provide an appropriate target for focal therapy. Cornud and colleagues correlate RP pathologic tumor volumes with preoperative mpMRI volume estimations for tumors greater than 0.2 cc and confirm prior reports on the limited accuracy of mpMRI tumor volume estimates (57-60). DWI, DCE and T2WI volume estimations were calculated individually using planimetry and compared against pathologic volumes. T2WI and DCE phases underestimate pathologic volumes by an average of 6% and 35%. Pathologic volumes correlate most closely with DWI volume estimates, yet still underestimate 49% of tumors by an average of 0.56 cc. This volume underestimation is proportionately greater in smaller tumors  $< 0.5$  cc. The authors employed two additional techniques for estimating radiographic tumor volume, which result in mean overestimation of 16% and 44%,

while still underestimating tumor volume in 32% and 17% of specimens (60).

Using an innovative technique, Priester and colleagues printed 3-dimensional custom molds created from T2WI contours of the prostate capsule and cancer suspicious regions in order to align 3-dimensional reconstructions of tumors from whole mount sections and evaluated the correlation between mpMRI and pathologic tumor size. The authors demonstrate that mpMRI consistently underestimates the size and extent of prostate tumors with significant implications for focal therapy planning. PCa foci exceed the radiographic area of interest by an average of 11 mm and pathologic tumor volume is on average three times greater than indicated on T2WI. The median tumor extends 13.5 mm beyond the boundary of the MRI contour and 80% of cancer volume from matched tumors is located outside of the radiographic region of interest (61).

### **Future directions**

mpMRI is revolutionizing the detection, localization, risk stratification, and treatment of PCa, and its benefits in the pretreatment setting are substantial. It is important to understand the potential role for mpMRI in clinical practice, but also the limitations that continue to make PCa treatment decisions challenging for patients and clinicians. Further technologic advancements, improvements in functional sequence techniques, the coupling of molecular and genomic markers with imaging, as well as greater expertise and experience will continue to improve the management of localized PCa.

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### **Footnote**

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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