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Should men undergo MRI before prostate biopsy − CON

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Abstract

Prostate magnetic resonance imaging (MRI) is increasingly used prior to biopsy in response to the overdiagnosis and overtreatment of prostate cancer (CaP) associated with prostate-specific antigen (PSA) based screening. However, technical limitations in the conventional diffusion-weighted imaging (DWI) sequences as well as the high degree of radiologist-to-radiologist variability in interpreting prostate MRI result in inadequate accuracy. Specifically, the insufficient negative predictive value (NPV) of prostate MRI (76%−87%) does not allow biopsy to be omitted in the negative MRI setting. Additionally, the variable, and relatively low positive predictive value (PPV) of MRI (27%−44%) provides only an incremental improvement in risk prediction compared to readily available clinical tools such as the Prostate Cancer Prevention Trial risk calculator. This small benefit is likely confined to the minority of patients with positive MRI findings in a typically under-sampled region of the prostate (e.g., anterior lesions), which may be obviated by newer biopsy approaches and tools such as transperineal prostate biopsy and micro-ultrasound technology. With these considerations in mind, pre-biopsy prostate MRI in its current form is unlikely to provide a clinically significant benefit, and should not be considered as routine practice until its accuracy is sufficiently improved.

Keywords: Prostate cancer; Prostate-specific antigen; MRI; Biopsy

1. Introduction

Prostate cancer (CaP) screening using prostate-specific antigen (PSA) became controversial in large measure because of the overdiagnosis and associated overtreatment of low-risk CaP [1-3]. In order to reduce overdiagnosis and unnecessary biopsies, the urologic community has increasingly used adjuvant tests, including prostate magnetic resonance imaging (MRI), to better select patients with an elevated PSA for biopsy [4]. This is supported by the most recent guidelines from the European Association of Urology as well as the American Urological Association, which support the use of prostate MRI in men prior to their first biopsy [5,6]. Although prostate MRI prior to biopsy can be beneficial in some patients, the routine use of prostate MRI prior to initial biopsy should be carefully considered. In addition to increased upfront costs [7,8], the clinical value of prostate MRI must be assessed with attention to its limitations, changes in biopsy approaches, and other available biomarkers. Herein, we will discuss why *men should not routinely undergo prostate MRI prior to initial biopsy*. For the basis of this discussion, we will not comment on the merits of prostate MRI in the setting of active surveillance or prior negative biopsy.

2. Commentary or Discussion

2.1. Limitations of prostate MRI to accurately predict the presence of clinically significant cancer

During prostate MRI interpretation, the Prostate Imaging-Reporting and Data System (PI-RADS) is used to provide standardized risk prediction of clinically significant CaP on a 1 to 5 scale. For this classification system, the diffusion weighted imaging (DWI) sequence has the greatest impact in determining the overall PI-RADS classification [9]. High grade CaP is likely to cause diffusion restriction on DWI, because of the higher cell density seen with high grade architecture as compared to normal glands. However, DWI is known to have technical limitations in modeling the

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nuances of human tissue behavior [10], and as a result can be confounded by benign conditions that increase cellular density, such as stromal hyperplasia seen in BPH, and inflammation seen in prostatitis [11,12].

As a result of these technical limitations to prostate MRI, significant inter-observer variability occurs during MRI interpretation even when using PI-RADS. Therefore, individual differences in accurately predicting clinically significant CaP are unavoidable. In a study of four radiologists blinded to each other's reads, we found that agreement for PI-RADS classification for a prostate MRI was poor (kappa 0.29) [13]. We also noted substantial differences in accuracy among individual radiologists, likely influenced by experience [14]. In a large study of 26 medical centers including 3449 men, the diagnostic accuracy of prostate MRI for clinically significant CaP was noted to be widely variable (26%−75%) and importantly the positive-predictive value (PPV) was noted to be relatively low (27%−44%) [15]. In fact, the relatively low PPV of prostate MRI has been demonstrated in a number of other studies [16,17], including a meta-analysis of 59 studies with a pooled PPV of 48% [18]. The observed low PPV is reflective of the technical challenges of prostate MRI interpretation, as radiologists seem likely to "over-call" rather than risk a missed diagnosis, leading to false positives, and unnecessary biopsies. Moreover, urologists' varying capabilities to accurately target suspicious sites via various biopsy approaches may further confound our understanding of the true role of prostate MRI in evaluating men with an elevated PSA.

Given these known technical limitations of MRI and its resulting impact on radiologists' interpretation, the skill, and experience of the radiologist is critical. One study of an 'expert' reader re-reviewing prostate MRI from 11 referring medical centers demonstrated a change in PI-RADS classification occurred in 64% of cases (52% of which were downgraded and 12% of which were upgraded) [19]. *Thus, widespread routine performance of pre-biopsy MRI cannot be recommended without careful consideration of who will be available to interpret those images.*

2.2. Biopsy cannot be omitted even if the prostate MRI is negative

For the reasons delineated above, the negative predictive value (NPV) of prostate MRI is inadequate to safely omit prostate biopsy. In a study of "real world" NPV of prostate MRI, we found a 10.3% risk of high-grade CaP in biopsy naïve patients, and 16.7% risk of high grade CaP in those with a previous negative biopsy. The pooled NPV across the currently available studies at that time was approximately 85% [20]. In a systematic review of 42 studies of prostate MRI, the NPV of prostate MRI using PI-RADS classification ≤2 as a cut-off for high grade CaP (Gleason ≥7) was 86.8% [21]. The most important finding in this study as well as previous systematic reviews focusing on the NPV of negative prostate MRI is the high variability from individual study to study, which may be a function of CaP prevalence but may be strongly influenced by the individual radiologist interpreting the study as discussed above [22].

More importantly, one must consider the reference standard used in the above studies to define NPV for negative prostate MRI. Most of these studies used 12-core standard transrectal ultrasound (TRUS) biopsy as the definition of "truth" when calculating the false negative rate. Although this may be standard clinical practice, we know that the accuracy of 12-core TRUS is poor when compared to transperineal template prostate mapping (TPM) biopsy (AUC 0.69 vs. 0.91) when compared to radical prostatectomy specimens [23]. Since patients who are not diagnosed with clinically significant CaP (and some who are) do not undergo prostatectomy, the most accurate assessment of NPV for negative prostate MRI may be the PROMIS study. In this study, all patients underwent prostate MRI, TRUS, and TPM biopsy. The authors demonstrated that MRI was more accurate than TRUS; however, the NPV of MRI when compared to TPM biopsy was 76% [24]. *PROMIS study provides clear evidence that biopsy should not be omitted in the case of negative prostate MRI, which largely eliminates the clinical benefit of routine pre-biopsy MRI in the case of negative MRI.*

2.3. Incremental benefit of prostate MRI even when positive

As noted above, the clinical utility of prostate MRI when it is negative is equivocal since the NPV of prostate MRI is inadequate to change management. However, well-designed large studies have demonstrated improved cancer detection when using an MRI based strategy over systematic TRUS biopsy alone [25]. Thus, it can be reasonably inferred that the clinical benefit of prostate MRI relies on improved detection of clinically significant PCa when the prostate MRI is positive (e.g., a lesion is identified). A positive prostate MRI can impact clinical care in two ways: 1) a positive prostate MRI can be used as a risk stratification tool to predict for high grade disease, and 2) a positive prostate MRI can be used as a technical tool to perform MRI-targeted biopsy. *These clinical benefits of a positive prostate MRI are incremental.*

For risk stratification, we noted earlier in this discussion that the PPV of a positive MRI is variable and overall, relatively low (27%−44%) [15]. Numerous studies have demonstrated an objectively small improvement over existing clinical tools when using prostate MRI to predict clinically significant PCa. Studies of MRI based models have demonstrated statistically significant differences in risk stratification over the Prostate Cancer Prevention Trial (PCPT) risk calculator; however, the observed differences are questionably clinically significant (AUC 0.80 vs. 0.76; 0.78 vs. 0.74) [26,27]. As for MRI-targeted biopsy, studies have demonstrated that MRI-targeted biopsy outperforms systematic TRUS biopsy alone; however, combined MRI-

targeted + systematic TRUS biopsy significantly outperforms MRI-targeted biopsy alone. MRI-targeted biopsy was found to miss ~10% of PCa and was associated with under-grading in ~22% of patients diagnosed with PCa [28]. Thus, in the positive prostate MRI setting, systematic TRUS biopsy must still be performed even when an MRI-targeted biopsy is performed. The observed real-world impact of these considerations may be evident by the increasing utilization of pre-biopsy prostate MRI in the U.S. from 2010 through 2016, with no corresponding increase in the rates of PCa diagnosis [29].

2.4. Different biopsy approaches may further reduce the incremental benefit of prostate MRI

If the benefit of pre-biopsy prostate MRI is limited to those with positive findings and the overall benefit to those with positive MRI appears to be incremental, then there may be a specific subset of patients who benefit from a positive prostate MRI. In fact, in a multi-institutional study, MRI-targeted biopsy was found to be specifically useful for patients with anterior lesions seen on prostate MRI [30]. Similarly, the large prospective series from the National Cancer Institute that was influential in increasing adoption of pre-biopsy MRI across the U.S., a substantial proportion of the cohort was noted to have anterior lesions on their prostate MRI (44%). Of the biopsy naïve patients in their cohort, 34% of men were found to have anterior lesions [31] Considering that anterior sampling of the prostate is uncommonly performed during standard 12-core systematic TRUS biopsy, prostate MRI may be specifically beneficial for those patients found to have a positive MRI with an anterior lesion.

Given the increasing rates of antibiotic resistance and known infectious complications of TRUS [32,33], transperineal approaches to prostate biopsy have been increasingly utilized by urologists [34]. As noted above, the accuracy of transperineal TPM is significantly higher than standard TRUS [23]. Additionally, anterior sampling of the prostate is routinely performed during transperineal biopsy. Therefore, the incremental benefit for a positive pre-biopsy prostate MRI may be negated by transperineal TPM biopsy. Supporting this hypothesis, we have found that upstaging at the time of radical prostatectomy is significantly lower for patients who underwent transperineal TPM biopsy vs. software-fusion MRI targeted biopsy and systematic biopsy (5.6% vs. 25.2%) [35]. With increasing use of transperineal approaches in the office setting [36], the clinical benefit of pre-biopsy prostate MRI may be further reduced. Furthermore, new ultrasound technologies like ExactVu^{TM} micro-ultrasound may allow for real time visualization of the prostate lesions seen on MRI [37]. *Particularly considering the costs of MRI, the advancements in ultrasound technology, and movement to an in-office transperineal biopsy approach may eliminate the incremental benefit of pre-biopsy prostate MRI.*

3. Conclusions

We have discussed that prostate MRI is insufficiently accurate and has a high degree of radiologist-to-radiologist variability owing to benign conditions that mimic the DWI signals of PCa. As a result, routine pre-biopsy prostate MRI: 1) does not provide clinical benefit when the MRI is negative due to insufficient NPV to omit biopsy, and 2) has incremental (and likely not clinically significant) improvements in risk prediction over currently available clinical tools like the PCPT risk calculator when the MRI is positive due to a relatively low PPV. Furthermore, the benefit to those patients who have a positive MRI with an anterior lesion is likely eliminated by increasing use of transperineal biopsy approaches and new micro-ultrasound imaging technology. For very select high-volume centers with the requisite experience and expertise in radiology, pre-biopsy prostate MRI may be considered. For most centers, routine pre-biopsy prostate MRI is very unlikely to provide clinical benefit. An alternative approach compared to a pre-biopsy prostate MRI strategy may be to use serum or urine biomarkers to risk stratify patients to safely avoid biopsy when possible and then use transperineal and/or micro-ultrasound imaging approaches to perform prostate biopsy [38-42]. With all the above in mind, routine pre-biopsy MRI should not be recommended until the accuracy of prostate MRI can be significantly improved.

Disclosures

Dr. Eric Kim has no disclosures or conflicts of interest. Dr. Gerald Andriole is a consultant for Stratify Genomics and OPKO.

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