Review Article

MRI findings guiding selection of active surveillance for prostate cancer: a review of emerging evidence

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Abstract: Active surveillance (AS) for prostate cancer (PCa) is generally considered to be a safe strategy for men with low-risk, localized disease. However, as many as 1 in 4 patients may be incorrectly classified as AS-eligible using traditional inclusion criteria. The use of multiparametric magnetic resonance imaging (mpMRI) may offer improved risk stratification in both the initial diagnostic and disease monitoring setting. We performed a review of recently published studies to evaluate the utility of this imaging modality for this clinical setting. An English literature search was conducted on PubMed for original investigations on localized PCa, AS, and magnetic resonance imaging. Our Boolean criteria included the following terms: PCa, AS, imaging, MRI, mpMRI, prospective, retrospective, and comparative. Our search excluded publication types such as comments, editorials, guidelines, reviews, or interviews. Our literature review identified 71 original investigations. Among these, 52 met our inclusion criteria. Evidence suggests mpMRI improves characterization of clinically significant prostate cancer (csPCa) foci, and the enhanced detection and risk-stratification afforded by this modality may keep men from being inappropriately placed on AS. Use of serial mpMRI may also permit longer intervals between confirmatory biopsies. Multiple studies demonstrate the benefit of MRI-targeted biopsies. The use of mpMRI of the prostate offers improved confidence in risk-stratification for men with clinically low-risk PCa considering AS. While on AS, serial mpMRI and MRI-targeted biopsy aid in the detection of aggressive disease transformation or foci of clinically-significant cancer undetected on prior biopsy sessions.

Keywords: Prostatic adenocarcinoma; multiparametric magnetic resonance imaging (multiparametric MRI); cancer imaging; cancer grading

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Introduction

In 2017 there will be an estimated 161,000 new cases of prostate cancer (PCa) in the United States. This represents nearly 20% of new cancer diagnoses, the most common among non-cutaneous neoplasms in men (1). Following the introduction of prostate specific antigen (PSA) screening in the 1990s, the incidence of PCa has steadily risen while cancer-specific mortality has declined considerably (2). The former has been attributed to increased detection of low-risk, localized disease which may not pose a significant threat to a patient's longevity. Consequently, the appropriateness of aggressive intervention in the setting of increased detection has been brought under question (2,3). For those individuals with low-risk, localized disease, a less invasive management approach may be more appropriate to avoid the potential negative impact the effects of medications, radiation therapy, and surgery may have on a

patient's quality of life (4,5).

Close monitoring of low-risk patients by active surveillance (AS) includes serial serum PSA level assessments, digital rectal examinations, and transrectal ultrasound (TRUS) biopsies, and more recently, multiparametric magnetic resonance imaging (mpMRI). The decision to place a patient on AS, and ultimately determining when to depart from AS, is challenging due to limitations in both disease monitoring and reliable risk stratification criteria (6-8). It is estimated that as many as 1 in 4 patients may be improperly placed on AS based on data supporting the undergrading and underassessment of tumor volume on systematic prostate biopsy for diagnosis and risk-stratification (9,10). Indeed, nearly half of men initially placed on AS will at some point have pathologic progression and require oncologic intervention (11). Therefore, it is incumbent upon clinicians to improve risk-stratification and cancer surveillance protocols to minimize patient oncologic risk.

Over the past decade, mpMRI has emerged as a reliable diagnostic and monitoring adjunct for men on AS (12-14). This approach affords better visualization of the prostate and surrounding structures than traditional TRUS imaging used primarily for systematic tissue sampling at the time of biopsy (15). Specifically the improvements in magnetic resonance imaging technology and optimization of functional imaging sequence techniques such as diffusion weighted imaging (DWI) and volumetric estimation algorithms have permitted superior tumor characterization (16-18).

While variable, mpMRI sequences typically consist of high-resolution T2-weighted imaging, diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) mapping, and dynamic contrast-enhanced imaging (DCEI) (15,17). T2-weighted imaging reflects the generalized water content of tissues which is applicable since normal benign prostatic tissue is water-rich, cancerous tissue is water-poor, and the prostatic capsule is commonly well-defined (15). DWI quantifies the degree of water diffusing through tissues, and similarly aids in differentiating benign tissue from more densely packed malignant prostate tissue (15). The ADC, a measurement of the impedance of water molecule diffusion based on DWI sequences, further distinguishes benign from malignant prostatic tissue with a quantified value that can be mapped as a surrogate image (15). DCEI evaluates tissue vasculature and differentiates benign from malignant tissue based on the altered patterns of angiogenesis observed in cancerous lesions (19). We therefore performed a review of recently published literature to characterize the emerging evidence in support of using mpMRI to properly select patients for AS.

Methods

An English literature search was conducted on PubMed for original investigations on localized PCa, AS, and MR imaging. All articles published within the past few years (January 1st, 2014 through November 28th, 2017) were considered. Our Boolean criteria included the following terms: "PCa", "AS", "imaging", "MRI", "mpMRI", "prospective", "retrospective", and "comparative". Our search excluded publication types including commentaries, editorials, guideline statements, review articles, or interviews. We identified 71 original studies. Among these, 52 publications met our final inclusion criteria. A total of 28 studies evaluated the usefulness of mpMRI for detection of clinically significant prostate cancer (csPCa) in the setting of AS. We identified 18 studies examining the role of mpMRI specifically in guiding prostate biopsy in the context of AS management protocols. Six studies considered using serial mpMRIs in place of routine biopsy to survey men on AS meeting certain risk criteria.

Review

Improved detection of significant PCa

We identified multiple studies that demonstrated the value of using mpMRI during the initial diagnostic workup to classify patients as AS-eligible better than traditional criteria alone without advanced imaging (14,20,21). Ouzzane *et al.* reviewed 281 patients who were initially deemed appropriate for AS based on clinical and biopsy results. They found 10% of the cohort was later reclassified as ineligible for AS following mpMRI and subsequent biopsy of clinically occult lesions found and sampled based on mpMRI results (20). Porpiglia *et al.* went one step further to suggest the use of mpMRI alone may reliably predict pathologically significant disease without confirmatory biopsy (14).

DWI sequencing, which affords calculation of the ADC values for different imaging voxels, gives providers an additional tool to evaluate suspicious prostatic lesions. In a retrospective study of 86 AS-eligible patients who eventually underwent radical prostatectomy, Henderson *et al.* demonstrated a low ADC, defined as lower than their single-institution median value, may independently predict

time to undergoing curative intervention and/or detection of adverse histology (17). Morgan *et al.* compared interval suspicious lesion growth and ADC change in a cohort of 151 men on AS who underwent serial mpMRI over a median two-year interval. They found tumor growth was inversely correlated with change in the ADC, and therefore a significant decrease in ADC may be a sign of impending AS failure based on PCa progression (22).

As processing software continues to improve, there is emerging evidence to suggest even greater PCa detection sensitivity may be achieved with mpMRI. Sharif-Afshar *et al.* conducted a pilot trial comparing standard versus a novel high resolution DWI (HR-DWI) sequencing software in the evaluation of biopsy-confirmed PCa lesions. This technique uses smaller voxel size and also achieves a greater signal-to-noise ratio for greater spatial resolution. They found a 5-fold improvement in spatial resolution with a nearly 35% greater sensitivity in detecting biopsy-proven csPCa (23). Of note, use of 5-alpha-reductase inhibitors does not appear to alter the ability to detect cancerous tissue on prostate mpMRI (24).

It has been shown that automated calculations of lesion volume on mpMRI may correspond with PCa presence (17,25). Marin *et al.* found that using semi-automated sizing algorithms to measure tumor dimensions reliably correlates with actual tumor diameter on final pathology (25). Stensland *et al.* retrospectively evaluated 1,633 patients with available mpMRIs who underwent radical prostatectomy, and concluded tumor lesions <5 mm on mpMRI most likely represent clinically-insignificant disease on final pathology (26). However in a retrospective study of 118 patients, Dianat *et al.* observed 8.3% of men with mpMRI invisible tumors harbored csPCa (27). In a separate study of 298 patients by Park *et al.*, 14% of AS-eligible patients without an identifiable lesion had their PCa upgraded on final pathology following radical prostatectomy, but just one was found to have a positive surgical margin and no patients had greater than either form of Gleason 7 disease (28). Sahibzada *et al.* reached a similar conclusion in their retrospective cross-sectional validation study of 100 patients, and suggest mpMRI may have greater reliability in the post-TRUS biopsy surveillance setting (29).

Incorporation of PIRADS into AS protocols

Over the past ten years, the Prostate Imaging Reporting and Data System (PIRADS) has become an increasingly useful tool for evaluating suspicious prostatic neoplasms (30-32). Suspicious lesions are rated on a five-point Likert scale with a score of 5 being the most concerning for a malignant tumor (33,34). Venderink *et al.* retrospectively evaluated 1,000 patients on AS, and when compared to PSA density, they found a PIRADS score of ≥3 better predicts significant PCa on repeat biopsy (31). In a study by Grey *et al.* that retrospectively reviewed 201 men on AS who underwent both mpMRI and prostate biopsy, they similarly concluded that those with a PIRADS score of <3 could safely forgo a subsequent repeat biopsy. However, 2.3% of the men with PIRADS <3 lesion(s) still harbored csPCa (Gleason pattern 4 or ≥6 mm cancer core length), bringing into question whether it is acceptable to potentially 'miss' a small number of presumably indolent cancers in the population and rely on other parameters in the surveillance protocol to pick these up at a later time point (30). A different study by Porpiglia *et al.* retrospectively analyzed 126 patients who underwent radical prostatectomy, and found incorporating PIRADS into the existing Epstein and/or Prostate Cancer Research International Active Surveillance (PRIAS) criteria would have increased csPCa detection by 5% and 7%, respectively (35). We identified three additional original investigations that compared a widely-accepted AS protocol with a predictive nomogram incorporating PIRADS, and they also demonstrated a significant improvement in risk-stratification (36-38).

More recently, a proposed PIRADS version 2 (PIRADSv2) was developed to capture the increasingly complex MRI characterization of a single lesion with the application of multiple sequences such as DWI and DCEI for interpretation (32,34,39). Studies comparing it to the original PIRADS algorithm are underway in the setting of AS. Yim *et al.* recently found that using the PIRADSv2 scoring system may reliably classify suspicious lesions as clinically-insignificant PCa, therefore permitting safe selection for AS (40). Lim *et al.* found patients with PIRADSv2 scores ≥3 on mpMRI with a prior TRUS biopsy of 3+4=7 PCa have a higher chance of pathological upgrading at the time of radical prostatectomy. Therefore, the PIRADSv2 system could predict AS failure in this select patient population (41).

Alternatively, Nougaret *et al.* suggest PCa may be overlooked as often as 5% of the time when using PIRADSv2 scores of ≥3 as a threshold cutoff (32). In addition, there is concern that central zone (CZ) lesions may not be accurately characterized when using the PIRADS algorithm. In a review of 73 patients who underwent MRI-fusion biopsy, only two (7.7%) of 26 CZ lesions that were designated PIRADS ≥3 actually contained clinically-

significant disease (42). Since there is evidence to suggest PCa originating from the CZ can be more aggressive, relying on the PIRADS score alone may overcall lesions and lead to unnecessary confirmatory biopsy sessions (43,44).

Prostate biopsy in the era of MRI-US fusion

MRI-US fusion technology utilizes the improved visualization of anatomy afforded by MRI to perform targeted biopsy of suspicious prostatic lesions (45,46). Multiple investigations suggest performing MRI-US fusion targeted biopsy may be superior to standard systematic template TRUS-guided tissue sampling to detect new csPCa for men on AS (47-52). Siddiqui *et al.* suggest performing MRI-US fusion targeted biopsy may reduce the number of insignificant PCa diagnoses, thus sparing patients from unnecessary biopsies (53). We identified two studies showing improved csPCa detection when utilizing mpMRI-US fusion technology for transperineal prostate biopsy (54,55). Penzkofer *et al.* found this approach to be of particular benefit in the setting of anteriorly located tumors when utilizing an in-bore MRI-guided approach (55). Felker *et al.* also achieved satisfactory cancer detection rates when performing in-bore MRI-guided biopsy via transrectal approach (56).

However, there is conflicting data over whether performing MRI targeted biopsy in isolation, abandoning the standard twelve core template sampling approach, is a safe monitoring strategy for men on AS (48-50,57). Nassiri *et al.* retrospectively evaluated 250 patients undergoing MRI-fusion biopsy and observed that 32 of 33 cases with pathological upgrading were a result of positive MRI-targeted cores (50). Da Rosa *et al.* reported a 100% negative predictive value for detecting a Gleason score 6 to 7 upgrade when using MRI-fusion technology in their cohort of 72 men on AS (49). Conversely, Marliere *et al.* observed that standard template biopsy at the time of MRI-targeted sampling still has utility for the detection of new and significant cancer foci. In their cohort of 41 men on AS undergoing combined standard template and MRI-targeted confirmatory biopsy, pathological upstaging was attributable to standard template core tissue more than half of the time (57).

Of all of the prostate biopsy modalities, there is strong evidence in support of saturation biopsy (24 or 30 cores templated sampling) as the technique with greatest sensitivity for detecting significant PCa in the initial AS period (58-60). However, it subjects patients to the burden of acquiring a significant amount of tissue, and may not reliably predict the location or extent of disease on pathology following radical prostatectomy (61). Alternatively, Galosi *et al.* proposed a hybrid approach to saturation biopsy called 'cognitive zonal fusion biopsy' (60). For this, patients undergo mpMRI prior to fusion biopsy. If during the biopsy there is a discrepancy between what was found on MRI and what is seen on US, several cores are obtained from the MRI region of interest. This approach reliably detected csPCa in their prospective study of 58 men who were either biopsy naïve, had a prior negative biopsy, or were on AS (60). In a study of 48 men on AS with prior negative TRUS biopsy, Lai *et al.* also achieved satisfactory PCa detection using this technique (62).

Could mpMRI allow safe surveillance without repeat tissue biopsy?

There is emerging evidence to suggest that serial mpMRIs alone may be sufficient to monitor men on AS, and the time interval for repeat confirmatory biopsy could be prolonged (7,63-67). Both Walton Diaz *et al.* and Felker *et al.* reported that stable mpMRI findings reliably correlated with Gleason score stability in their cohorts of men on AS meeting standard inclusion criteria (63,65). Frye *et al.* also appreciated reliable detection of cancer progression using mpMRI alone in a retrospective review of 162 men (7).

Several recent investigations evaluated the usefulness of predicting pathologic progression of an index lesion based on size criteria. In a review of more than 150 men on AS, those with index lesions 7mm or less were found to have no change in either size or pathologic characteristics during a two-year follow-up period (66). Thus, men otherwise meeting AS criteria could potentially defer PCa surveillance for up to a two-year interval of time without compromising care. Based on serial mpMRIs on a cohort of men who underwent regularly scheduled biopsies, Siddiqui *et al.* developed a predictive nomogram for pathological progression. Their nomogram would have theoretically avoided repeat biopsy in 68% of men in their study (64). Lai *et al.* developed a similar predictive nomogram for low-risk men on AS with certain mpMRI criteria but also incorporating clinical parameters for each case (38).

Discussion

AS for low-risk, localized PCa has become a widely adopted strategy, and offers adequate disease control while optimizing quality of life. Nonetheless, this strategy remains

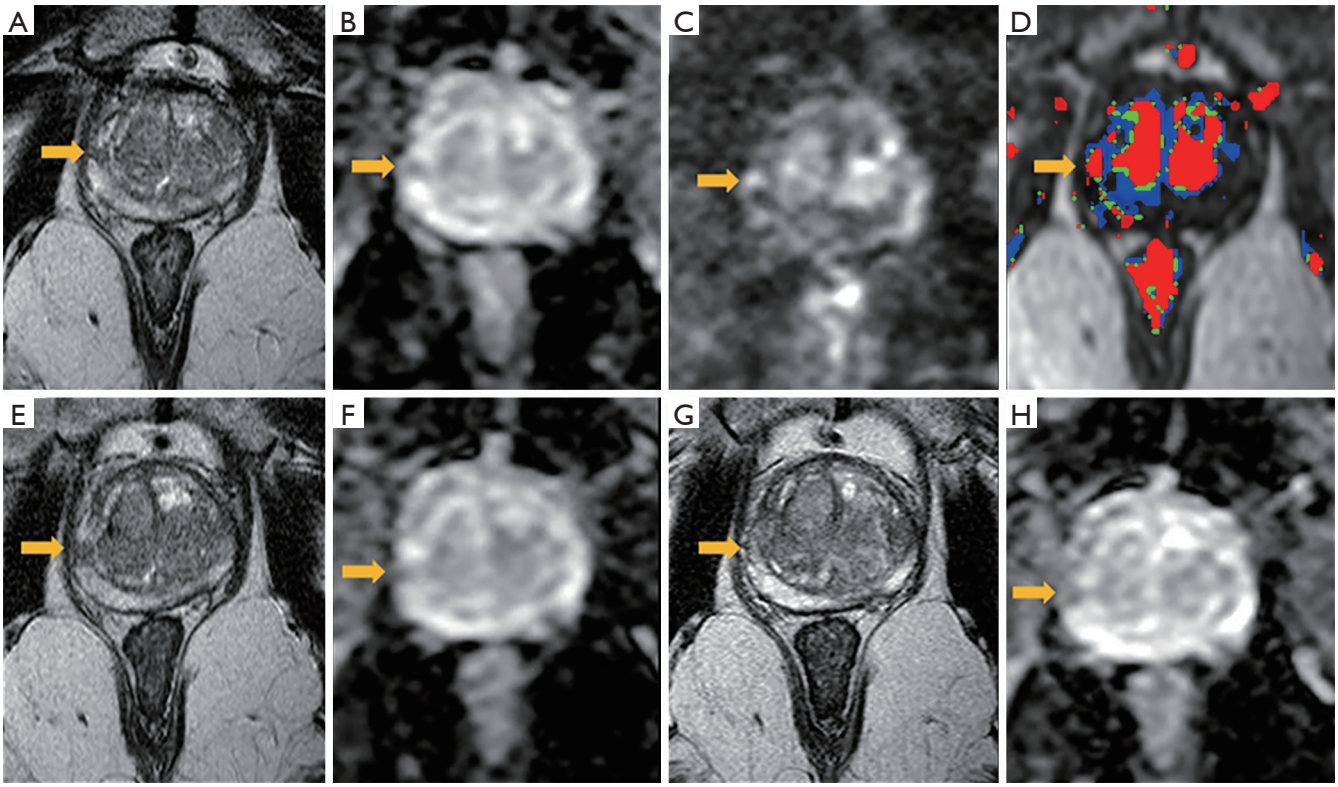

Figure 1 A 65-year-old male with a history of TRUS biopsy performed at another institution presents for repeat biopsy. Pathology from the TRUS biopsy showed atypical small acinar proliferation and the patient's PSA was 5.35ng/mL. Prior to the repeat biopsy, the patient underwent prostate mpMRI (A-D). A circumscribed, focal lesion in the right mid lateral peripheral zone (A) was identified with hypointensity on ADC (B) with associated hyperintensity on high b-value DWI (C). This lesion demonstrated associated abnormal perfusion (D) and was suspicious for csPCa. The patient underwent MR-US fusion biopsy with Gleason 3+3=6 disease on pathology and elected for AS. Subsequent mpMRI in one year demonstrated stability of this focal lesion on T2-weighted images (E) and ADC (F). The lesion remains stable at two-year follow up on T2-weighted images (G) and ADC (H).

a challenge due to disease variability, inconsistencies on optimal surveillance regimens and a wide variety of available diagnostic tests. A majority of AS protocols use serial digital rectal examinations, serum PSA levels, and TRUS-guided systematic biopsies to monitor patients (3-5). However, since nearly half of all patients on AS have been shown to ultimately require some form of intervention, improved surveillance strategies are needed to monitor for disease progression in an effective and efficient manner (6,7,9-11,68).

Novel MRI sequencing techniques and improved technology has allowed for meticulous characterization of suspicious intraprostatic lesions (*Figure 1*). Recent evidence suggests that using mpMRI to characterize suspicious foci within the prostate allows for better detection than prior imaging techniques and systematic sampling alone, and may allow for safe AS while potentially decreasing the frequency of invasive biopsy sessions (14,16-18,20,21). Furthermore, mpMRI may even detect more aggressive disease not found on the initial standard template biopsy, and, therefore, may keep the patient from being inappropriately placed on AS (20). For these reasons, there has been a push towards formally incorporating mpMRI findings into existing AS criteria such as the Epstein criteria and PRIAS (35-38).

When performing a prostate biopsy is warranted, novel MRI fusion technology permits targeted tissue sampling with unparalleled accuracy (*Figure 2*) (48-51). Compared to saturation biopsies, recent evidence suggests that MRI-targeted biopsies may be just as reliable for csPCa detection with improved efficiency (58-60,69). This would spare patients, urologists and pathologists the task of acquiring and interpreting numerous cores obtained from a saturation biopsy approach and may decrease the frequency of finding

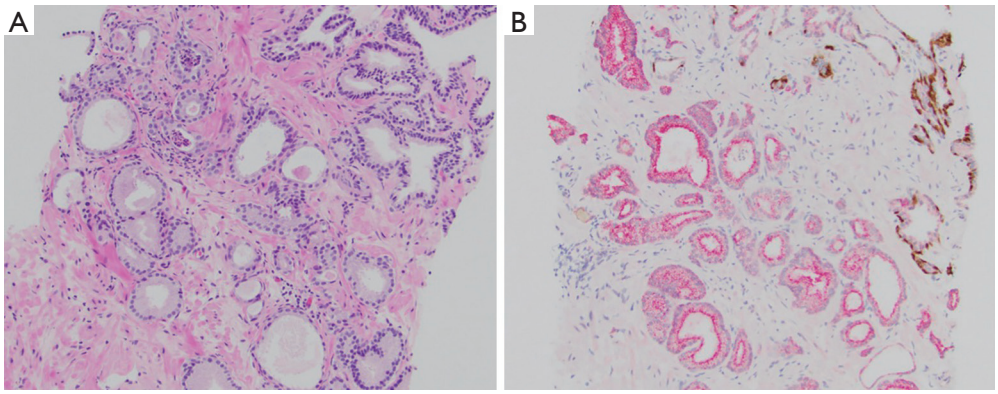

Figure 2 Tissue core at 20× magnification obtained from MRI-US fusion biopsy of 65-year-old male in *Figure 1*. (A) Hematoxylin and eosin stained slide showing infiltrating small, well-formed glands with cytologic atypia, consistent with prostatic adenocarcinoma, Gleason score 3+3=6 (grade group 1); (B) immunohistochemical-stained slide showing positivity in the atypical glands for racemase (pink) and lack of staining for p63 (nuclear staining, brown, and high molecular weight cytokeratin (cytoplasmic staining, brown) confirming prostatic adenocarcinoma.

insignificant disease (59). Furthermore, we identified two studies suggesting that in-bore MRI-guided biopsy may offer an even greater detection rate (55,56). Conversely, other evidence suggests MRI-US fusion alone may not be adequate in the initial diagnostic setting, and standard template biopsy may be equally diagnostic in biopsy naïve men (57). Several other studies suggest that men with small enough index lesions could avoid repeat biopsy altogether, and instead be followed by serial mpMRIs with equivocal detection and omission rates (7,64,66).

Conclusions

In the era of ever increasing use of AS for men with low-risk PCa, improved strategies for proper stratification are needed to balance overtreatment with underassessment of true risk. mpMRI has dramatically enhanced the detection of clinically-significant PCa, and may permit less-invasive surveillance strategies compared to currently accepted protocols. Further investigation is warranted to determine the most appropriate utilization of mpMRI in the setting of serial imaging and to also identify to what extent targeted versus templated systematic prostate biopsy should be performed.

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Footnote

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