Review Article

Imaging for the selection and monitoring of men on active surveillance for prostate cancer

Maria C. Velasquez[1], Nachiketh Soodana Prakash[1], Vivek Venkatramani[1], Bruno Nahar[1], Sanoj Punnen[1,2]

[1]Department of Urology, [2]Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA

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Correspondence to: Dr. Sanoj Punnen. Department of Urology, University of Miami Miller School of Medicine, 1120 NW 14th Street, Suite 1560, Miami, FL 33136, USA. Email: s.punnen@miami.edu.

Abstract: Traditional prostate imaging is fairly limited, and only a few imaging modalities have been used for this purpose. Until today, grey scale ultrasound was the most widely used method for the characterization of the prostatic gland, however its limitations for prostate cancer (PCa) detection are well known and hence ultrasound is primarily used to localize the prostate and facilitate template prostate biopsies. In the past decade, multiparametric magnetic resonance imaging (mpMRI) of the prostate has emerged as a promising tool for the detection of PCa. Evidence has shown the value of mpMRI in the active surveillance (AS) population, given its ability to detect more aggressive disease, with data building up and supporting its use for the selection of patients suitable for surveillance. Additionally, mpMRI targeted biopsies have shown an improved detection rate of aggressive PCa when compared to regular transrectal ultrasound (TRUS) guided biopsies. Current data supports the use of mpMRI in patients considered for AS for reclassification purposes; with a negative mpMRI indicating a decreased risk of reclassification. However, a percentage of patients with negative imaging or low suspicion lesions can experience reclassification, highlighting the importance of repeat confirmatory biopsy regardless of mpMRI findings. At present, no robust data is available to recommend the substitution of regular biopsies with mpMRI in the follow-up of patients on AS and efforts are being made to determine the role of integrating genomic markers with imaging with the objective of minimizing the need of biopsies during the follow up period.

Keywords: Active surveillance (AS); magnetic resonance imaging (MRI); MRI-targeted biopsy; prostate cancer (PCa); transrectal ultrasound (TRUS)

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Introduction

Active surveillance (AS) is an alternative to immediate treatment with the goal of deferring definitive therapy until it's truly needed based on tumor progression. Any AS strategy relies on two important components: (I) selection of appropriate patients; and (II) careful monitoring for disease progression. Previously, inclusion criteria were based on clinical information, with most decision-making being based on the grade and extent of cancer found on the biopsy. While most men do well on AS, and have no compromise in cancer outcomes even if they progress and require treatment, a small handful may suffer an adverse outcome, usually due to underestimating the degree of cancer on the initial assessment (1). Furthermore, when expanding AS to intermediate risk patients we have seen an increase in the proportion of men who develop clinical metastasis (2). Therefore, it is obvious that better indicators of aggressive disease are desperately needed to help select men who can safely observe their tumors, versus those

Table 1 Key points from the review article

TRUS is not a reliable method for PCa detection and should only be used as a guidance tool to localize the prostate and facilitate random biopsies. Color Doppler and elastography don't add extra information and shouldn't be used routinely
Several well-designed studies strongly support the role of mpMRI in detecting and ruling out significant prostate cancer with a high negative predictive value and diagnostic accuracy
All patients enrolled in AS protocols regardless of mpMRI findings, should have a systematic TRUS biopsy plus a targeted biopsy when suspicious lesions are seen on mpMRI for reclassification and confirmatory purposes
mpMRI plus biomarkers and/or genomic testing is a promising field that might help avoid unnecessary biopsies in patients on AS protocols
The existence of a significant radiologist learning curve, accessibility, costs and the possibility of overcalling lesions when patients are under AS, are some of the mayor limitations of mpMRI and mpMRI fusion biopsies

TRUS, transrectal ultrasound; PCa, prostate cancer; mpMRI, multiparametric magnetic resonance imaging; AS, active surveillance.

who require immediate treatment. In the past, options for imaging the prostate to localize cancer within the gland were limited. Transrectal ultrasound (TRUS), for instance, does not reliably detect regions of cancer within the prostate and is used primarily to identify the prostate gland to facilitate template biopsy of the prostate (3). More, recently, multiparametric magnetic resonance imaging (mpMRI) has emerged as the most reliable method of localizing cancer within the prostate, and has rapidly gained in popularity in many aspects of prostate cancer (PCa), including AS.

In this review, we will begin with a brief discussion on the use and limitations of simple TRUS to select and monitor men for AS. The review will then focus on the emergence of prostate MRI, and the evidence for its use in the selection and monitoring of men on AS. Finally, we will conclude with a discussion of limitations of mpMRI, and future directions in the field of imaging for AS. We highlight the main take home messages for this review in *Table 1*.

TRUS

TRUS guided template biopsy of the prostate; which to date is the most widely used technique for PCa diagnosis, was first introduced in 1989 by Hodge and colleagues (4). Despite technological advances in the field, greyscale TRUS has an accuracy of 60% and a negative predictive value (NPV) of only 6% for the detection of PCa. Additionally, evidence suggests that TRUS directed biopsy at hypoechoic lesions have a low yield (5), further supporting the limited utility of TRUS for detecting cancer within the prostate gland. As a result, TRUS is primarily used to localize the prostate to facilitate template biopsy, making PCa the only major cancer in which a diagnosis is made routinely by random, albeit, systematic biopsy of the prostate (6).

To increase the accuracy of TRUS to identify cancer within the prostate, several additional parametrics have been assessed, including color Doppler TRUS and elastography. Color Doppler TRUS can be used to detect areas in the prostate that demonstrate increased blood flow, which could signal the presence of a significant tumor. However, several studies have demonstrated that color doppler TRUS has poor sensitivity and specificity for PCa diagnosis, and doesn't add substantially to grey-scale TRUS (7-9). Elastography is an image modality that maps the elastic properties of soft tissue and creates a color map of stiffness, with stiffer regions being more suspicious for cancer. In a recent study by Schiffman *et al.* (10), 679 patients underwent elastography and systematic biopsy of the prostate for evaluation of PCa. The study found that elastography had a low sensitivity (19%) for PCa detection and concluded that it has limited application for PCa diagnosis.

mpMRI

MRI of the pelvis was originally used in PCa staging to identify extracapsular extension, however with the addition of several parametrics, this imaging technique has emerged as the most popular method for the identification and localization of significant PCa within the prostate. mpMRI incorporates functional sequences in addition to a high-resolution anatomical image. Dynamic contrast enhancement (DCE) assesses the uptake of contrast in the blood to regions of the prostate, with earlier and more pronounced enhancement occurring in cancerous lesions compared to normal healthy tissue. Diffusion-weighted

imaging (DWI) assesses the random movement of water molecules within the prostatic tissue, showing restricted diffusion in cancerous regions. The apparent diffusion coefficient (ADC) map is a reconstruction of the DWI, with darker regions of lower ADC being associated with more significant tumors. Lastly, spectroscopy, which is used less frequently today, evaluates the presence and concentration of various metabolites in the prostate gland, with PCa lesions showing an increased ratio of choline and creatinine to citrate. T2-weighted images demonstrate anatomy and allow the differentiation between peripheral and transitional zones, as well as the identification of any extra-prostatic extension (11,12). Currently some groups still use an endo-rectal coil especially when utilizing a 1.5 Tesla strength MRI, however it has fallen out of favor over the years with more widely available 3 Tesla machines.

With the aim of promoting a global standardization of interpreting prostate mpMRI, the Prostate Imaging Reporting and Data System (PI-RADS) has become the most popular classification scheme being used to risk stratify regions of interest on mpMRI (13). PI-RADS uses T2, DWI and DCE sequences to determine the risk of malignancy of any suspicious target seen on mpMRI using a 1–5-point scale. A score of 1–2 corresponds to a benign appearing target, 3 to an indeterminate appearing target, and 4–5 to a malignant appearing target. Other methods, such as a 3- or 5-point Likert scale have also been employed in the interpretation of mpMRI of the prostate (14).

To date, current guidelines have displayed differing opinions on the role of mpMRI in AS. For example, the National Institute for Health and Care Excellence (NICE) in the U.K strongly recommends mpMRI after an initial decision for AS enrollment (15), Similarly current AS guidelines from the Canadian Urological association recommend mpMRI when a patient's clinical findings are discordant with the pathologic findings (16). Conversely, the most recent AUA guidelines did not mention any use of mpMRI in men on AS (17).

mpMRI for PCa detection

While this review is focused on the role of imaging in AS, the strongest evidence supporting mpMRI comes from the diagnostic literature, with a recent multicenter paired validation study comparing mpMRI to TRUS-biopsy by the PROMIS group in the United Kingdom. In this study, Ahmed *et al.* (18) assessed the feasibility of mpMRI as a primary test to detect significant cancer and reduce unnecessary biopsies in patients undergoing evaluation of PCa. The primary cohort consisted of 576 biopsy naïve men, all of whom underwent an mpMRI and TRUS biopsy. Each patient also underwent a trans-perineal template mapping (TPM) biopsy, with cores taken at every 5 mm of the prostate, which served as the gold standard truth for the trial. Clinically significant cancers were defined as Gleason grade ≥4+3 or a maximum core involvement of >6 mm. The study found that MRI had a better Sensitivity (93% *vs.* 43%, P<0.001) and NPV (89% *vs.* 74% P<0.001) compared to TRUS biopsy. Of note, 158 (37%) patients had a negative mpMRI, of which only 17 had clinically significant PCa on TPM-biopsy. None of these patients had primary Gleason 4 or higher cancer. Alternatively, 452 men had no cancer or only Gleason 6 cancer on TRUS biopsy, of which 119 were found to have clinically significant cancer on TPM biopsy, 13 of which were primary Gleason pattern 4. This study found that mpMRI outperformed TRUS biopsy in detecting clinically significant cancer and strongly supports its role in the detection and exclusion of aggressive disease.

Similarly, Futterer *et al.* (19) conducted a systematic review to determine the diagnostic accuracy of mpMRI for clinically significant cancers and reported a pooled sensitivity and specificity of 58–96% and 23–87%, respectively, while the pooled NPV ranged from 64–98%. Additionally, Moldovan *et al.* (20) looked at 48 studies and found the median NPV for any cancer, and significant cancer was 82.4%, and 81% respectively. These reviews show us that while mpMRI is not perfect for ruling out aggressive disease, it preforms better than standard TRUS biopsy, suggesting it may be a useful imaging tool for men who are contemplating surveillance and trying to rule out the presence of a significant tumor.

While multiple studies have validated the role of mpMRI in cancer detection, many have commented on the concerns with false positives and a lower specificity compared to TRUS biopsy (18). As a result, most groups would advocate that a biopsy is still indicated and treatment decisions should not be based on the mpMRI findings alone. Siddiqui *et al.* (21) conducted a prospective clinical trial which included 1,003 patients with abnormal mpMRI and elevated PSA or/and abnormal digital rectal examination. Patients underwent a targeted biopsy by one physician, followed by a standard 12-core biopsy performed by another physician unaware of the mpMRI results. Results of the study showed that 69% of patients demonstrated accurate agreement between targeted and standard biopsy, however targeted biopsies diagnosed 30% more high risk and 17% fewer low-risk

PCa. Furthermore, the authors assessed 170 patients who went on to radical prostatectomy allowing a comparison to whole-gland surgical pathology results as a gold standard. Assessment of the ability of preoperative biopsy to predict whole-gland pathology revealed the sensitivity for targeted biopsies was 77% compared to 53% for standard TRUS biopsy, while the specificity was similar for both procedures (68% *vs.* 66%). The authors concluded that targeted MR/ultrasound fusion biopsy compared with standard extended sextant ultrasound guided biopsy, significantly increased the detection of high-risk PCa.

While there have been a number of studies, similar to the one mentioned above, which show a benefit of mpMRI targeted biopsy in the detection of clinically significant PCa, there are concerns about over sampling the tumor, which may have an impact on eligibility for AS. In a recent study done at the University of Miami (Nahar, 2016, unpublished data), we identified 100 patients who underwent mpMRI fusion targeted biopsy plus extended template biopsy and were eligible for at least one of seven different AS protocols based on their 12-core standard biopsy. The main objective of our study was to determine how many patients would have been excluded from AS after the addition of the targeted cores. Results showed that using an absolute maximum number of cores as an inclusion criterion (usually 2), resulted in the largest number of patients becoming ineligible for AS. AS protocols that used a percentage of positive cores, instead of an absolute number, allowed for fewer men being excluded. The study concluded that most of the published AS criteria may no longer be appropriate in the era of MRI targeted biopsy, and the need for a change in these protocols to account for the addition of targeted biopsy cores is necessary.

mpMRI for reclassification of patients eligible for AS protocols

Currently, one of the key aspects of AS is the proper identification of patients diagnosed with seemingly low risk disease, who are truly harboring more aggressive cancer that would portend a bad outcome if left untreated. In a previous systematic review, Schoots *et al.* (22) assessed 10 studies looking at men who were candidates for AS and underwent surgery. The study found that the rate of upgrading was much higher in men with a positive mpMRI (43%) compared to those with a negative mpMRI (27%). However, caution must be excercised when extrapolating surgical data to all men on surveillance, as those getting surgery are more likely to harbor higher volumes of cancer, compared to the average man on AS. The authors also assessed 7 studies looking at men who were diagnosed with low risk tumors, and undergoing repeat confirmatory biopsy on AS, and found that 70% of men were found to have a positive mpMRI. Men who had a positive mpMRI were much more likely to experience reclassification (39%), compared to those with a negative mpMRI (17%). When restricted to studies using mpMRI targeted biopsy, the reclassification rate for men with a positive mpMRI increased to 47%. These studies highlight the fact that a positive mpMRI suggests an increased risk of harboring an aggressive cancer that may not be appropriate for AS. However, it should also be noted that men with a negative mpMRI also had reasonable risk of harboring a more aggressive tumor. This promotes the need for confirmatory biopsy, regardless of the findings on mpMRI. We feel that while a negative mpMRI may allow one to delay a confirmatory biopsy, it should not permit you to avoid it.

In a similar study by Recabal *et al.* (23), the authors evaluated whether mpMRI and mpMRI targeted biopsy could replace systematic biopsies in the detection of clinically significant disease in men on surveillance. Among 206 men with low risk PCa, 34% had a negative or low suspicion mpMRI and underwent systematic biopsy only, while 64% had at least one region of suspicion on mpMRI, and underwent targeted and systematic biopsy. Results showed upgrading in 35% of the cohort, with 47% of men who had a suspicious mpMRI being found to have a more aggressive cancer within the prostate. While the amount of cancer found on the systematic biopsy decreases with an increasing level of mpMRI suspicion, the authors found that a reasonable proportion of clinically significant cancer was found only on the systematic biopsies (10–17%). This suggests that both targeted and systematic biopsy should be used for the optimal detection of clinically relevant cancer in men on AS.

A recent diagnostic meta-analysis evaluating the performance of mpMRI in AS assessed 7 studies, encompassing 1,028 men (24). Three of the studies included only very low-risk patients who met the Johns Hopkins AS criteria, three included low-risk patients, and only one study allowed intermediate risk patients. Pooled data showed a sensitivity of 69%, a specificity of 78%, and a high NPV of 91% for reclassification. The authors concluded that mpMRI has a moderate diagnostic accuracy for disease reclassification among AS patients due to its high NPV and specificity, which may indicate that a negative mpMRI

could support a patient remaining under AS, whereas the presence of a suspicious lesion (>10 mm) may suggest an elevated risk for disease progression.

These studies and others provide a considerable level of support for the role of mpMRI in the detection of clinically significant cancer in men on AS. While a negative mpMRI may portend a decreased risk of reclassification, a significant proportion of men with a negative or low suspicion mpMRI also experience reclassification, stressing the importance of repeat confirmatory biopsy, regardless of mpMRI findings. Furthermore, data suggests that a reasonable number of significant tumors are found only on the systematic biopsies, and these should not be excluded when performing an mpMRI targeted biopsy.

MRI for monitoring of patients on AS

While there are many studies focused on mpMRI in selecting men for AS, there is little data available on its role for monitoring tumor progression. Secondly, the ability of mpMRI to replace or delay a biopsy is unknown. Most of the helpful literature in this area is limited to small, single institution studies. A previous study from the National Institute of Health (NIH) assessed 58 men with Gleason 6 in 2 or less cores, who remained on AS after a confirmatory biopsy, and had subsequent mpMRI's and biopsies with a median of 16 months follow up. The study defined mpMRI progression as an increase in mpMRI suspicion, lesion diameter, or number of lesions and looked at its ability to detect pathologic progression defined as an upgrade to Gleason 7 or higher cancer. The authors found that mpMRI progression had a sensitivity and specificity of 53% and 80%, respectively, for detecting pathological progression. The NPV for predicting pathological progression was 80%, suggesting 20% of men with no change on mpMRI experienced clinical progression on biopsy (25). Another study looked at 49 men with Gleason 6 cancer who underwent mpMRI and biopsy at baseline, and again a median of 28 months later. Here the authors defined mpMRI progression as an increase in lesion suspicion, lesion volume, or a decrease in the ADC. The sensitivity, specificity, and NPV of mpMRI progression were 37%, 69%, and 70%, respectively, for predicting clinical progression to Gleason 7 or higher cancer. A logistic model based on mpMRI progression had an area under the curve (AUC) of 0.63 for predicting clinical progression, compared to 0.87 for a clinical model consisting of maximum core length at baseline and PSA density greater than 0.15 ng/mL at follow-up (26). While these studies are limited in their follow up and sample size, they suggest a significant proportion of men with no change on the mpMRI may actually undergo clinical progression.

Additionally, while these studies may shed light on the performance of mpMRI for monitoring tumor progression, there is much that remains unknown. If an mpMRI shows no change, can we be sure the cancer hasn't changed? The previous studies suggest we can't. However, these studies used an endpoint of Gleason 3+4 or higher to define progression, which would include men with low volumes of Gleason pattern 4. When assessing the performance of mpMRI in monitoring tumor progression on AS, we must ask ourselves what we are asking it to do. Perhaps detecting the initial emergence of pattern 4 disease may be impractical, but detecting the growth of a clinically significant tumor to allow timely, and curative therapy maybe much more realistic. While a lack of change in an mpMRI may allow us to avoid a biopsy here and there, a complete dependence on it to predict tumor progression may not be wise. However, what is clear is that more research with larger numbers of men and prospective follow up are detrimental to reducing our knowledge gap in this area.

MRI limitations

Despite all its advantages, mpMRI of the prostate has some limitations. For example, the variability in image interpretation and the learning curve of the radiologist can be a challenge to the implementation of any successful mpMRI program. Recently, Rosenkrantz *et al.* (27) evaluated the learning curve for tumor detection using prostate MRI among 6 novice readers, with 3 of the readers receiving continual feedback after each case. In both groups, there was an initial rapid improvement, with slowing of this initial increase after approximately 40 reviewed images and a plateau across the remaining examinations. The continual feedback did not substantially affect this trend. Therefore, the authors concluded that the learning curve in PCa detection largely reflects self-directed learning and strongly recommend caution when imaging is being interpreted by a novice radiologist, as diagnostic accuracy is heavily dependent upon reader experience. Another potential limitation would be the cost of prostate mpMRI. A recent study done in Australia (28), was conducted with the objective of evaluating the cost-effectiveness of mpMRI and its effects on AS. The authors found that mpMRI by

itself was not cost-effective, however when considering the impact in reducing overtreatment and its consequences, mpMRI became more economically viable.

MRI: future directions

While mpMRI performs well for localizing cancer within the prostate, there has been some promising research looking at enhancing MRI by combining it with positron emission tomography (PET) imaging with prostate specific membrane antigen (PSMA) conjugated agents (29). Unlike previous PSMA agents that bound an intracellular epitope, leading to false positive findings, newer PSMA agents bind extracellular epitopes and have an excellent accuracy for detecting PCa. In a previous study of 12 men who underwent PSMA PET and mpMRI before radical prostatectomy, the authors found that mpMRI had better sensitivity for cancer detection, but PSMA PET was more sensitive for the detection of high grade cancers with a better specificity, suggesting that combining the two would improve the overall performance beyond that of either test alone (30). However, more research is needed to assess its incremental value in men on AS.

In addition to mpMRI, a number of tissue based genomic markers have become available for determining the genomic profile of the tumor for prognosis and treatment decision making (31-33). These tests allow risk stratification beyond the histopathology and claim to address the heterogeneity of PCa. However, in a recent study by Wei *et al.* (34), the authors sequenced four consecutive radical prostatectomy specimens and found significant variation in the genomic profiles using the same test in different biopsy cores throughout the RP specimen. This suggests that what you sample is important for both clinical and genomic risk stratification. Therefore, one strategy for integrating mpMRI and genomic markers would be to use mpMRI to localize and sample tissue from the most suspicious region of the prostate to allow genomic profiling of the tumor that is most likely to predict progression.

Unfortunately, there are very few studies available on the integration of mpMRI and genomic markers in AS. As a result, we opened the MIAMI MAST trial to shed some light on this subject for men considering AS of their PCa. All men on the trial have an mpMRI and confirmatory targeted and 12 core template biopsies within 3 months of enrollment, and every year after for three years. At each biopsy, tissues from multiple cores are sent for genomic sequencing. The trial is well into its accrual, and we expect it to answer some important questions such as the variation in genomic profiles from targeted and systematic cores, or high grade and low grade tumors within the same prostate. We hope it will allow us to assess the various methods of integrating these tests to develop a strategy that provides the most informed risk stratification possible. Furthermore, all men will prospectively have an mpMRI and subsequent biopsy every year for three years, providing a robust resource to truly investigate the association between mpMRI progression and clinical progression.

Conclusions

AS has gained increasing popularity during the last decade, however there has been a minimal role of the imaging in the management of these patients. The advent of mpMRI has led to a better characterization of the prostate anatomy, allowing lesion identification and risk stratification that correlate with disease severity. There is growing evidence regarding the use of mpMRI for the selection of patients for AS and its utility during the follow up period, as well as the superiority of combined MRI fusion and systematic biopsy for the optimal detection of clinically significant cancer in these men. However robust data from prospective studies is needed before widespread adoption of any imaging modality is incorporated into guidelines for AS.

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Footnote

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