Published in final edited form as:

Curr Urol Rep. 2015 June ; 16(6): 42. doi:10.1007/s11934-015-0507-9.

The Role of MRI in Active Surveillance for Prostate Cancer

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Abstract

Approximately one in seven American men will be diagnosed with prostate cancer during his lifetime, and at least 50 % of newly diagnosed patients will present with low-risk disease. In the last decade, the decision-making paradigm for management has shifted due to high rates of disease detection and overtreatment, attributed to prostate-specific antigen screening, with more men deferring definitive treatment for active surveillance. The advent of multiparametric magnetic resonance imaging (MP-MRI) and MRI/ transrectal ultrasound-guided fusion-guided prostate biopsy has refined the process of diagnosis, identifying patients with clinically-significant cancer and larger disease burden who would most likely benefit from intervention. In parallel, the utilization of MP-MRI in the surveillance of low-grade, low-volume dis-ease is on the rise, reflecting support in a growing body of literature. The aim of this review is to appraise and summarize the data evaluating the role of magnetic resonance imaging in active surveillance for prostate cancer.

Keywords

Active surveillance; Prostate cancer; Multiparametric MRI; Outcomes; Cancer detection

Introduction

Prostate cancer (PCa) has historically been diagnosed by prostate-specific antigen (PSA) testing and digital rectal exam (DRE) prompting an extended sextant 12-core transrectal ultrasound (TRUS)-guided biopsy. The ubiquitous use of PSA screening has been responsible for increased rates of PCa detection and associated increased rates of cancer

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Compliance with Ethics Guidelines

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

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

treatment. This overdetection and overtreatment of low-grade PCa has resulted in climbing healthcare costs and concerns for patient morbidity, including incidence of erectile dysfunction, urinary incontinence, and anxiety associated with decreased quality of life in patients with low-risk disease [1]. These risks and additional findings ultimately prompted the US Preventive Services Task Force (USPSTF) recommendation against PSA screening [2].

This recommendation caused a larger paradigm shift in the urologic community. Active surveillance (AS), a management strategy involving serial PSA testing and biopsies, was developed to allow safe monitoring of disease progression while reducing rates of overtreatment. Multiparametric magnetic resonance imaging (MP-MRI), an imaging modality demon strating improved detection rates in a variety of clinical scenarios, has since been utilized in AS protocols to guide clinical decision-making [3, 4••, 5, 6]. This enables a tumor to be directly monitored with imaging rather than indirectly monitored with PSA and random biopsy. Approximately one in seven American men will be diagnosed with prostate cancer during his lifetime, and 50 % of newly diagnosed patients will present with low-risk disease [7]. MP-MRI may specifically identify patients with high-grade, high-volume disease who would benefit from subsequent treatment, and simultaneously reduce unnecessary evaluation and treatment of patients with low-grade, low-volume disease.

The Prostate Intervention Versus Observation Trial (PIVOT) was among the first studies to reveal the limited benefit of PCa treatment in a subset of patients identified by PSA and subsequent 12-core prostate biopsy [8]. While men with high-risk disease benefited from radical prostatectomy (RP), there was no evidence of benefit or difference in long-term outcomes including overall and prostate-cancer specific mortality between the intervention and observation arms in men with favorable risk disease. PIVOT elucidated the role of observation in management of patients with low-grade, low-volume disease, discouraging unnecessary biopsies and treatment-related morbidity without tangible benefit.

The concept of active surveillance has subsequently evolved into more intensive monitoring with the goal of diagnosing potentially lethal disease within the window of cure. Improved understanding of PCa pathophysiology and its slow rate of growth have allowed for the dissemination of AS. The central concept of AS is to defer treatment until such time as pathologic progression occurs, whereupon therapeutic interventions with curative intent are initiated. Results of long-term follow-up on large AS cohorts have reinforced its safety and efficacy. Klotz et al. followed 993 patients for a median of 6.4 years (range, 0.2 to 19.8 years) and found prostate cancer actuarial survival after first biopsy was 98.1 and 94.3 % at 10 and 15 years, respectively [9]. Additionally, Welty et al. followed 810 men prospectively for a median of 60 months (IQR, 36–91 months) with a 98 % 5-year overall survival; 462 (60 %) men remained treatment-free, with no prostate cancer deaths in the entire cohort [10]. AS has become an established method of managing patients with low-risk disease.

The Rationale for MRI in Active Surveillance

Use of AS alone, however, has not sufficiently addressed concerns with overdetection and overtreatment of disease. The need for objective and improved patient screening has led clinicians to seek novel imaging techniques. Ultrasound alone has not provided adequate

information regarding tumor location, characterization, or disease progression [11]. Urologists have thus turned to MRI, a modality initially employed in the late 1980s to stage disease by detecting seminal vesicle invasion and extraprostatic extension [12]. As technology has advanced, the potential of MRI began to evolve from a rudimentary staging study with limited clinical utility to a powerful diagnostic tool. Increased magnet strength, the additions of the endorectal and surface coil improving signal-to-noise ratio, and the optimization of MRI sequences have allowed for significantly better discrimination and diagnostic yield [3]. Novel software has allowed for MRI fusion with real-time ultrasound to localize lesions for targeted biopsy sampling. The combination of multiparametric MRI and MRI/TRUS fusion-guided prostate biopsy seeks to aid PCa detection of clinically significant tumors and biopsy methodology.

MP-MRI provides adjunct information to pre-treatment staging, improving patient selection and lesion targeting for biopsy, monitoring patient disease burden with serial imaging, and most recently, enabling targeted focal therapy with curative intent [13]. Accurate grading of lesions by MP-MRI and targeted biopsy, in conjunction with standard TRUS biopsy, allow clinicians to distinguish patients that require definitive treatment from those with indolent disease. The combination of parameters in MP-MRI allow for more reliable detection than any individual technique alone, providing both anatomical and functional information about suspicious lesions in the prostate [14].

The parameters of MP-MRI include: T2-weighted imaging (T2W), dynamic contrast enhancement (DCE), apparent diffusion coefficient (ADC) on diffusion weighted imaging (DWI), and at some centers MR spectroscopic imaging (MRSI). T2W imaging, reflecting tissue water content, provides the highest spatial resolution and zonal anatomy. DCE MRI consists of a series of fast T1-weighted sequences before and after injection of contrast, assessing the focal kinetics of contrast uptake and washout in the prostate [14]. DWI reflects the diffusion of water within tissue and is more restricted within tumors; thus, DWI is very sensitive for detecting cancers especially in the peripheral zone of the prostate. ADC values have been shown to correlate with Gleason grade when compared to prostate histology, allowing for risk stratification of patients based on imaging suspicion and Gleason score [15]. MRSI detects relative levels of the prostate metabolites, specifically focusing on choline and citrate, in order to assess glandular involvement of disease.

Investigations adding these MRI parameters to risk stratification scores are altering patient management; the addition of imaging and targeted biopsy methods are allowing clinicians to ascertain disease burden to aid in patient-centered decision making. Hence, the objective of this article is to review published literature utilizing MP-MRI as a technology to manage PCa patients on AS.

Screening and Patient Selection

In order to safely monitor patients on AS, urologists must reliably and confidently identify patients with low-risk disease, which are most likely to follow an indolent course. It has been in this setting that MP-MRI and fusion biopsy (FB) have shown recent promise. Assessing MP-MRI in selecting AS patients, however, has been challenging with the various screening measures and risk stratification methods that are currently in use, each with their

own inclusion criteria and definitions for progression of disease. MRI has a broadening role in AS, with value from initial patient selection to continued monitoring.

Diagnosis

The strongest argument in favor of the addition of MRI in the diagnostic pathway is in clinical scenarios where TRUS and 12-core biopsy have fallen short [16, 17]. MP-MRI and MRI/ TRUS fusion-guided prostate biopsy improve the cancer detection in patients with low apical lesions, anterior lesions, enlarged prostates, and even disease outside the prostate [18–21]. It has also been especially useful in patients with an elevated PSA despite negative TRUS biopsy where MRI has proven potential [22–24]. Of 195 men with prior negative TRUS biopsy, 73 (37 %) were found to have cancer on subsequent fusion biopsy [24]. Twenty-one of these had Gleason ≥8, while the remainder were harboring Gleason 3+3=6 (n=or Gleason 7 (n=24) disease. In this cohort, 55 % (12/21) were missed by TRUS biopsy obtained in the same session.

Risk Stratification

Histopathology on biopsy is the definitive feature used to risk-stratify patients prior to therapy. MP-MRI suspicion scores for disease significantly correlated with age, PSA, and prostate volume with increasing MRI suspicion score correlated strongly with Gleason score and cancer detection rates. MP-MRI performed with sensitivities of 94 and 98 % for Gleason 7 or greater and Gleason 8 or greater cancers, respectively [25]. MP-MRI was useful in guiding clinicians to key lesions of the prostate for directed sampling, but was equally useful for distinguishing which patients were appropriate for treatment versus those with lesser disease burden. When considering low suspicion lesions alone, fusion biopsy yielded 77 patients with no cancer, 38 with Gleason 6, and 10 with Gleason 3+4=7 disease [26]. Fifteen patients went on to RP, with no pathologic upgrading on final histologic analysis. By 2011 National Comprehensive Cancer Network guidelines, 107 males, or 88 %, of the cohort had no cancer or clinically insignificant disease, suggesting that they were suitable for AS because of their low probability of harboring high-risk PCa [26].

Work done by Siddiqui et al. to assess Gleason scores and upgrading on MP-MRI found that MRI/TRUS fusion-guided biopsy detected PCa in 54 % of patients and upgraded 32 % of cases when compared to 12-core, suggesting that 12-core alone may incorrectly underestimate the risk of about one-third of patients who actually harbor significant disease better served by definitive therapy [27•].

MRI suspicion scores to evaluate patients have been crucial in detecting AS eligible patients and have been demonstrated to accurately risk stratify patients [25, 28]. Degree of suspicion on MRI was the most powerful predictor of cancer detection in a study of 105 subjects with prior negative biopsy and elevated PSA; these men underwent MP-MRI and biopsy to reveal 21 of 23 (91 %) targeted biopsies with significant cancer and 12 of 14 (86 %) subjects had highly suspicious MRI targets [29]. By detecting fewer insignificant cancers with overall improved diagnostic yield one could defer treatment in patients that then qualified for AS. MP-MRI demonstrated high specificity (97 %) and negative predictive value (NPV; 90 %) in correctly classifying MP-MRI identified lesions in 50 males on an AS protocol with

pathology confirmed index lesions [30]; non-suspicious MP-MRIs were associated with an absence of pathologic lesions and reclassification of patients was more common in those patients whose MRI screened positive [30, 31].

Negative Predictive Value of MRI

Management with a negative prostate MP-MRI has been shown to vary in the literature, reaching greater than a 95 % NPV for clinically-significant cancer [32, 33]. Patients without an identified tumor on MP-MRI are more suitable for AS compared to those with a visible tumor on MP-MRI [34]. Several groups have been successful with MRI implementation in the form of their own risk scales, such as the use of an ordinal five-point scale applied to a 5-mm template prostate map coupled with MP-MRI in 129 men with no prior biopsy history that detected 87 % of cancers, with a sensitivity of 100 % when detecting Gleason 4 + 3 disease and an NPV of 89–100 % [35, 36]. Conversely, lesions not identified on MP-MRI were assigned low-risk and low burden and were more likely to be triaged in AS. The reported high NPV of MP-MRI has been useful in counseling patients with low and intermediate risk in order to encourage AS of their PCa [32].

Confirmation of Candidacy for Active Surveillance

Defining both functional and morphological features on MP-MRI to predict candidacy of AS for patients on confirmatory and surveillance biopsy has been of recent interest. Stamatakis et al. found 29 % of their cohort (25/85 men) were no longer eligible for AS after confirmatory MP-MRI fusion biopsy [37••]. Number of lesions, MRI suspicion, and lesion density were the significant MRI predictors of patients that would be poor AS candidates. Lesion density had been defined previously using MRI segmentation software to determine lesion volume and divide the resulting value by total prostate volume [26]. Using these same MRI-based factors associated with biopsy reclassification, a nomogram was created that quantified the probability of being an AS candidate on confirmatory biopsy or remaining one under strict criteria.

MP-MRI may be able to better identify men at risk for immediate reclassification at their initial assessment, as it has been shown that up to 35 % of men on AS experience reclassification during their follow-up [30]. A study of 105 men with prior negative biopsies were assessed for AS entry using four different AS criteria to identify significant disease and determine course of management; 27/36 were harboring clinically significant disease and no longer qualified for AS [29]. Additionally, in a prospective comparison of MRI/TRUS fusion-guided biopsy versus TRUS biopsy alone in 72 AS patients, 19/72 (26 %) were found to have clinically-significant cancer (Gleason≥7) after their initial fusion biopsy, with 7/19 (37 %) identified by MP-MRI alone compared to 2/19 (11 %) by TRUS biopsy alone.

Using MRI to specifically select patients has been controversial but hopes to better select men who have a low-risk of disease progression, a major problem with current AS eligibility criteria [38, 39]. In the D'Amico scoring system, AS eligibility (or low risk disease) is demonstrated by a PSA level ≤10 ng/mL, clinical stage T2a or lower, and no Gleason pattern 4 or 5 on biopsy. Turkbey and colleagues previously compared suitability for AS based on MP-MRI findings to D'Amico, Epstein, and Cancer of the Prostate Risk Assessment

(CAPRA) validated risk-stratification tools [6]. AS was therein defined as a dominant tumor measuring less than 0.5 mL without Gleason pattern 4 or 5 on biopsy and without evidence of extraprostatic extension or seminal vesicle invasion. Amidst 133 patients, MP-MRI was superior for predicting AS eligibility with a sensitivity of % and an overall accuracy of 92 % [6]. These findings suggest that imaging supplements clinico-pathologic criteria and improves identification of patients for AS.

A prospective cohort study was completed assessing MP-MRI in selecting and reclassifying patients with low-grade, localized PCa [40]. Sixty men were screened who underwent MP-MRI and stratified by normal MRI, MRI showing a lesion >1 cm and MRI concordant with initial biopsy. Within each cohort, rates of biopsy concordance were calculated, comparing previous biopsy with recent MRI. Positive and negative predictive values of MRI compared to confirmatory biopsy were 83 and 81 %, respectively. Within the cohort where MRI detected a lesion, 10 of 13 patients (17 % of the entire cohort) were reclassified and found to have significant PCa.

Furthermore, data collected on MRI and risk assignment has been studied in a cohort of 113 men enrolled in AS who met Epstein criteria but went on to receive an MP-MRI and fusion biopsy [41]. In doing so, 41 men (36 % of the cohort) were reclassified based on high-volume of Gleason 6 (15 men) or due to increased Gleason grade disease detection (26 men). Lower grade targets (Gleason primary pattern 3) were less likely to be reclassified, giving confidence to MRI's ability to discern AS appropriate candidates. Their rates of reclassification suggested that AS criteria using MP-MRI targeted lesions prior to assigning risk should be reevaluated. High suspicion targets on MRI (Gleason primary pattern grade 4 and 5) were reclassified at rates greater than three times those of lower suspicion targets [41].

Finally, a prospective evaluation of MP-MRI with FB versus 12-core biopsy was recently reported [4••]. Of 72 patients on AS referred for rising PSA or appropriate re-biopsy interval 19/72 (26 %) had cancer Gleason ≥7, with 37 % detected by FB alone. Of patients with a PI-RADS score of ≥2, the NPV of MP-MRI for detection of Gleason 6, >50 % core involvement or any Gleason ≥7 disease was 100 %. Most importantly, MP-MRI suspicion score was an independent predictor of progression to high-volume Gleason 6 or Gleason ≥7 PCa, even when adjusting for age, PSA, and time from MRI to biopsy.

Monitoring and Surveillance

Determining tumor progression in AS patients is a major challenge given that PCa is a multifocal and often indolent disease, and there exist inaccuracies of standard clinical and histological parameters. Current standard-of-care includes serial PSA testing and repeat 12-core TRUS-guided biopsy. In order to assess specific lesions more unambiguously, MP-MRI could significantly reduce the number of unnecessary surveil-lance biopsies with high accuracy, thereby resulting in less invasive AS protocols. Despite the lack of standardized radiological definition of progression, several works have assessed low-risk lesion evolution on MRI during serial patient monitoring sessions.

Prostate Specific Antigen and Multiparametric MRI

Despite varying institution-specific inclusion criteria in contemporary AS populations (Table 1), published protocols all rely on PSA, DRE, and TRUS biopsy results to determine eligibility, monitor patients, and define triggers for intervention. The variation present in current criteria represents a fundamental challenge in AS: avoiding overtreatment without compromising the window for cure [42].

PSA remains an integral component of surveillance as serial measurements are acquired every 3–6 months. PSA kinetics includes PSA doubling time, density and velocity; as triggers for initiating treatment, however, these measures have their limitations. PSA density, for example, has been found to have no correlation with progression on serial biopsy, nor has it been shown to correlate with upgrading or worse final histopathology for patients who undergo RP [43]. In the European Randomized Study of Screening for Prostate Cancer (ERSPC), PSA velocity—thought to be more accurate in predicting progression compared to PSA density—failed to contribute as an independent prognostic factor [44]. Since the correlation between PSA kinetics and progression on repeat biopsy remains unclear, PSA as a trigger for re-biopsy appears to be insufficiently supported as a criterion for progression alone [45]. The role of MP-MRI in the PSA era has been of recent interest to determine which patient populations would most benefit from an image-guided approach [46, 47]. Efforts to establish a PSA cutoff found 90 % of clinically-significant PCa was detected by MP-MRI and fusion biopsy using a cutoff PSA value of 5.2 ng/mL, suggesting that lower values had a lower likelihood of association with clinically-significant disease [47].

Serial Multiparametric MRI and Fusion Biopsy

Early work has shown successful monitoring of PCa using MRI to Belectronically track^ specific tumors with the ability to return to the site of prior concern [48]. Electronically tracked MRI and TRUS-guided biopsy targets were compared by relative accuracy of resampling between modalities. MRI targets, when resampled in 53 AS men, were more likely to show cancer than resampling of tumors at systematic sites (61 % versus 29 %, p=0.005), suggesting improved and high accuracy in MRI-aided resampling methods over TRUS-guided biopsy [29]. Additionally, serial FB allows for reassigning prior areas of concern (on 12-core or imaging) as targets for subsequent sessions [49].

There have been several studies showing that patients with visible lesions on MP-MRI have an increased overall risk of cancer progression, and patients with a lesion identified on MP-MRI tripled the risk of overall cancer progression [5]. Subsequently, small index lesions measuring <7 or <5 mm (correlating with established cutoffs for low-volume disease) were identified to form two cohorts aimed at identifying the time interval during which cancerous lesions would progress on serial imaging [50]. A majority of the patients demonstrated benign findings (86.2 and 87.5 %, in respective cohorts) or low-grade Gleason 6 PCa (13.8 and 12.5 %, respectively). Over a period of 2.3–2.4 years, no change in size was demonstrated in either cohort (p=0.93 and p=0.36). The authors proposed that MP-MRI identified indolent lesions may be observed for at least 2 years without significant change, and therefore, MP-MRI could assuredly be used to monitor such AS patients [50].

Most recently, the only study to establish the value of serial MP-MRI and serial FB in an AS population meeting strict Epstein criteria was reported [51••]. On the first confirmatory fusion biopsy, 22.4 % of the patients were no longer AS candidates based on Gleason score alone. The negative predictive value of a stable MP-MRI was found to be 80 %, potentially allowing for increasing the interval between surveillance biopsies. The number needed to biopsy for one Gleason progression was 8.74 men for standard biopsy versus 2.90 men for FB; the authors concluded that there was value in both biopsy methods and FB should be performed in conjunction with 12-core biopsy in AS.

Conclusion

The advent of MP-MRI has led to better-defined intraprostatic anatomy, allowing lesion identification and assigning suspicion scores that correlate with disease severity. Published and scientifically supported rationale for using MP-MRI in active surveillance protocols relies on improved lesion detection, accurate grading of lesions, and less invasive strategies for serially monitoring patients. The goal of surveillance MRI to supplant prostate biopsy is potentially attainable, but not justified at the current time, though MRI may impart confidence over PSA alone and allow for extension of the interval between biopsy. Prospective evaluations will begin to address and elucidate the longitudinal predictors on MRI, determine timing of biopsy in relation to MRI, and elaborate on the role of genomic markers on PCa screening and AS.

Acknowledgments

The National Institutes of Health (NIH) Medical Research Scholars Program is a public-private partnership supported jointly by the NIH and generous contributions to the Foundation for the NIH from Pfizer Inc., The Doris Duke Charitable Foundation, The New-port Foundation, The American Association for Dental Research, The Howard Hughes Medical Institute, and the Colgate-Palmolive Company, as well as other private donors.

Conflict of Interest Peter A. Pinto reports a patent US 8447384B2 issued. Michele Fascelli, Arvin K. George, Thomas Frye, Baris Turkbey, and Peter L. Choyke each declare no potential conflicts of interest.

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Table 1

Active surveillance strategies—inclusion criteria

Protocol		Gleason score	Clinical stage	PSA (ng/mL)	PSAD (ng/mL/cc)	Positive cores (*n*)	Single core involvement (%)
NCCN	Mohler et al. [52]	6	≤T1c	≤10	<0.15	≤2	≤50
PRIAS	Thomsen et al. [53]	6	≤T2a	≤10	<0.2	≤2	
UCSF	Dall'Era et al. [11]	6[a]	≤T2a	≤10		≤33 % (minimum 6 cores)	≤50
Toronto	Klotz et al. [54]	6[a]	≤T2b	≤10			
Epstein	Tosoian et al. [55]	6	≤T1c		<0.15	≤2	≤50
Royal Marsden	Selvadurai et al. [56]	6	≤T2	≤15			≤50
D'Amico	D'Amico et al. [57]	6	≤T2a	≤10			

NCCN National Comprehensive Cancer Network, *PRIAS* Prostate Cancer Research International Active Surveillance, *UCSF* University of California, San Francisco

[a]AS cohorts allowed for limited inclusion of Gleason ≤3+4 patients