

REVIEW

Multiparametric magnetic resonance imaging in the active surveillance of prostate cancer: protocol, risk stratification, and surveillance

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Abstract

Active surveillance serves as a vital management strategy for patients diagnosed with low-risk, organ-confined prostate cancer and is aimed at reducing overtreatment, cost minimization and enhancing patients' quality of life. However, the comprehensive implementation of active surveillance faces various challenges necessitating improvement, such as refining screening criteria, optimizing surveillance procedures, and establishing clear guidelines for active intervention. Multiparametric magnetic resonance imaging (mp-MRI) has assumed an increasingly pivotal role in the context of active surveillance. It provides essential supplementary insights into the identification and characteristics of prostate cancer. mp-MRI improves the precision of risk stratification, thus enhancing patient selection and compliance. Furthermore, it facilitates continuous disease monitoring, thereby reducing the probability of missed treatment opportunities during follow-up. This review, characterized by its meticulous analysis, aims to comprehensively examine the utilization and advancements of mp-MRI in the active surveillance of prostate cancer.

Keywords

Prostate cancer; Active surveillance; Multiparametric magnetic resonance imaging; Risk stratification

1. Introduction

Prostate cancer (PCa) is a commonly diagnosed malignancy in elderly men, ranking as the second most prevalent cancer among males [1]. The primary methods for early PCa detection currently involve prostate-specific antigen (PSA) testing and targeted biopsies, which have significantly increased early diagnosis rates and reduced PCa mortality. However, concerns are rising regarding overdiagnosis and overtreatment [2], as numerous cases of PCa involve slow-growing tumors with a low likelihood of causing symptoms or mortality [3]. In clinically detected organ-confined low-risk PCa, radical prostatectomy has been associated with reduced mortality but at the expense of causing greater harm. Thus, the effectiveness of radical prostatectomy may be limited to younger individuals and those with intermediate-risk disease [4]. Surgical and radiotherapy interventions not only impose financial burdens and anxiety on patients but also elevate the risk of complications, including sexual dysfunction and urinary tract issues, which negatively affect patients' quality of life [2, 5].

To achieve a balance between avoiding unnecessary treatment and adopting a more aggressive approach, active surveillance (AS) has gained increasing importance in the management of prostate cancer (PCa) [6]. Multiparametric magnetic resonance imaging (mp-MRI) provides a more precise assess-

ment of tumor size and extent, improves risk stratification, and aids in treatment allocation, and is recommended by several international guidelines for assessing the risk of PCa [7–9]. Concerns have arisen regarding how to define the boundaries of AS and active treatment safely, as well as the selection of appropriate procedures for conducting AS once initiated and the role of imaging markers in the AS of these patients.

In this present review, we outline the current status of AS in PCa management, the protocol and risk stratification associated with mp-MRI in PCa patients.

2. Current status of active surveillance in PCa

PCa ranks as the second most prevalent cancer and the fifth leading cause of cancer-related death in males globally. In 2020, the incidence of PCa in men exceeded that of lung cancer in Europe and Japan [10]. The burden of PCa varies significantly, with higher mortality rates in low-income countries and greater incidence in high-income countries. Globally, there has been an upward trend in PCa incidence but a downward trend in mortality rates, particularly in Europe. Notably, there has been an increase in incidence among individuals aged under 50 years [11]. In China, the cancer landscape is evolving, marked by a rapid rise in the incidence and burden of breast cancer,

colorectal cancer and PCa. Moreover, compared to the United States and the United Kingdom, China exhibits lower cancer incidence but higher cancer mortality and disability-adjusted life year rates [12]. The age-standardized incidence rate of PCa in Asia stands at 11.5 per 100,000 men, which is one-sixth of the incidence observed in continental North America [13].

The acceptance of AS varies across countries, medical institutions and healthcare professionals [14]. For instance, in the United States, the proportion of patients opting for AS increased from 14.5% in 2010 to 42.1% in 2015 following an initial diagnosis of low-risk organ-confined PCa [15, 16]. The Swedish National Prostate Cancer Registry also reported a significant increase in AS acceptance rates, rising from 40% to 74% between 2009 and 2014, respectively [17]. In Australia, the overall enrollment rate for AS was recorded at 25% in the Victoria Prostate Cancer Registry between 2008 and 2012 [18].

The data regarding AS for PCa in Asia significantly lag behind those in European and American countries for several reasons. First, the historical incidence of PCa in Asia has been notably lower than that in Western countries, with an incidence of 13.9 per 100,000 in East Asia, in contrast to 73.7 per 100,000 in North America [19]. Second, in Asia, a comprehensive PSA screening model has not been adopted for PCa, and thus, it cannot directly emulate the established Western screening approach [20]. In China, PCa cases are frequently diagnosed at later stages, often characterized by higher-grade disease, rendering them less suitable for AS. Moreover, research suggests that Asian patients face an elevated risk of pathological progression post-prostatectomy, possibly due to factors such as lower body mass index, smaller prostate volume and genetic variations, making AS less suitable for this patient group [21]. Additionally, differences in cultures and cognitive aspects of PCa management between Asian and Western patients influence their preference for active treatment over AS, with Asian patients showing a higher inclination toward active treatment [22]. To encourage the selection and adherence of low-risk Asian PCa patients to AS, it is important to harness expertise in chronic disease management and develop PCa screening protocols and surveillance procedures tailored specifically for Asian populations.

3. Methods and screening criteria for active surveillance

AS has become a widely adopted approach for managing patients with low-risk PCa. However, there is a lack of consensus regarding the optimal AS protocol. Urologists primarily rely on indicators of disease progression, such as elevated PSA levels, increased PCa volume and rising Gleason scores, to determine the need for active treatment. Nonetheless, the ongoing debate surrounding PSA testing, which has persisted since 1991, revolves around its ability to detect clinically significant disease earlier than its clinical manifestation and to evaluate the effectiveness of therapy for this disease [23]. Furthermore, conventional ultrasound-guided transrectal biopsy may miss lesions in the anterior or central regions of the prostate and can inaccurately sample the core of the tumor, leading to an underestimation of cancer stage and grade [24]. In contrast, mp-MRI offers a distinct advantage in

detecting prostate lesions. Studies have shown that mp-MRI has a sensitivity of 93% in detecting clinically significant PCa, whereas the sensitivity of transrectal ultrasound-guided biopsy is only 48% [25]. The improved ability of mp-MRI to provide more precise assessments of tumor size and extent of the disease enhances risk stratification and supports informed treatment decisions.

Currently, patients who undergo AS for PCa primarily belong to the very low-risk group, as defined by the risk classification system of the International Comprehensive Cancer Network. This group includes individuals with the following criteria: stage T1c, a Gleason score of 6, PSA level below 10 ng/mL, fewer than 3 positive biopsy cores, $\leq 50\%$ cancer involvement in each core, and a PSA density of < 0.15 ng/mL². Additionally, patients falling into the low-risk group (stage T1–2a, Gleason score ≤ 6 , and PSA < 10 ng/mL) and specific subgroups within the intermediate-risk category (3 + 4 Gleason score, stage T1 or T2, and PSA < 10 ng/mL, with a low number of positive biopsies) may also be considered for AS. However, there is an ongoing debate among experts regarding the suitability of AS for patients in the intermediate-risk group with a Gleason score of 3 + 4, and they recommend additional confirmation or follow-up biopsies within 6 to 12 months [26].

4. mp-MRI protocol for active surveillance

The latest version (2.1) of the Prostate Imaging Report and Data System (PI-RADS) mandates that mp-MRI includes a multiplane sequence comprising axial, coronal and sagittal T2-weighted (T2W) sequences, axial T1-weighted (T1W) sequences, high b-value diffusion-weighted imaging (DWI), and the computation of the apparent diffusion coefficient (ADC) using a “high b-value” [27]. Among these sequences, the most commonly used ones are T2W, DWI and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). T1W images are valuable for distinguishing the prostate, lymph nodes, distant metastasis and other anomalies, while T2W images can effectively outline the anatomy of the prostate zones (including the peripheral zone, transitional zone and central zone) and can assess peripheral invasion of PCa. DWI is instrumental in identifying PCa, particularly in the peripheral zone, by reflecting the diffusion of water molecules. ADC values are routinely used in prostate MR examinations, and research has explored their potential as a quantitative marker for PCa [28]. DWI plays a pivotal role in the multiparametric evaluation of prostate lesions. The derived ADC can serve as a valuable quantitative biomarker for malignant growth but faces challenges related to low reproducibility [29]. The importance of DCE-MRI in the PI-RADS V2.1 guidelines has diminished, and it is now primarily recommended for assessing positive and negative peripheral zone lesions, particularly for PI-RADS 3 lesions of the peripheral zone [27]. Furthermore, metabolic imaging holds promise in identifying cancer lesions to guide prostate biopsy and assess PCa aggressiveness.

Magnetic resonance spectroscopy (MRS) aids in diagnosing PCa by assessing cell metabolism and proliferation [30]. In prostate MRS examinations, the analysis typically involves citrate, choline and creatine metabolites. Citrate levels have been

found to be higher in both normal and hyperplastic prostate tissues, while choline levels are elevated in PCa tissues. However, there is no statistically significant difference in creatine content between PCa and normal prostate tissues. Several MRS studies have consistently shown a significantly higher metabolic ratio of (choline + creatine)/citrate in malignant areas of the prostate peripheral zone compared to the surrounding benign areas. Additionally, correlations have been observed between choline/creatine or (choline + spermidine + creatine)/citrate ratios and Gleason scores [31]. Thus, prostate MRS examinations can effectively detect pathophysiological tissue changes by quantifying choline and its metabolites, offering promise for PCa diagnosis. However, further research and clinical validation are imperative to establish the accuracy and reliability of this technique in clinical practice.

Amide proton transfer (APT)-weighted imaging is an emerging molecular imaging technology that leverages the signal generated by proton exchange between mobile protein and polypeptide amide protons and free water [32]. Guo *et al.* [33] confirmed the effectiveness of APT imaging in differentiating between benign hyperplasia and PCa. Additionally, Qin *et al.* [34] showed that both APT and apparent diffusion coefficient (ADC) are independent predictors for stratifying PCa risk. Receiver operating characteristic (ROC) curve analysis has demonstrated that APT values have a sensitivity of 61.1% and specificity of 81.0% for PCa of transitional origin, while ADC values have a sensitivity of 83.3% and specificity of 61.9% [34]. Furthermore, the combined APT and ADC models have shown significantly higher accuracy than APT or ADC models alone (transitional zone: $p = 0.002$ and $p = 0.020$; peripheral zone: $p = 0.033$ and $p < 0.001$). APT values are anticipated to serve as imaging markers for eligibility screening and disease progression assessment in AS for PCa [34].

MRI-based radiomics, a noninvasive method, has gained popularity for extracting imaging features from PCa images and developing predictive models for clinical tasks [35]. Recent studies have explored the correlation between imaging models and genetic characteristics to better understand the inherent biological nature of PCa [36]. However, despite the superiority of MRI-based radiomics over radiologist-reported outcomes, it is essential to consider variability before translating it into clinical practice [37].

Deep learning has made significant advancements in the field of artificial intelligence applied to medical imaging, becoming an indispensable tool in the pursuit of personalized medicine for PCa. Schelb *et al.* [38] developed a U-net-based deep learning algorithm to assess the probability of diagnosing clinically significant PCa using magnetic resonance images of the prostate, achieving a sensitivity ranging from 92% to 96%. Winkel *et al.* [39] found that computer-aided diagnosis using deep learning not only improved the accuracy of detecting suspicious lesions but also reduced variability. In their test set, Netzer *et al.* [40] observed a sensitivity of 97% for identifying PI-RADS greater than or equal to 3 and 90% for identifying PI-RADS greater than 4. The specificity for identifying PI-RADS greater than or equal to 3 was 19%, while the specificity for identifying PI-RADS greater than 4 was 59.6% [40].

Positron emission tomography-magnetic resonance

imaging (PET-MRI) scanners diagnose diseases by combining metabolic information with anatomical and functional MRI imaging. While most PET-MRI studies focus on reevaluation after PCa treatment, there has been growing interest in using prostate-specific membrane antigen (PSMA) radioligands to diagnose significant prostate lesions and characterize them with PET-MRI. Research has shown that the use of PSMA PET-MRI can enhance the diagnostic accuracy of PCa compared to mp-MRI alone [41]. However, further investigation is necessary to determine whether PSMA PET-MRI is suitable for the initial diagnosis of PCa and to evaluate the trade-offs between benefits and costs.

Taken together, mp-MRI offers the advantage of utilizing multiple sequences and parameter combinations for prostate diagnosis. When combined with quantitative parameters and artificial intelligence, it can transform subjective lesion information into objective data, facilitating quantitative differentiation and differential diagnosis between tumors and normal tissues. However, various examination methods have their strengths and weaknesses, and different imaging techniques have their own limitations, such as the need for highly skilled operators, involvement of complex procedures, increase in examination time and aggravating the financial burden of patients. Therefore, it is important to have a comprehensive understanding of these methods and to judiciously select and integrate them based on specific clinical conditions, which can enable earlier and more accurate disease diagnosis and provide patients with more evidence-based treatment options.

5. Application of mp-MRI in active surveillance for PCa

Numerous tools are available for tailoring clinical decision-making in men with low-risk PCa. mp-MRI has proven particularly valuable for the initial risk stratification of PCa in men under AS, especially in cases with negative PSA results [42]. Turkbey *et al.* [43] revealed that mp-MRI may effectively identify populations suitable for AS, achieving a sensitivity of 93% and a positive predictive value of 57%, resulting in an overall accuracy of 92%. However, despite the promise shown by mp-MRI in PCa risk stratification, significant challenges related to inconsistencies and a lack of diagnostic efficacy reproducibility persist and require attention. A recent literature review on mp-MRI for PCa risk stratification has highlighted several key issues (Table 1): (1) Considerable variability exists in the diagnostic efficacy of different parameters within a single study or the same parameter across various studies for PCa risk stratification (area under the curve (AUC) range: 0.48 to 0.97); (2) Inconsistencies observed in the sensitivity and specificity of PCa risk stratification among different parameters or the same parameter across studies (sensitivity range: 53% to 91%; specificity range: 53% to 100%); and (3) Variations in the cut-off values of the same parameter for predicting PCa risk stratification across different studies [34, 44–48].

While MRI remains a valuable imaging modality, it cannot replace biopsy, and further research is needed to fully integrate MRI into AS for PCa. Targeted biopsy guided by mp-MRI can significantly enhance PCa diagnosis and risk stratification. By

TABLE 1. Literature review on mp-MRI for prostate cancer risk stratification in the past three years.

First author, Year of publication	Prostate zone	Risk stratification	Parameters	AUC	Cut-off	Sensitivity	Specificity
Qin, 2003 [34]	TZ	GS < 3 + 4	APT	0.743	3.35	0.611	0.810
	TZ	GS < 3 + 4	ADC	0.774	1.25	0.833	0.619
	PZ	GS < 3 + 4	APT	0.878	3.31	0.740	0.836
	PZ	GS < 3 + 4	ADC	0.760	0.79	0.940	0.534
Yin, 2021 [44]	Prostate	GS < 7	MK	0.839	0.99	0.700	0.857
	Prostate	GS < 7	MD	0.829	0.85	0.700	0.857
	Prostate	GS < 7	APT	0.818	3.35	0.800	0.928
Nilsson, 2023 [45]	Prostate	GS < 3 + 4	T2	0.480	\	0.780	0.350
	Prostate	GS < 3 + 4	ADC	0.600	\	0.670	0.540
	Prostate	GS < 3 + 4	Ktrans	0.680	\	0.530	0.820
Park, 2022 [46]	Prostate	GS ≤ 3 + 3	ve	0.643	0.26	0.660	0.530
Żurowska, 2023 [47]	Prostate	GS < 3 + 3	Dapp	0.806	1.16	0.864	0.667
	Prostate	GS < 3 + 3	K	0.861	1.17	0.730	0.733
	Prostate	GS < 3 + 3	ADC	0.823	0.77	0.770	0.733
	TZ	GS < 3 + 3	Dapp	0.624	1.16	0.827	0.600
	TZ	GS < 3 + 3	K	0.849	1.24	0.610	1.000
	TZ	GS < 3 + 3	ADC	0.685	0.78	0.905	0.600
	PZ	GS < 3 + 3	Dapp	0.853	1.12	0.851	0.600
	PZ	GS < 3 + 3	K	0.847	1.10	0.802	0.800
Michallek, 2022 [48]	Prostate	GS < 3 + 3	ADC	0.770	\	0.910	0.610
	Prostate	GS < 3 + 3	Fractal dimension	0.970	\	0.910	0.860

Abbreviations: MK: mean kurtosis; MD: mean diffusion; ve: extracellular extravascular space volume fraction; Ktrans: volume transfer constant; ADC: apparent diffusion coefficient; Dapp: apparent diffusion coefficient; GS: Gleason score; TZ: transitional zone; PZ: peripheral zone; APT: Amide proton transfer; AUC: area under the curve.

conducting targeted biopsies on suspicious lesions identified through mp-MRI, low-risk PCa patients can be appropriately categorized for AS. In cases involving anterior prostate tumors, systemic biopsy often fails to detect this area. However, targeted biopsy with mp-MRI overcomes this limitation by effectively sampling suspicious lesions in both the anterior and posterior regions, thus improving the diagnostic accuracy of anterior PCa [24].

One study's findings revealed that, following mp-MRI and subsequent targeted biopsy, as many as 40.7% of patients under AS displayed a Gleason score of 7, leading to treatment escalation [49]. In a retrospective study on prostatectomy samples, over 50% of patients examined with mp-MRI showed an increase in their postoperative Gleason score [50]. While mp-MRI and MRI-guided targeted biopsies can improve the detection of "clinically insignificant" PCa, determining the suitability of PCa with favorable risk for AS requires additional evaluations. Before undergoing a subsequent biopsy, patients should be recommended to undergo mp-MRI examination and

systematic MRI-targeted biopsies. AS can only be considered if both results meet the inclusion criteria [26]. High-grade findings on targeted biopsies were identified as a significant predictor of higher-grade transition, while the risk of non-organ-confined disease remained high and was not accurately predicted by MRI or features of systematic/targeted biopsies [44]. Thus, integrating clinical parameters with mp-MRI may offer a more precise prediction of AS eligibility [51, 52].

mp-MRI not only aids in determining eligibility for AS but also plays a crucial role during AS periods. However, due to variations in the inclusion criteria for AS patients with clinically significant PCa and the definition of radiological progression, the specific role and timing of MRI in this context remain to be established in clinical practice [53]. To address these challenges, the sequence assessment of PCa was introduced at the second European College of Oncology Active Surveillance Workshop, referred to as the Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) [54]. These guidelines have contributed

to establishing diagnostic criteria for assessing radiological progression through follow-up, utilizing a 1–5 point scoring system for AS patients. Early studies have indicated that when the PRECISE score reaches 4, biopsy results show a significantly increased likelihood of PCa progression, with a predictive value of up to 0.96 [55]. Therefore, the PRECISE score may serve as the basis for determining whether patients should continue with the AS protocol.

The study data revealed that multiparametric mp-MRI exhibited a high negative predictive value of 93% but a low positive predictive value of only 34% [56]. However, the negative predictive value can be further improved to 100% by combining negative mp-MRI results with the biomarker known as prostate cancer antigen 3 [57]. Additionally, the detection rate could be enhanced by integrating mp-MRI with clinical parameters, such as follow-up PSA density or the length of the cancer core at diagnosis. For patients with an initially negative mp-MRI, conducting follow-up mp-MRI examinations every 2–3 years during the surveillance period can assist physicians in assessing the necessity for additional targeted biopsy before proceeding with transrectal ultrasound biopsy [58]. Furthermore, for patients with an index lesion detected on mp-MRI but a negative biopsy result for clinically significant prostate cancer, it is advisable to have a shorter follow-up interval of 1–2 years and to consider a repeat targeted biopsy if significant changes are observed during the follow-up period [59]. Additionally, if there is clinical suspicion of disease progression, such as a significant increase in PSA levels, performing mp-MRI for targeted biopsy is warranted.

Negative results from mp-MRI scans can offer patients psychological reassurance and contribute to improved adherence to the AS protocol [60]. Conversely, positive mp-MRI scans, particularly those with a PI-RADS score of 4 or 5, indicate a higher risk of disease progression. Therefore, mp-MRI can assist in stratifying the subsequent risk of disease progression and guide treatment decisions [60, 61].

Overall, ongoing monitoring through mp-MRI is considered highly effective in helping patients with decision-making regarding AS and in monitoring disease progression. Additionally, negative mp-MRI results can increase confidence in extending the biopsy interval during AS. Combining MRI-based targeted biopsy with systemic mp-MRI can enhance risk stratification and provide a reliable basis for patients to choose between AS or active treatment considerations [62].

6. Conclusion and outlook

The utilization of mp-MRI has proven to be highly influential in the evaluation and selection of PCa patients for AS. It offers supplementary insights into PCa identification and its characteristics. Among the key parameters of mp-MRI, ADC has been extensively researched and clinically applied. However, the cut-off value and diagnostic effectiveness of ADC are not consistent across different scanners, vendors and b values. Consequently, there is a need for validating novel and reliable parameters. With the clinical adoption of emerging MRI technologies such as APT and omics, various parameters or MRI techniques can be combined to achieve collaborative diagnosis and produce complementary effects,

thereby enhancing the screening capability for AS patients. As future studies are based on multicenter, large sample datasets and involve continuous optimization of relevant quantitative parameters, mp-MRI is estimated to progressively assume a more crucial role in the precise diagnosis of PCa, screening and evaluation process of AS.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

XYQ and XQZ—designed the research study. XYQ—performed the research. XYQ, JL and XQZ—wrote the manuscript. All authors contributed to editorial changes in the manuscript. All the authors have read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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