Review Article | Genitourinary Imaging

eISSN 2005-8330
https://doi.org/10.3348/kjr.2020.1224
Korean J Radiol 2021;22(7):1087-1099

Korean Journal of Radiology
KJR

Multiparametric MRI in Active Surveillance of Prostate Cancer: An Overview and a Practical Approach

Chau Hung Lee[1], Teck Wei Tan[2], Cher Heng Tan[1, 3]

Departments of [1]Radiology and [2]Urology, Tan Tock Seng Hospital, Singapore; [3]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

MRI has become important for the detection of prostate cancer. MRI-guided biopsy is superior to conventional systematic biopsy in patients suspected with prostate cancer. MRI is also increasingly used for monitoring patients with low-risk prostate cancer during active surveillance. It improves patient selection for active surveillance at diagnosis, although its role during follow-up is unclear. We aim to review existing evidence and propose a practical approach for incorporating MRI into active surveillance protocols.

Keywords: *Review; Prostate cancer; Magnetic resonance imaging; Active surveillance; Image-guided biopsy*

INTRODUCTION

Multiparametric MRI (mpMRI) of the prostate has become integral in the management of prostate cancer. MpMRI can identify the areas within the prostate that are most suspicious for malignancy using a combination of T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI), and dynamic contrast-enhanced (DCE) imaging, allowing for MRI-guided targeted biopsy [1]. Compared with conventional systematic transrectal ultrasound (TRUS) biopsy, MRI-guided targeted biopsy has been shown to increase the detection of "clinically significant" prostate cancer (csPCa), defined as a Gleason score of 7 and above, and reduce the detection of "insignificant" prostate cancers with a Gleason score of 6 [2-4].

Active surveillance (AS) is a management option for patients with low-risk prostate cancer, including Gleason score 6 cancers. This regime aims to reduce overtreatment of this group of patients by closely monitoring the disease status rather than offering radical treatment at diagnosis. Definitive treatment is instituted when there is clinical evidence of disease progression, and this has been shown to have a minimal impact on the eventual outcome of the disease [5]. Studies have shown that targeted biopsy based on mpMRI improves the selection of patients for AS by allowing the detection of lesions that can progress from a clinically insignificant cancer to a cancer of a higher grade [6-8].

This article aims to provide a review of the potential role of mpMRI in AS for prostate cancer and its incorporation into AS protocols.

Received: October 8, 2020 **Revised:** December 8, 2020
Accepted: January 8, 2021
Corresponding author: Cher Heng Tan, MBBS, FRCR, Department of Radiology, Tan Tock Seng Hospital, Lee Kong Chian School of Medicine, Nanyang Technological University, 11 Jalan Tan Tock Seng, 308433 Singapore.
• E-mail: cherhengtan@gmail.com

Active Surveillance in ASIA

AS data in Asia are generally limited [9]. One of the reasons may be that the incidence of prostate cancer in Asia has historically been much lower than that in the West, with an incidence of 13.9 per 100000 in East Asia compared to 73.7 per 100000 in North America [10]. Moreover, prostate cancer screening using serum prostate-specific antigen (PSA) is generally not well-established in Asia because of the lack of established evidence within Asian populations and the inability to directly apply established screening models from the West [11]. Prostate cancer, therefore, tends to be more

advanced and of a higher grade at diagnosis, making several patients ineligible for AS based on consensus criteria [12]. There is also evidence suggesting that Asians are at a higher risk of pathological progression after prostatectomy, which is thought to be related to a lower body mass index, smaller prostate sizes, and possibly genetic differences compared to the West, making AS in Asia less favorable [13]. Moreover, the differing cultural pressures, perceptions, and fears of Asian and Western patients also influence the choice between AS and definitive treatment, with several Asian patients opting for the latter, even among those with low-risk clinically insignificant prostate cancers [14].

However, there is a recent trend of a rising incidence of prostate cancer in Asia, which is attributed to the longer lifespan and the "westernization" of lifestyle and diet intake [15]. Increased awareness and accessibility to serum PSA screening also allows early-stage and lower-grade prostate cancers to be diagnosed [16]. We foresee that AS, as a management option, is likely to be more widely accepted in Asia over time.

Conventional Active Surveillance Protocols

Patients with low-risk localized prostate cancer are eligible for AS. Several established international guidelines define the eligibility criteria for AS based on various clinical parameters, such as a Gleason score of 6, PSA of less than 10 ng/mL, and a clinical local T-staging of not more than T2a [17].

Conventional AS protocols before the era of mpMRI were centered around regular PSA monitoring to assess PSA kinetics (such as PSA density and PSA velocity), regular digital rectal examinations, and regular systematic TRUS biopsy [18,19]. After low-risk prostate cancer is diagnosed based on the initial diagnostic systematic TRUS biopsy, and the patient is deemed eligible for entry into AS, a repeat systematic TRUS biopsy (known as the confirmatory biopsy) is usually performed within the first year to confirm a low-risk status. Subsequent surveillance with systematic TRUS biopsy is usually performed every 2 to 3 years, or more frequently, depending on the changes in the clinical status of the disease or PSA kinetics.

The conventional AS protocols have limitations. Some patients may have difficulty adhering to the strict follow-up required for AS, and there is also concern over missed windows of opportunity for curative treatment with delays in definitive treatment [20,21]. This may impact patients psychologically during the duration of AS for their disease. Most significantly, TRUS biopsy has been shown to underestimate the Gleason score and local extent of cancer, thereby underestimating the clinical risk profile even at diagnosis [2,3,22].

As such, there is a need to improve protocols to improve patient selection and the outcomes for AS, including the use of saturation template biopsy, molecular biomarkers, and imaging [23].

Multiparametric MRI during Active Surveillance: When to Do It?

At Diagnosis

Multiparametric MRI has been established as an important modality for the detection of prostate cancer, and it is recommended by various international guidelines as the first-line investigation for patients with suspected prostate cancer who are candidates for curative treatment [24,25]. Central to mpMRI is the Prostate Imaging-Reporting and Data System (PI-RADS). The PI-RADS scoring system allows the stratification of the probability of prostate cancer based on T2WI, DWI, and DCE imaging findings, each ranked on a scale of 1–5 [1]. MRI-guided ("targeted") biopsy pathways, where lesions with PI-RADS scores of 3–5 undergo targeted biopsy, have been shown to increase the detection of csPCa compared with conventional systematic TRUS biopsy, with an associated reduction in the number of biopsy cores [2,3,26].

Although MRI-guided biopsy pathways also aim to reduce the detection of "clinically insignificant" cancers with a Gleason score of 6, such low-risk prostate cancers will continue to be diagnosed in clinical practice. One reason is that systematic biopsy is often still recommended for patients with negative mpMRI (PI-RADS 1 or 2), as it has been shown that mpMRI may miss some cancers detected by systematic biopsy, with a false-negative rate of up to 26% [27]. Another reason is that the use of mpMRI is not routine for several health systems, particularly in developing countries in Asia, and several patients still undergo systematic biopsy as an initial work-up.

It has been shown that mpMRI with subsequent targeted biopsy can detect prostate cancers with Gleason scores of ≥ 7 in up to 40% of patients initially deemed eligible for AS based on clinical parameters [6,8,28]. Studies based on retrospective reviews of prostatectomy specimens showed that a positive baseline mpMRI (PI-RADS 3–5) predicted

https://doi.org/10.3348/kjr.2020.1224

Korean Journal of Radiology
KJR

the pathological progression, represented by the Gleason score, in almost 50% of patients, and combining the clinical parameters with mpMRI more accurately predicted AS eligibility than either of them [29,30]. Overall, mpMRI with targeted biopsy is superior to conventional clinical parameters (such as PSA, PSA density, clinical staging, and systematic biopsy) for defining AS eligibility by detecting suspicious foci that result in an increase in clinical risk through the upgrading of the Gleason score [30-33]. Therefore, mpMRI is increasingly being recommended as an important tool for risk stratification to improve patient selection for AS at the time of diagnosis [34,35].

During Surveillance

At present, the role of mpMRI in the follow-up of patients undergoing AS is controversial. The European Association of Urology recommends mpMRI before confirmation biopsy (usually performed within the first year of initial diagnosis), with targeted biopsy in addition to systematic biopsy if a focal lesion is detected on imaging [35]. However, the usefulness of mpMRI before confirmatory biopsy appears to be equivocal, with some studies suggesting that this combined targeted and systematic approach for confirmatory biopsy improves reclassification for eligibility for AS, while other studies do not demonstrate a significant advantage of targeted biopsy over systematic biopsy [7,28,36].

Beyond the first year of AS, mpMRI shows rather high negative predictive values for csPCa (up to 93%) but positive predictive values as low as 34% [37,38]. Combining a negative mpMRI with a biological marker such as prostate cancer antigen 3 gene has been shown to increase the negative predictive value to 100% [6,39]. Combining mpMRI with clinical parameters such as PSA density at follow-up or cancer core length at diagnosis have also been shown to improve the detection of disease progression [40]. However, whether the combined role of mpMRI and the clinical parameters or biomarkers can replace surveillance systematic biopsy is yet to be established.

The comparisons between mpMRI (with targeted biopsy) and systematic biopsy for the detection of disease progression in patients undergoing AS beyond the first year also show varying results. One study showed that serial mpMRI with targeted biopsy detected disease progression with a reduced number of biopsies compared with systematic biopsy alone. Another study showed that beyond the first year of AS, the value of MRI-guided targeted biopsy may be limited, only 3% of cancers progressed to a Gleason score of 7 or above with mpMRI, whereas 27% progressed with systematic biopsy [41,42]. Interestingly, lower AS failures and disease progression rates over the subsequent 2 years were reported in the Active Surveillance Magnetic Resonance Imaging Study (ASIST) trial, although no significant benefit of mpMRI with targeted biopsy over systematic biopsy was observed for patients undergoing confirmatory biopsy within the first year of diagnosis [43].

Beyond the first year, the optimal interval between follow-up scans is not clear, and most guidelines currently do not specify a recommended interval between surveillance mpMRI scans. However, incorporating mpMRI into the surveillance protocol can alter the follow-up interval. Patients with negative initial mpMRI can undergo follow-up mpMRI every 2–3 years before surveillance systematic TRUS biopsy to decide on the need for additional targeted biopsy [44,45]. For patients with an index lesion on mpMRI (PI-RADS 3–5) but a negative biopsy for csPCa, a shorter follow-up interval of 1–2 years was suggested, and repeat targeted biopsy was performed if there was a significant interval change [45]. Alternatively, mpMRI may be performed when there is clinical suspicion of disease progression, such as suspicious PSA kinetics, with a view to targeted biopsy [46,47].

Overall Value of mpMRI in AS

The median duration of AS before clinical progression is approximately 2 years, although it can be as long as 17 years [5]. There are also institutions in which MRI may not be readily accessible. Therefore, resource availability, the cost of serial mpMRI scans, and the risk-benefit ratios, such as the potential risk of gadolinium toxicity from multiple scans, are important issues to consider when integrating mpMRI into AS protocols.

Patients on AS using a serial MRI-based protocol have similar 5-year survival rates; however, AS failure and disease progression rates are generally lower than those of standard AS protocols that utilize only surveillance with systematic biopsy [37,43,48]. This can be attributed to the improved patient selection at entry into the AS. Furthermore, it has been suggested that patients are psychologically reassured by a negative mpMRI scan, which could potentially lead to improved compliance with AS regimens [48]. Conversely, a positive baseline mpMRI scan (PI-RADS 4 or 5) appears to correlate with a higher risk of disease progression, which suggests that mpMRI can help stratify the risk of subsequent disease progression and the need for active

 https://doi.org/10.3348/kjr.2020.1224

treatment [48,49].

Whether MRI-based AS protocols would allow the omission of surveillance systematic biopsies remains controversial. One study showed that only 1 of 56 patients with a negative mpMRI had a high-grade cancer detected on subsequent systematic biopsy and suggested that systematic biopsy may not be necessary if surveillance mpMRI is negative [49]. However, we recommend that negative surveillance mpMRI and mpMRI with stable findings should not obviate the need for systematic biopsy although they can allow for an increase in the interval between surveillance mpMRI and biopsies [41]. Strategies combining targeted and systematic biopsy increase the detection of csPCa compared with either of them [50].

Overall, serial surveillance mpMRI appears to be an additional useful tool for improving patient selection for AS eligibility and the detection of disease progression, with a negative mpMRI providing greater confidence in prolonging intervals between surveillance biopsies during AS. The combination of targeted and systematic biopsies may be advantageous over either of them, but the increased number of biopsy cores may translate into higher cost and associated morbidity compared with either of the techniques. While further research into the cost-effectiveness of this strategy is warranted, considering the benefits of mpMRI for AS, we propose possible pathways for integrating mpMRI into an AS protocol (Fig. 1).

Multiparametric MRI in Active Surveillance: How to Report

As discussed, the two main roles of mpMRI in AS are to improve the selection of eligible patients at diagnosis and evaluate significant changes over serial scans that would indicate radiologic progression. The European School of Oncology Task Force has established a set of recommended guidelines for mpMRI in patients undergoing AS [51]. The Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) recommendations aim to provide a standardized definition and assessment of radiologic progression for mpMRI to guide clinical management and facilitate the collation of data across institutions for future multi-institutional studies.

PRECISE proposes the routine recording of baseline parameters, including prostate volume, PSA density, and assessment of PI-RADS score and sizes of target lesions, if any. Lesion size can be recorded as volume, bi-axial dimensions at the greatest diameter on the axial section, or the largest diameter in any plane. If an index lesion is identified, MRI-guided targeted biopsy may upgrade the Gleason score, making the patient ineligible for AS (Fig. 2). If a targeted biopsy does not show csPCa, patients remain eligible for AS, and surveillance mpMRI can be performed.

Follow-up mpMRI shows the probability of significant radiologic progression recorded as a PRECISE score on a Likert-like scale of 1–5, where 1 indicates a very low probability of radiologic progression and 5 indicates definite radiologic progression (Table 1). The recommended parameters for assessing changes on follow-up mpMRI are lesion size, conspicuity on DWI (usually assessed qualitatively), change in the PI-RADS score (indicating upgrade of existing lesions or new lesions), and extraprostatic disease (including extracapsular extension, seminal vesicle invasion, pelvic lymphadenopathy, and osseous metastasis).

Based on the probability of significant radiologic progression, a targeted biopsy can be recommended. PRECISE scores of 1–3 (where a lesion has either resolved, decreased in size, or remains stable) can usually be managed with continued imaging follow-up, while patients with a PRECISE score of 4 or 5 (where a lesion has increased in size or where new lesions or extraprostatic disease are evident) should undergo targeted biopsy. In the example illustrated in Figure 3, the baseline mpMRI of a patient with elevated PSA showed a PI-RADS 3 lesion in the transition zone, and both systematic and targeted biopsies showed a Gleason 6 cancer. The patient was placed on AS. Repeat mpMRI a year before confirmatory biopsy showed that the lesion had increased in size, although the PI-RADS score remained at 3. Based on the PRECISE recommendations, the lesion can be classified as having a high probability of radiologic progression (PRECISE score 4). Repeat targeted biopsy showed a Gleason 3 + 4 cancer, and the patient was satisfactorily treated with radical prostatectomy.

The main challenge for the assessment of radiologic progression is the significant interobserver and intraobserver variability in the visual grading of imaging features such as conspicuity on DWI [51]. To overcome this, quantitative analyses such as a reduction in the apparent diffusion coefficient values have been shown to correlate with disease progression [52]. However, a quantitative assessment may not be feasible in daily practice, and the assessment of changes in DWI remain qualitative for practical purposes. Even for the measurement of lesion

https://doi.org/10.3348/kjr.2020.1224

Korean Journal of Radiology
KJR

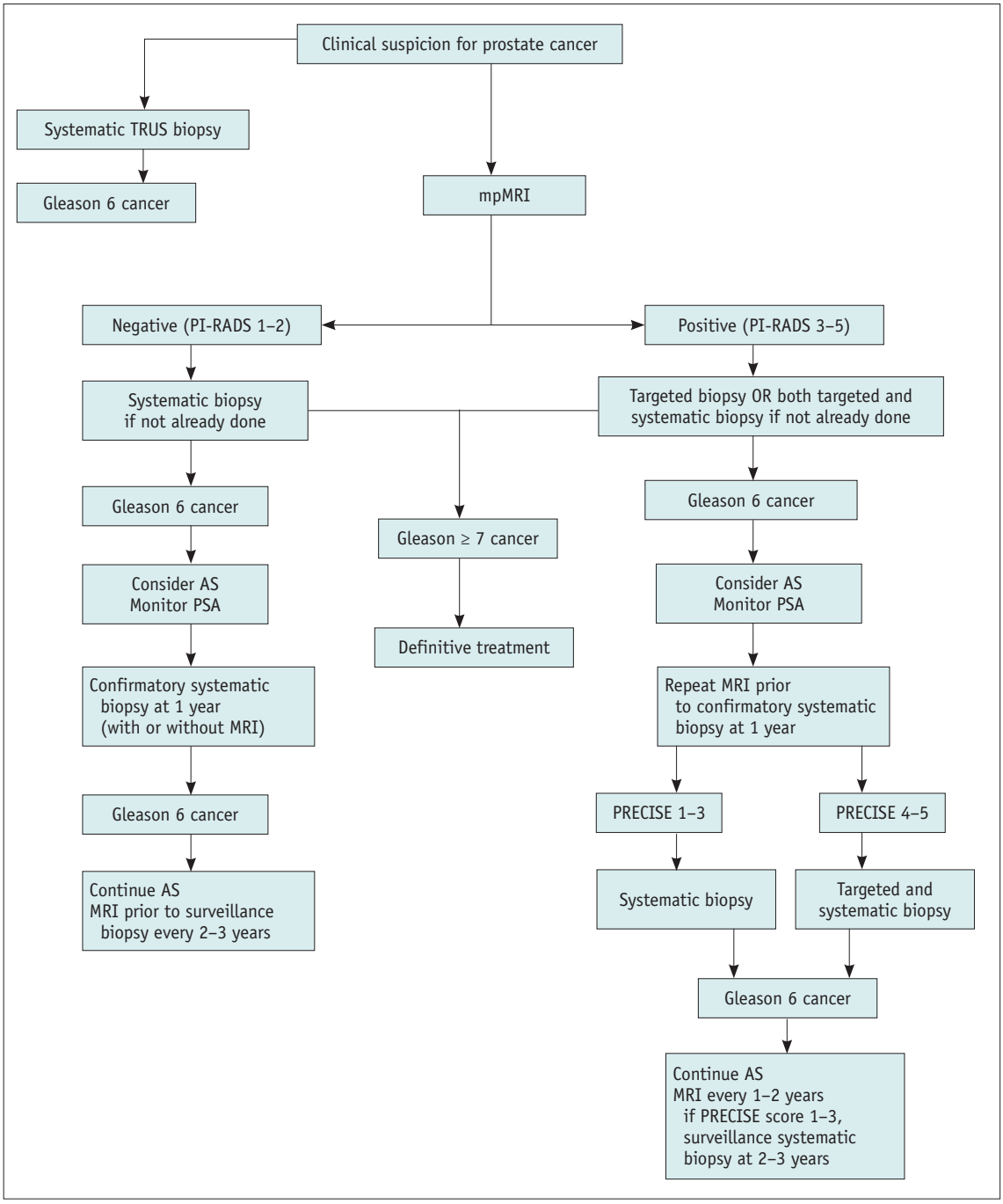

Fig. 1. Proposed pathways for integrating mpMRI into an AS protocol. AS = active surveillance, mpMRI = multiparametric MRI, PI-RADS = Prostate Imaging-Reporting and Data System, PRECISE = Prostate Cancer Radiological Estimation of Change in Sequential Evaluation, PSA = prostate-specific antigen, TRUS = transrectal ultrasound

size, the maximum lesion diameter, which is often used for convenience, is less reliable than volume in assessing the course of the disease [53]. Furthermore, natural variations in the appearance of prostate cancer and the prostate gland and changes related to benign prostatic hyperplasia over time may make it difficult to assess significant changes on mpMRI, an observation noted in several studies [38,40,41]. Notably, the current recommendations based on PRECISE are qualitative and therefore subject to further variability in evaluation although they are aimed at standardizing scan interpretation and reporting. These inconsistencies make it difficult to reliably define significant radiologic progression in clinical practice.

https://doi.org/10.3348/kjr.2020.1224

Fig. 2. A 61-year-old male presented with an elevated serum prostate-specific antigen of 13.6 ng/mL. Systematic transrectal ultrasound biopsy was performed, which showed a Gleason 3 + 3 prostate cancer in the left midgland. Multiparametric MRI was performed. **A.** T2-weighted imaging shows an ill-defined hypointense lesion in the transition zone at the left midgland (arrow). **B.** Apparent diffusion coefficient map shows a marked low signal (arrow). **C.** Diffusion-weighted imaging shows marked hyperintensity (arrow). This was graded as a Prostate Imaging-Reporting and Data System 4 lesion. MRI-ultrasound fusion targeted biopsy shows a Gleason 3 + 4 cancer. The patient was, therefore, ineligible for active surveillance based on baseline MRI.

Multiparametric MRI in Active Surveillance: Potential Diagnostic Problems

In practice, the application of MRI in AS is not as simple as it seems, largely due to the imperfection of mpMRI as a diagnostic tool. Therefore, clinicians need to consider other clinical features to appropriately manage and counsel patients who meet the criteria for AS. Here, we elaborate on three common scenarios.

PI-RADS 3 Lesions

The prevalence of PI-RADS 3 lesions on mpMRI is 6.4–45.7%, with 3.4–46.5% for harboring csPCa [54]. Studies have shown significant interobserver variability in the reporting of PI-RADS and PI-RADS 3 lesions [55,56]. Currently, there is no strong recommendation that PI-RADS 3 lesions should be subjected to immediate biopsy or undergo imaging surveillance [57]. However, given the relatively high incidence of reported PI-RADS 3 lesions and the low positive predictive value for csPCa, it may not be practical to routinely biopsy all PI-RADS 3 lesions.

To improve the detection rate of csPCa in PI-RADS 3 lesions, it has been suggested that the decision for targeted biopsy should depend on risk stratification based on additional clinical parameters such as PSA kinetics or family history, recommendation by a radiologist trained in prostate MRI, or lesion size [58-60].

Given the higher risk profile with known low-risk (Gleason 6) prostate cancer, the presence of PI-RADS 3 lesions on mpMRI for these patients should prompt close monitoring, including targeted biopsy, particularly if multiple lesions are encountered [61]. If a targeted biopsy is not elected, PI-RADS 3 lesions can be followed-up after 12–13 months, a sufficient time interval for radiologic progression or stability to be evaluable on mpMRI [62].

Table 1. Probability of Radiologic Progression on mpMRI Based on PRECISE Criteria, for Patients on Active Surveillance [51]

PRECISE Score	mpMRI Finding	Probability of Radiologic Progression
1	Lesion has resolved	Very low
2	Lesion has reduced in size Lesion is less obvious on DWI	Low
3	Stable findings	Intermediate
4	Lesion has increased in size Lesion is more obvious on DWI	High
5	New lesions (PI-RADS 3–5) Extraprostatic disease	Very high (definite)

DWI = diffusion-weighted imaging, mpMRI = multiparametric MRI, PI-RADS = Prostate Imaging-Reporting and Data System, PRECISE = Prostate Cancer Radiological Estimation of Change in Sequential Evaluation

PI-RADS 4/5 Lesions with Negative Biopsy

Index lesions with a PI-RADS score of 4 or 5 on mpMRI before confirmatory biopsy warrants a targeted biopsy before confirming eligibility for AS. However, a biopsy of such lesions occasionally turns out to be negative for csPCa. This can occur either because of the limitations of mpMRI (false positive) or targeted biopsy techniques (sampling error, i.e., false negative). A decision on whether to subject

https://doi.org/10.3348/kjr.2020.1224

Korean Journal of Radiology
KJR

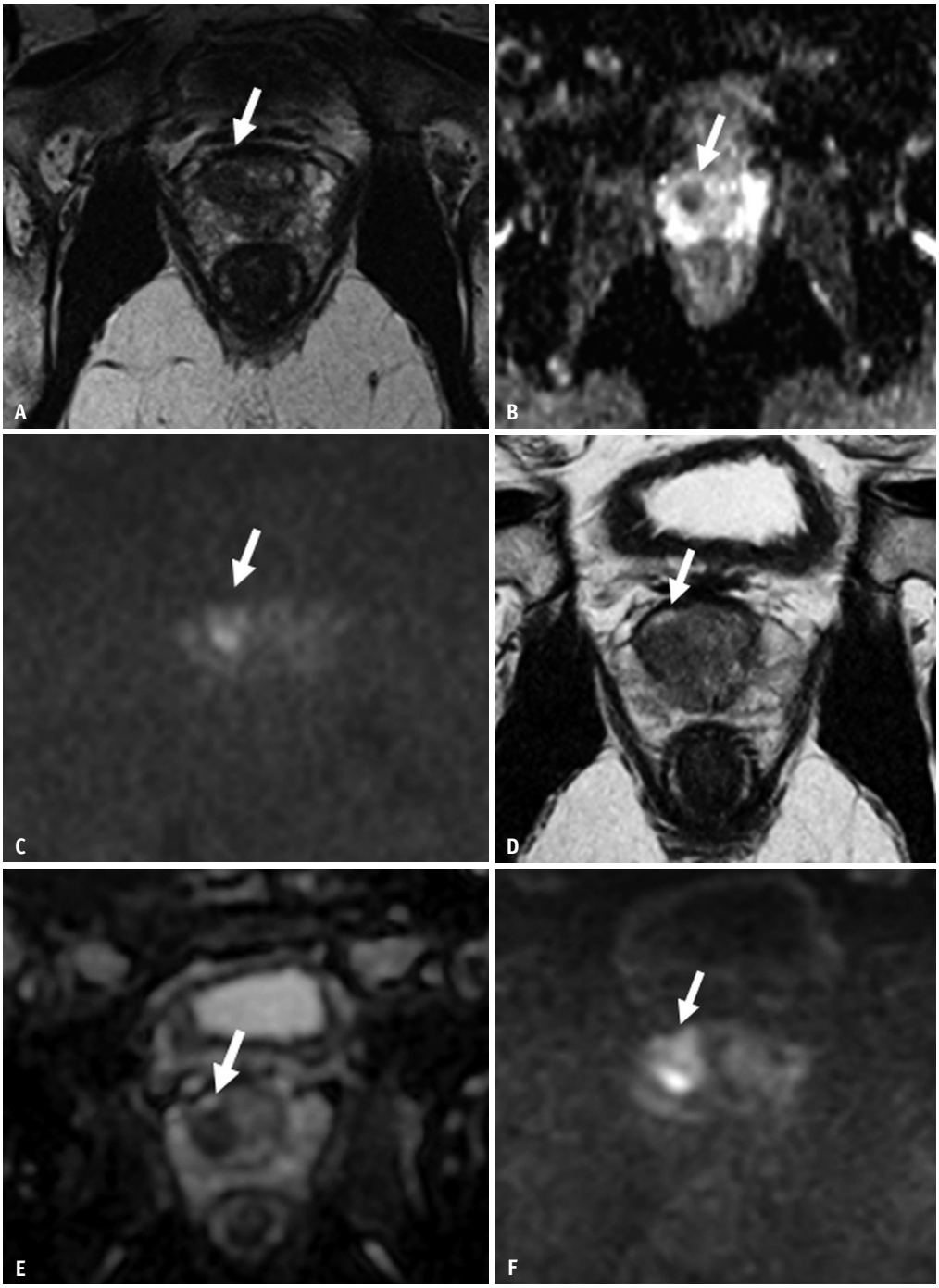

Fig. 3. A 66-year-old male presented with an elevated serum PSA of 6.2 ng/mL. mpMRI was performed as a first-line investigation. **A.** T2-weighted imaging shows a circumscribed hypointense lesion in the transition zone at the right midgland (arrow). **B.** ADC map shows a moderate low signal (arrow). **C.** DWI shows moderate hyperintensity (arrow). This was graded as a PI-RADS 3 lesion. Both systematic and targeted biopsies were performed, which showed only a Gleason 3 + 3 cancer. The patient was deemed eligible for AS. Follow-up mpMRI was performed 1 year after baseline mpMRI before the confirmatory biopsy. Serum PSA had increased to 10.5 mg/mL. **D.** T2-weighted imaging shows a slight increase in the size of the hypointense lesion in the transition zone at the right midgland, now also appearing more obscured (arrow). **E.** ADC map shows a moderate low signal (arrow). **F.** However, the lesion appeared more hyperintense on DWI (arrow). The lesion was graded as PI-RADS 3, similar to baseline mpMRI. However, this was assigned a Prostate Cancer Radiological Estimation of Change in Sequential Evaluation score of 4 because of the increased lesion size, suggesting a high probability of radiologic progression. Both systematic and targeted biopsies were repeated. MRI-ultrasound fusion targeted biopsy showed a Gleason 3 + 4 cancer. The patient was taken off AS. ADC = apparent diffusion coefficient, AS = active surveillance, DWI = diffusion-weighted imaging, mpMRI = multiparametric MRI, PI-RADS = Prostate Imaging-Reporting and Data System, PSA = prostate-specific antigen

https://doi.org/10.3348/kjr.2020.1224

the patient to an immediate rebiopsy or re-assessment at an interval with a follow-up mpMRI has to be made.

One study followed up subcentimeter PI-RADS 4 lesions with biopsy negative for csPCA and found no significant change in size over 2–3 years; most lesions remained stable or decreased in size [63]. This finding suggests that patients eligible for AS with subcentimeter index lesions that turn out to be negative on biopsy can be followed-up non-invasively rather than undergo immediate rebiopsy. A repeat targeted biopsy can be performed if there is lesion progression on follow-up mpMRI. For biopsy-negative PI-RADS 4 lesions larger than 1 cm or PI-RADS 5 lesions, we recommend that at least one repeat targeted biopsy should be considered before confirming eligibility for AS (Fig. 4).

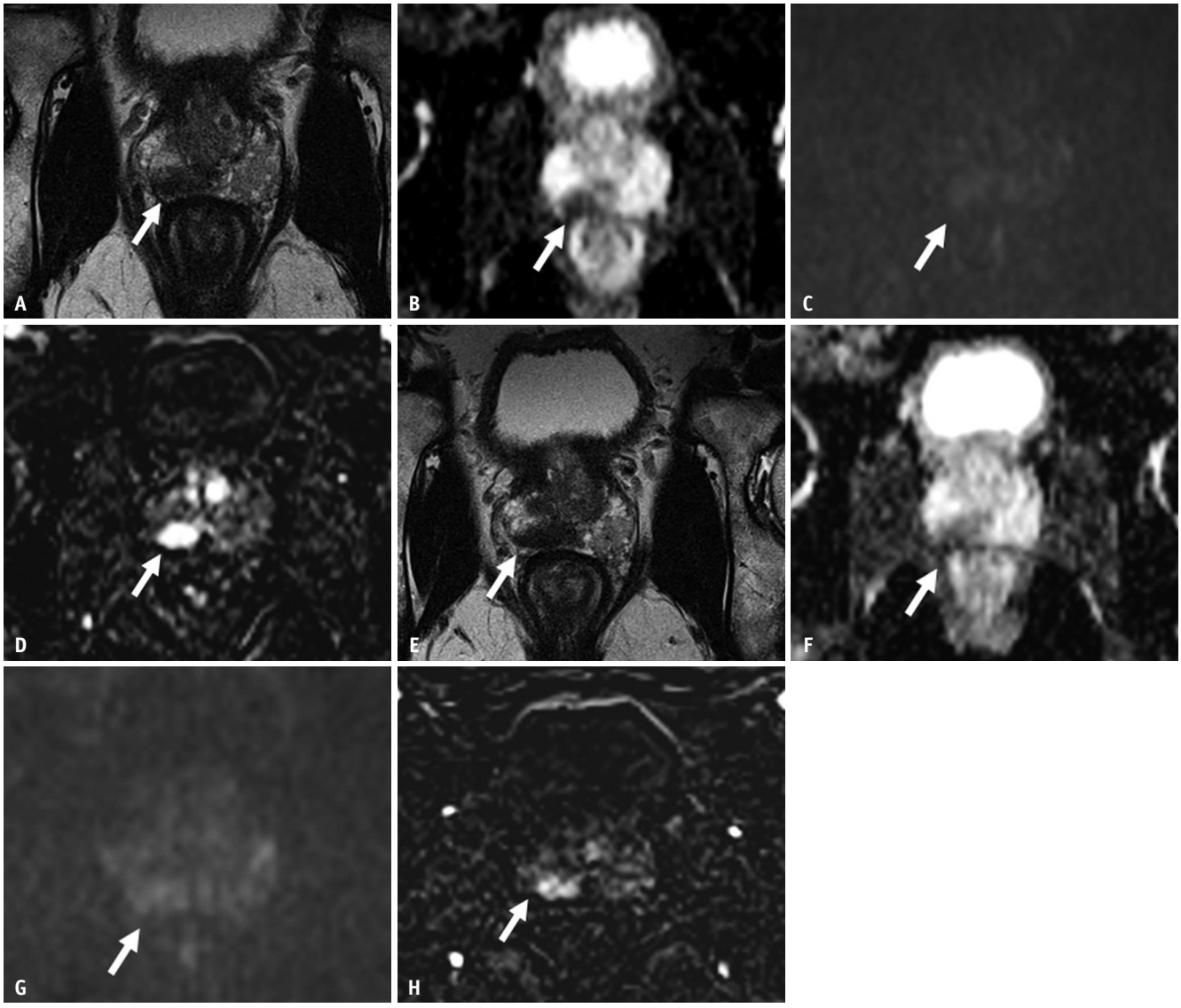

Fig. 4. A 62-year-old male presented with an elevated serum PSA of 5.9 ng/mL. mpMRI was performed as a first-line investigation. **A.** T2-weighted imaging shows a focal lesion in the peripheral zone at the right base (arrow). **B.** ADC map shows marked hypointensity (arrow). **C.** DWI shows mild hyperintensity (arrow). **D.** DCE imaging shows intense early enhancement (arrow). The lesion was graded as Prostate Imaging-Reporting and Data System 4. Systematic transrectal ultrasound biopsy showed a Gleason 3 + 3 cancer. Initial MRI-ultrasound fusion targeted biopsy was negative for malignancy. A repeat targeted biopsy was also negative, and the patient was enrolled for active surveillance. Repeat mpMRI was performed after 1 year before confirmatory biopsy. Repeat PSA was 5.7 ng/mL (stable). **E.** T2-weighted imaging shows a relatively stable size of the hypointense lesion in the right midgland peripheral zone (arrow). **F, G.** ADC map and DWI show similar findings as before (arrows). **H.** DCE imaging shows intense early enhancement (arrow). The lesion was deemed stable (Prostate Cancer Radiological Estimation of Change in Sequential Evaluation score 3), and targeted biopsy was not recommended. Patients underwent systematic confirmatory biopsy that showed a Gleason 3 + 3 cancer. Subsequent mpMRI before surveillance systematic biopsy at 2 years from initial diagnosis continued to show stable imaging findings. ADC = apparent diffusion coefficient, DCE = dynamic contrast-enhanced, DWI = diffusion-weighted imaging, mpMRI = multiparametric MRI, PSA = prostate-specific antigen

https://doi.org/10.3348/kjr.2020.1224

Korean Journal of Radiology
KJR

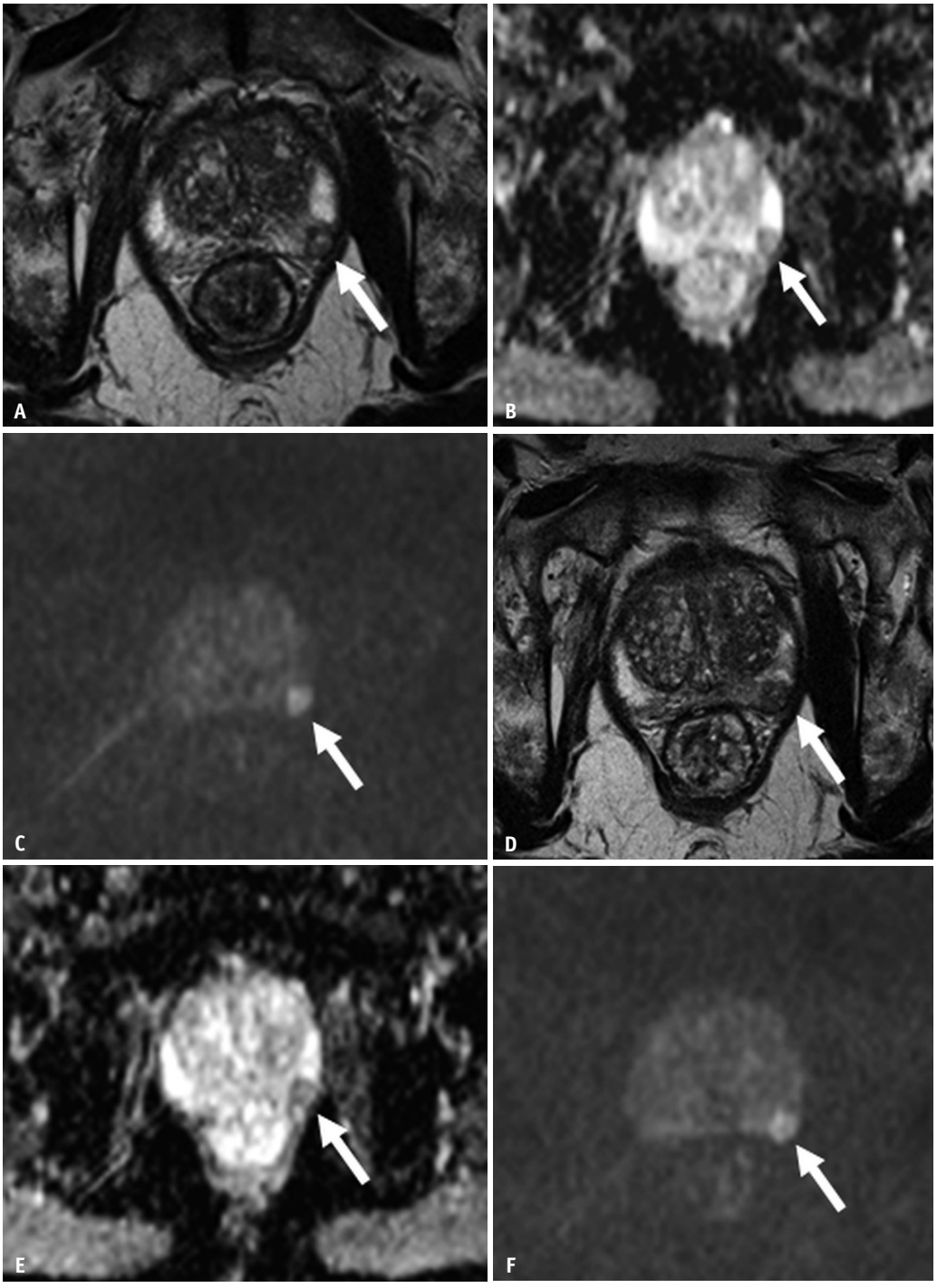

Fig. 5. A 77-year-old male presented with an elevated serum PSA of 11 ng/mL. Initial systematic transrectal ultrasound biopsy was negative for cancer. mpMRI was performed.
A. T2-weighted imaging shows a small lesion in the peripheral zone at the left midgland (arrow). **B.** ADC map shows focal marked hypointensity (arrow). **C.** DWI shows focal marked hyperintensity (arrow). The lesion was graded as Prostate Imaging-Reporting and Data System 4. MRI-ultrasound fusion targeted biopsy, however, showed a Gleason 3 + 3 cancer. A decision was made for the patient to undergo AS. Serial PSA levels over 1 year showed an increase to 18.1 ng/mL. Repeat mpMRI was performed before the confirmatory biopsy at 1 year. **D.** T2-weighted imaging shows a relatively stable size of the hypointense lesion in the peripheral zone at the left midgland (arrow). **E, F.** ADC map and DWI show marked restricted diffusion and similar findings as before (arrows). Although the imaging findings were deemed stable (Prostate Cancer Radiological Estimation of Change in Sequential Evaluation score 3), there was a high clinical suspicion for disease progression based on the PSA kinetics. Both systematic and targeted biopsy were repeated. MRI-ultrasound fusion targeted biopsy showed a Gleason 4 + 4 cancer. The patient was taken off AS. ADC = apparent diffusion coefficient, AS = active surveillance, DWI = diffusion-weighted imaging, mpMRI = multiparametric MRI, PSA = prostate-specific antigen

https://doi.org/10.3348/kjr.2020.1224

Stable mpMRI Findings

Stable serial mpMRI scans with or without an index lesion have been shown to have a negative predictive value for disease progression in approximately 80% of patients undergoing AS [41]. Another series showed that up to 32% of patients with negative or stable mpMRI during AS had an upgraded Gleason score on systematic biopsy [64]. This implies that systematic biopsy needs to remain an integral component of AS, despite incorporating mpMRI into the surveillance protocol.

In particular, patients undergoing AS with stable but positive mpMRI findings and clinical suspicion of disease progression should undergo systematic biopsy. In such patients, a repeat targeted biopsy is helpful for as long as there is an index lesion on mpMRI (PI-RADS 3–5), even if it appears stable on imaging (Fig. 5). Accordingly, we recommend that the interval between surveillance mpMRI scans be shortened.

CONCLUSION

With the increasing prostate cancer screenings and diagnoses in Asia, patients with low-risk localized prostate cancer qualifying for AS will increase. Prostate mpMRI is a useful risk stratification tool that is strongly recommended for baseline assessments at the time of diagnosis to improve patient selection for AS. The value of mpMRI over systematic TRUS biopsy beyond the first year of diagnosis is less clear. Furthermore, the optimal imaging follow-up interval is not well-established yet. Nonetheless, we propose that mpMRI should be included in the AS protocols, given that it is a non-invasive method for risk stratification, and it can allow for a reduction in the frequency of surveillance biopsy. Further data are required to determine the optimal strategy for incorporating mpMRI into AS protocols and its cost-effectiveness.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Cher Heng Tan, Chau Hung Lee. Methodology: Cher Heng Tan, Chau Hung Lee. Project administration: Cher Heng Tan. Resources: all authors. Supervision: Cher Heng Tan. Validation: Cher Heng Tan. Visualization: Cher Heng Tan, Chau Hung Lee. Writing—original draft: Chau Hung Lee. Writing—review & editing: all authors.

ORCID iDs

Chau Hung Lee
https://orcid.org/0000-0003-1795-812X
Teck Wei Tan
https://orcid.org/0000-0003-1376-7908
Cher Heng Tan
https://orcid.org/0000-0003-3341-3111

REFERENCES

1. Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G, et al. ESUR prostate MR guidelines 2012. *Eur Radiol* 2012;22:746-757
2. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. *N Engl J Med* 2018;378:1767-1777
3. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *Lancet* 2017;389:815-822
4. Kasivisvanathan V, Stabile A, Neves JB, Giganti F, Valerio M, Shanmugabavan Y, et al. Magnetic resonance imaging-targeted biopsy versus systematic biopsy in the detection of prostate cancer: a systematic review and meta-analysis. *Eur Urol* 2019;76:284-303
5. Welty CJ, Cowan JE, Nguyen H, Shinohara K, Perez N, Greene KL, et al. Extended followup and risk factors for disease reclassification in a large active surveillance cohort for localized prostate cancer. *J Urol* 2015;193:807-811
6. Alberts AR, Roobol MJ, Drost FH, van Leenders GJ, Bokhorst LP, Bangma CH, et al. Risk-stratification based on magnetic resonance imaging and prostate-specific antigen density may reduce unnecessary follow-up biopsy procedures in men on active surveillance for low-risk prostate cancer. *BJU Int* 2017;120:511-519
7. Klotz L, Loblaw A, Sugar L, Moussa M, Berman DM, Van der Kwast T, et al. Active surveillance magnetic resonance imaging study (ASIST): results of a randomized multicenter prospective trial. *Eur Urol* 2018;75:300-309
8. Nahar B, Katims A, Barboza MP, Soodana Prakash N, Venkatramani V, Kava B, et al. Reclassification rates of patients eligible for active surveillance after the addition of magnetic resonance imaging-ultrasound fusion biopsy: an analysis of 7 widely used eligibility criteria. *Urology* 2017;110:134-139
9. Kimura M, Tay KJ, Muto S, Horie S. *Focal therapy and active surveillance of prostate cancer in East and Southeast Asia*. In: Polascik T, ed. *Imaging and focal therapy of early prostate*

https://doi.org/10.3348/kjr.2020.1224

cancer, 2nd ed. New York: Springer, 2017:75-81
10. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394-424
11. Zhang K, Bangma CH, Roobol MJ. Prostate cancer screening in Europe and Asia. *Asian J Urol* 2017;4:86-95
12. Peyromaure M, Debré B, Mao K, Zhang G, Wang Y, Sun Z, et al. Management of prostate cancer in China: a multicenter report of 6 institutions. *J Urol* 2005;174:1794-1797
13. Tosoian JJ, JohnBull E, Trock BJ, Landis P, Epstein JI, Partin AW, et al. Pathological outcomes in men with low risk and very low risk prostate cancer: implications on the practice of active surveillance. *J Urol* 2013;190:1218-1222
14. Parker PA, Davis JW, Latini DM, Baum G, Wang X, Ward JF, et al. Relationship between illness uncertainty, anxiety, fear of progression and quality of life in men with favourable-risk prostate cancer undergoing active surveillance. *BJU Int* 2015;117:469-477
15. Zhu Y, Freedland SJ, Ye D. Prostate cancer and prostatic diseases best of Asia, 2019: challenges and opportunities. *Prostate Cancer Prostatic Dis* 2020;23:197-198
16. Mochtar CA, Andika RS. The value of prostate-specific antigen in Asia. *Ther Adv Urol* 2010;2:77-83
17. Komisarenko M, Martin LJ, Finelli A. Active surveillance review: contemporary selection criteria, follow-up, compliance and outcomes. *Transl Androl Urol* 2018;7:243-255
18. Dall'Era MA, Konety BR, Cowan JE, Shinohara K, Stauf F, Cooperberg MR, et al. Active surveillance for the management of prostate cancer in a contemporary cohort. *Cancer* 2008;112:2664-2670
19. Bayar G, Horasanlı K, Acinikli H, Tanrıverdi O, Dalkılıç A, Arısan S. The importance of active surveillance, and immediate re-biopsy in low-risk prostate cancer: the largest series from Turkey. *Turk J Urol* 2016;42:140-144
20. Ercole B, Parekh DJ. Active surveillance: pitfalls to consider. *Arch Esp Urol* 2011;64:695-702
21. Kalapara AA, Verbeek JFM, Nieboer D, Fahey M, Gnanapragasam V, Van Hemelrijck M, et al. Adherence to active surveillance protocols for low-risk prostate cancer: results of the Movember foundation's global action plan prostate cancer active surveillance initiative. *Eur Urol Oncol* 2020;3:80-91
22. Jin BS, Kang SH, Kim DY, Oh HG, Kim CI, Moon GH, et al. Pathological upgrading in prostate cancer patients eligible for active surveillance: does prostate-specific antigen density matter? *Korean J Urol* 2015;56:624-629
23. Tay KJ, Mendez M, Moul JW, Polascik TJ. Active surveillance for prostate cancer: can we modernize contemporary protocols to improve patient selection and outcomes in the focal therapy era? *Curr Opin Urol* 2015;25:185-190
24. Rouviere O, Moldovan PC. The current role of prostate multiparametric magnetic resonance imaging. *Asian J Urol* 2019;6:137-145
25. Richenberg J, Løgager V, Panebianco V, Rouviere O, Villeirs G, Schoots IG. The primacy of multiparametric MRI in men with suspected prostate cancer. *Eur Radiol* 2019;29:6940-6952
26. Padhani AR, Barentsz J, Villeirs G, Rosenkrantz AB, Margolis DJ, Turkbey B, et al. PI-RADS steering committee: the PI-RADS multiparametric MRI and MRI-directed biopsy pathway. *Radiology* 2019;292:464-474
27. Borofsky S, George AK, Gaur S, Bernardo M, Greer MD, Mertan FV, et al. What are we missing? False-negative cancers at multiparametric MR imaging of the prostate. *Radiology* 2018;286:186-195
28. Schoots IG, Nieboer D, Giganti F, Moore CM, Bangma CH, Roobol MJ. Is magnetic resonance imaging-targeted biopsy a useful addition to systematic confirmatory biopsy in men on active surveillance for low-risk prostate cancer? A systematic review and meta-analysis. *BJU Int* 2018;122:946-958
29. Park BH, Jeon HG, Choo SH, Jeong BC, Seo SI, Jeon SS, et al. Role of multiparametric 3.0-Tesla magnetic resonance imaging in patients with prostate cancer eligible for active surveillance. *BJU Int* 2014;113:864-870
30. Park JJ, Park BK. Role of PI-RADSv2 with multiparametric MRI in determining who needs active surveillance or definitive treatment according to PRIAS. *J Magn Reson Imaging* 2017;45:1753-1759
31. Turkbey B, Mani H, Aras O, Ho J, Hoang A, Rastinehad AR, et al. Prostate cancer: can multiparametric MR imaging help identify patients who are candidates for active surveillance? *Radiology* 2013;268:144-152
32. Tay KJ, Gupta RT, Holtz J, Silverman RK, Tsivian E, Schulman A, et al. Does mpMRI improve clinical criteria in selecting men with prostate cancer for active surveillance? *Prostate Cancer Prostatic Dis* 2017;20:323-327
33. Stamatakis L, Siddiqui MM, Nix JW, Logan J, Rais-Bahrami S, Walton-Diaz A, et al. Accuracy of multiparametric magnetic resonance imaging in confirming eligibility for active surveillance for men with prostate cancer. *Cancer* 2013;119:3359-3366
34. National Insitute of Health and Care Excellence. Prostate cancer: diagnosis and management (NICE guideline 131). Nice.org.uk Web site. https://www.nice.org.uk/guidance/ng131. Published May 9, 2019. Accessed September 4, 2020
35. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol* 2017;71:618-629
36. Yoo S, Hong JH, Byun SS, Lee JY, Chung BH, Kim CS. Is suspicious upstaging on multiparametric magnetic resonance imaging useful in improving the reliability of Prostate Cancer Research International Active Surveillance (PRIAS) criteria? Use of the K-CaP registry. *Urol Oncol* 2017;35:459.e7-459.e13
37. Thurtle D, Barrett T, Thankappan-Nair V, Koo B, Warren A, Kastner C, et al. Progression and treatment rates using an active surveillance protocol incorporating image-guided baseline biopsies and multiparametric magnetic resonance

imaging monitoring for men with favourable-risk prostate cancer. *BJU Int* 2018;122:59-65
38. Eineluoto JT, Järvinen P, Kenttämies A, Kilpeläinen TP, Vasarainen H, Sandeman K, et al. Repeat multiparametric MRI in prostate cancer patients on active surveillance. *PLoS One* 2017;12:e0189272
39. Perlis N, Al-Kasab T, Ahmad A, Goldberg E, Fadak K, Sayyid R, et al. Defining a cohort that may not require repeat prostate biopsy based on PCA3 score and magnetic resonance imaging: the dual negative effect. *J Urol* 2018;199:1182-1187
40. Felker ER, Wu J, Natarajan S, Margolis DJ, Raman SS, Huang J, et al. Serial magnetic resonance imaging in active surveillance of prostate cancer: incremental value. *J Urol* 2016;195:1421-1427
41. Walton Diaz A, Shakir NA, George AK, Rais-Bahrami S, Turkbey B, Rothwax JT, et al. Use of serial multiparametric magnetic resonance imaging in the management of patients with prostate cancer on active surveillance. *Urol Oncol* 2015;33:202.e1-202.e7
42. Hamoen EHJ, Hoeks CMA, Somford DM, van Oort IM, Vergunst H, Oddens JR, et al. Value of serial multiparametric magnetic resonance imaging and magnetic resonance imaging–guided biopsies in men with low-risk prostate cancer on active surveillance after 1 yr follow-up. *Eur Urol Focus* 2019;5:407-415
43. Klotz L, Pond G, Loblaw A, Sugar L, Moussa M, Berman D, et al. Randomized study of systematic biopsy versus magnetic resonance imaging and targeted and systematic biopsy in men on active surveillance (ASIST): 2-year postbiopsy follow-up. *Eur Urol* 2020;77:311-317
44. Glass AS, Dall'Era MA. Use of multiparametric magnetic resonance imaging in prostate cancer active surveillance. *BJU Int* 2019;124:730-737
45. Stavrinides V, Giganti F, Emberton M, Moore CM. MRI in active surveillance: a critical review. *Prostate Cancer Prostatic Dis* 2019;22:5-15
46. Sanda MG, Cadeddu JA, Kirkby E, Chen RC, Crispino T, Fontanarosa J, et al. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part I: risk stratification, shared decision making, and care options. *J Urol* 2018;199:683-690
47. Morash C, Tey R, Agbassi C, Klotz L, McGowan T, Srigley J, et al. Active surveillance for the management of localized prostate cancer: guideline recommendations. *Can Urol Assoc J* 2015;9:171-178
48. Stavrinides V, Giganti F, Trock B, Punwani S, Allen C, Kirkham A, et al. Five-year outcomes of magnetic resonance imaging–based active surveillance for prostate cancer: a large cohort study. *Eur Urol* 2020;78:443-451
49. Gallagher KM, Christopher E, Cameron AJ, Little S, Innes A, Davis G, et al. Four-year outcomes from a multiparametric magnetic resonance imaging (MRI)-based active surveillance programme: PSA dynamics and serial MRI scans allow omission of protocol biopsies. *BJU Int* 2019;123:429-438
50. Connor MJ, Miah S, Jayadevan R, Khoo CC, Eldred-Evans D, Shah T, et al. Value of systematic sampling in an mp-MRI targeted prostate biopsy strategy. *Transl Androl Urol* 2020;9:1501-1509
51. Moore CM, Giganti F, Albertsen P, Allen C, Bangma C, Briganti A, et al. Reporting magnetic resonance imaging in men on active surveillance for prostate cancer: the PRECISE recommendations—a report of a European School of Oncology Task Force. *Eur Urol* 2017;71:648-655
52. Morgan VA, Riches SF, Thomas K, Vanas N, Parker C, Giles S, et al. Diffusion-weighted magnetic resonance imaging for monitoring prostate cancer progression in patients managed by active surveillance. *Br J Radiol* 2011;84:31-37
53. Marin L, Ezziane M, Comperat E, Mozer P, Cancel-Tassin G, Coté JF, et al. Comparison of semi-automated and manual methods to measure the volume of prostate cancer on magnetic resonance imaging. *Diagn Interv Imaging* 2017;98:423-428
54. Maggi M, Panebianco V, Mosca A, Salciccia S, Gentilucci A, Di Pierro G, et al. Prostate imaging reporting and data system 3 category cases at multiparametric magnetic resonance for prostate cancer: a systematic review and meta-analysis. *Eur Urol Focus* 2020;6:463-478
55. Schoots IG. MRI in early prostate cancer detection: how to manage indeterminate or equivocal PI-RADS 3 lesions? *Transl Androl Urol* 2018;7:70-82
56. Sonn GA, Fan RE, Ghanouni P, Wang NN, Brooks JD, Loening AM, et al. Prostate magnetic resonance imaging interpretation varies substantially across radiologists. *Eur Urol Focus* 2019;5:592-599
57. Schlenker B, Apfelbeck M, Armbruster M, Chaloupka M, Stief CG, Clevert DA. Comparison of PIRADS 3 lesions with histopathological findings after MRI-fusion targeted biopsy of the prostate in a real world-setting. *Clin Hemorheol Microcirc* 2019;71:165-170
58. Mendhiratta N, Meng X, Taneja SS. Using multiparametric MRI to 'personalize' biopsy for men. *Curr Opin Urol* 2015;25:498-503
59. Hansen NL, Koo BC, Warren AY, Kastner C, Barrett T. Sub-differentiating equivocal PI-RADS-3 lesions in multiparametric magnetic resonance imaging of the prostate to improve cancer detection. *Eur J Radiol* 2017;95:307-313
60. Scialpi M, Martorana E, Aisa MC, Rondoni V, D'Andrea A, Bianchi G. Score 3 prostate lesions: a gray zone for PI-RADS v2. *Turk J Urol* 2017;43:237-240
61. Yaguchi G, Tang HJ, Deebajah M, Keeley J, Pantelic M, Williamson S, et al. The effect of multiplicity of PI-RADS 3 lesions on cancer detection rate of confirmatory targeted biopsy in patients diagnosed with prostate cancer and managed with active surveillance. *Urol Oncol* 2020;38:599.e9-599.e13
62. Steinkohl F, Gruber L, Bektic J, Nagele U, Aigner F, Herrmann TRW, et al. Retrospective analysis of the development of PIRADS 3 lesions over time: when is a follow-up MRI reasonable? *World J Urol* 2018;36:367-373
63. Rais-Bahrami S, Türkbey B, Rastinehad AR, Walton-Diaz A,

https://doi.org/10.3348/kjr.2020.1224

Hoang AN, Siddiqui MM, et al. Natural history of small index lesions suspicious for prostate cancer on multiparametric MRI: recommendations for interval imaging follow-up. *Diagn Interv Radiol* 2014;20:293-298

64. Schoots IG, Moore CM, Rouvière O. Role of MRI in low-risk prostate cancer: finding the wolf in sheep's clothing or the sheep in wolf's clothing? *Curr Opin Urol* 2017;27:238-245

 https://doi.org/10.3348/kjr.2020.1224