INTRODUCTION

The global incidence of prostate cancer (PCa) has been on the rise, including in Asian countries, in recent years [1]. The rate of PCa incidence is escalating rapidly, and it is projected to become the most commonly diagnosed male cancer in Korea starting from 2022 [2, 3]. Consequently, the appropriate management of PCa has emerged as a global priority. Among the various initial treatments, active surveillance (AS) for PCa is widely recommended as the preferred approach for men with low-risk PCa to mitigate the risks of overtreatment [4-6]. AS typically involves meticulous monitoring through regular prostate-specific antigen (PSA) tests and protocol-based biopsies. However, there is no consensus characterizing these AS methods, and a variety of protocols are in place [7-9]. Given the heterogeneity of PCa, the primary challenge in AS is to discern between “the wolf in sheep’s clothing or the sheep in wolf’s clothing.”

After a median follow-up period of 6.4 years, it was found that 27% of men had received treatment, while 55% of patients remained untreated and continued with AS at the 15-year mark in a large prospective cohort [10]. A recent population-based study in Canada revealed that AS was linked to a higher risk of metastasis (hazard ratio [HR], 1.34; 95% confidence interval [CI], 1.15–1.57), overall mortality (HR, 1.12; 95% CI, 1.01–1.24), and PCa-specific mortality.
(HR, 1.66; 95% CI, 1.15–2.39) when compared to initial treatment [11]. This suggests that there may still be potential for improvement in the selection of patients and the surveillance protocol.

Meanwhile, in recent years, magnetic resonance imaging (MRI) and MRI-targeted prostate biopsies for the diagnosis of PCa have been actively incorporated into clinical practice. This shift was spurred by the PROMIS (Prostate MRI Imaging) study, which demonstrated that multiparametric MRI (mpMRI) had higher sensitivity compared to conventional transrectal ultrasound (TRUS)-guided systematic biopsies [12]. When it came to detecting clinically significant PCa, mpMRI proved to be more sensitive (93%; 95% CI, 88%–96%) than TRUS biopsies (48%; 42%–55%; p<0.0001). This allowed 27% of men to avoid a primary biopsy and decreased the diagnosis of clinically insignificant cancers by 5%. Following this, the PRECISION (Prostate Evaluation for Clinically Important Disease: Sampling Using Image-guidance Or Not) trial further established the superiority of MRI-targeted biopsies over conventional TRUS biopsies [13].

Despite the existence of various MRI-targeted methods [14], MRI-targeted biopsies have emerged as a standard diagnostic approach [5].

MRI and MRI-targeted biopsies have garnered significant attention for their potential to enhance AS outcomes. This is largely due to MRI's high sensitivity and negative predictive value (NPV) for aggressive cancer, which optimizes selection criteria and monitoring protocol. In fact, a 2017 practice pattern survey revealed that 72.5% of respondents utilized MRI-targeted biopsy for AS [15]. By 2023, this percentage is expected to increase significantly. This review aimed to delineate the role of MRI and MRI-targeted biopsies in AS for men with low-risk PCa. MRI-targeted biopsies can be performed using various methods, such as cognitive targeted biopsy, MRI/ultrasonography fusion biopsy (MR/US fusion biopsy), or MRI in-bore biopsy. Currently, the most common method for MRI-targeted biopsies is MR/US fusion biopsy. Therefore, within the context of this scholarly review, the term “MRI-targeted biopsy” refers to a range of techniques, but primarily denotes MR/US fusion biopsies.

### ROLE OF MRI AND MRI-TARGETED BIOPSIES FOR THE SELECTION OF AS CANDIDATES

The effectiveness of AS is largely dependent on the precise selection of patients. In the past, systematic biopsies were the standard method for this process. However, recent research has highlighted the significant role that mpMRI plays in improving patient selection.

Our prior research demonstrated a significant association between the apparent diffusion coefficient (ADC) grade and unfavorable pathological features in men who, despite being potential candidates for AS, underwent radical prostatectomy [16]. In a multivariate model, an ADC grade greater than 3 was associated with a higher risk of presenting unfavorable pathology compared to an ADC grade of 3 or less (odds ratio [OR], 11.274; 95% CI, 2.622–48.471; p=0.001). We did not find any instances of insignificant cancer among patients with an ADC grade of 5, which suggests that lesions classified as Prostate Imaging Reporting and Data System (PI-RADS) 5 should be excluded from AS programs.

A research team at the National Cancer Institute investigated the role of mpMRI and MRI-targeted confirmatory biopsies during screening in men who fulfilled the Johns Hopkins criteria for AS. These criteria are known for their strictness and include a PSA density of ≤0.15 ng/mL, a Gleason score of ≤6, a clinical stage of T1c, ≤2 positive cores, and ≤50% tumor in any core [17]. The team discovered that 29% of these patients did not actually meet the criteria for AS. Three MRI-based factors—the number of lesions, the degree of suspicion, and lesion density—were linked to adverse pathology and reclassification. Marliere et al. [18] also showed that repeated confirmatory TRUS biopsies and MRI-targeted biopsies upstaged 59% of the candidates at selection for AS, thereby enhancing the precision of initial risk stratification. This observation was supported by Ouzzane et al. [19], who demonstrated that MRI and MRI-targeted biopsies improved selection for AS based on systematic biopsies by reclassifying approximately 10% of patients. Patients who were reclassified had a smaller prostate volume (37 mL vs. 52 mL) and were older (66.5 vs. 63 years) than those who were not (p<0.05). Furthermore, mpMRI has been proven to enhance the detection of significant cancer
in men on AS [20, 21]. The importance of 3-T mpMRI and MRI-targeted biopsies in risk stratification for AS was highlighted by Pessoa and colleagues, who demonstrated that these techniques provided superior risk assessment [22]. In addition, Radtke and colleagues observed that supplementary MRI-targeted biopsies with transperineal saturation biopsy could further decrease the disqualification rates for AS selection compared to standard systematic biopsies [23].

The ROMAS (Role of Multiparametric MRI in Active Surveillance for Low-Risk Prostate Cancer) trial, a prospective, randomized controlled, multicenter study, evaluated the impact of mpMRI and MRI-targeted biopsies on early reclassification [24]. Candidates fulfilling the Prostate Cancer Research International Active Surveillance (PRIAS) criteria [7] were randomized at a 1:1 ratio to a study group or control group. The study group underwent mpMRI 3 months after enrollment, and MRI-targeted biopsies were performed on patients with PI-RADS 3 or higher lesions. The trial enrolled a total of 124 patients (62 in the study group and 62 in the control group). In the study group, approximately 34% (21 of 62) had positive mpMRI findings, and 17.7% (11 of 62) were reclassified by MRI-targeted biopsies. When considering the intention-to-treat population, the reclassification rate at the 12-month protocol biopsy was 6.5% for the study group and 29% for the control group (p<0.001). Therefore, the early use of mpMRI for active surveillance patients enrolled after random TRUS can significantly decrease misclassification.

MRI-targeted and confirmatory biopsies, in conjunction with other developing techniques, greatly improve the identification of appropriate patients for AS in clinically low-risk PCa. This underscores the growing importance of mpMRI and MRI-targeted biopsies in this setting, offering more accurate risk stratification during screening or shortly thereafter.

**ROLE OF MRI AND MRI-TARGETED BIOPSIES IN THE MONITORING OF MEN ON AS**

AS primarily involves monitoring patients through regular PSA tests and protocol-based biopsies to identify any progression that necessitates active treatment. mpMRI can be used to determine whether a biopsy is necessary. Furthermore, to enhance the accuracy of the biopsy, MRI-targeted biopsies may be utilized.

Risk stratification based on MRI and PSA density (PSAD) could potentially reduce unnecessary follow-up biopsy procedures in men undergoing AS for low-risk PCa [25]. It has been observed that at least 20% of men on AS experienced upgrading based on their first MRI and MRI-targeted biopsy. However, men with a PI-RADS score of 1–3 and a PSAD of less than 0.15 ng/mL² were not upgraded. Therefore, taking these parameters into account could enhance patient selection and follow-up protocols [25]. A study conducted at the Royal Marsden in the United Kingdom found that a decrease in the ADC on diffusion-weighted imaging was linked to pathological progression [26]. Specifically, a 10% reduction in ADC could predict pathological progression with a sensitivity of 93% and a specificity of 40%. The same research group showed that the use of serial mpMRI and MRI-targeted biopsies could reduce the number of biopsies needed to detect one pathological progression from 8.75 to 2.89 [27]. Felker and colleagues proposed using multiple radiological factors to define radiological progression, which included an increase in lesion suspicion score, size, or ADC, and found it to be associated with pathological progression [28]. Several other studies have also shown a correlation between the mpMRI suspicion score and pathological upgrading and the initiation of active treatment [29-31]. Lai et al. [32] developed a nomogram to predict upgrading using the duration to MRI-targeted biopsy, total lesion density, MRI suspicion score, and PSAD.

However, a significant proportion of pathological progression was only identified through systematic TRUS biopsies [32, 33]. Consequently, the combination of systematic biopsy with MRI-targeted biopsies and protocol-based TRUS biopsies remains necessary, even after a negative finding on mpMRI.

**SERIAL CHANGES OF MRI DURING AS**

In patients undergoing AS, there were no significant differences in the growth rates of PCa tumors between grade I and grade II (18% vs. 23%, p=0.16), as determined by mpMRI [34]. However, another study identified tumor diameter and small-volume ADC as significant predictors of pathological
progression during AS [35]. Specifically, a 20% increase in tumor diameter and a 10% decrease in small-volume ADC were proposed as threshold values. A retrospective study assessed the diagnostic accuracy and prognostic value of serial mpMRI, using the PI-RADS version 2 score [36]. Of the 125 men on AS, 38% saw an increase in their PI-RADS scores. The sensitivity and positive predictive value (PPV) of a PI-RADS score of ≥3 for grade ≥2 disease improved from the initial MRI to the follow-up MRI (from 85% to 91% and from 26% to 49%, respectively). An increase in PI-RADS scores from the baseline to the follow-up MRI was associated with grade ≥2 (OR, 4.8; 95% CI, 1.7–13.2), compared to PI-RADS scores of 1–3 on both MRI scans. Patients with PI-RADS scores of 4–5 on both MRIs were more likely to be in grade ≥2 than men with PI-RADS scores of 1–3 on both scans (OR, 3.3; 95% CI, 1.3–8.6). Any increase in PI-RADS scores was significantly associated with a transition to definitive treatment (HR, 3.9; 95% CI, 1.3–11.9).

**PRECISE SCORE**

The European School of Oncology Task Force developed the Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) recommendations and scoring system to enable comprehensive data collection and to evaluate the natural progression of MRI findings in men undergoing AS [37]. The PRECISE score, which ranges from 1 to 5, is based on the risk of radiological progression (Fig. 1, Table 1). A score of 3 is given when there is a stable appearance with no new lesions. Scores from 1 to 2 suggest a decrease in features, while scores of 4 and 5 indicate progression, with the degree of suspicion determining the

![PRECISE score diagram](https://doi.org/10.22465/juo.234600260013)

**Table 1.** PRECISE score for estimating the likelihood of radiologic progression on magnetic resonance imaging in men on active surveillance

<table>
<thead>
<tr>
<th>PRECISE score</th>
<th>Assessment of likelihood of radiological progression</th>
<th>Example</th>
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<tbody>
<tr>
<td>1</td>
<td>Resolution of previous features suspicious on MRI</td>
<td>Disappeared suspicious lesion</td>
</tr>
<tr>
<td>2</td>
<td>Reduction in volume and/or conspicuity of previous features suspicious on MRI</td>
<td>Size reduction of a lesion that was previously suspicious for significant disease</td>
</tr>
<tr>
<td>3</td>
<td>Stable MRI appearance, no new focal/diffuse lesions</td>
<td>All lesions stable in size and appearance</td>
</tr>
<tr>
<td>4</td>
<td>Significant increase in size and/or conspicuity of features suspicious for prostate cancer</td>
<td>A lesion becoming visible on diffusion-weighted imaging, significantly increased size of previously seen lesion</td>
</tr>
<tr>
<td>5</td>
<td>Definitive radiologic stage progression</td>
<td>Appearance of clinical T3 or higher stage</td>
</tr>
</tbody>
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PRECISE, Prostate Cancer Radiological Estimation of Change in Sequential Evaluation; MRI, magnetic resonance imaging.
In a study involving 196 men on AS, the changes in size over time between PRECISE scores 2–3 and 4–5 were examined [38]. The study found a significant difference in the annual volume change between PRECISE 2–3 and PRECISE 4–5, with a 39.64% difference for planimetry and a 46.78% difference for the ellipsoid formula. These results demonstrated that the PRECISE score is a significant predictor of radiological progression. Another study focused on MR-targeted biopsy in AS patients. That study analyzed delta-radiomics (Rarenclitic, LASSO, and random forests) and the PRECISE score in 27 progressors and 37 nonprogressors over a median follow-up period of 46 months [39]. The study found that the PRECISE scores had the highest specificity (94.7%) and PPV (90.9%), while random forests had the highest sensitivity (92.6%) and NPV (92.6%). The area under the curve (AUC) for the PRECISE score was 84.4%, indicating that it performed well in predicting PCa progression in AS patients.

Dieffenbacher et al. evaluated the value of MRI and MRI-targeted biopsies using the PRECISE score over a 4-year follow-up period in 273 men who were selected for active surveillance based on PRIAS criteria [40]. They found a significantly lower rate of pathological progression in the group that underwent MRI-targeted biopsies compared to the group that only had systematic TRUS biopsies, when stratified by the initial biopsy method (19% vs. 59%, p<0.001). The AUC of the PRECISE score during active surveillance was 0.83, and none of the men with a PRECISE score of 1 or 2 were reclassified during active surveillance. Consequently, they concluded that confirmatory MRI-targeted biopsies are necessary for selecting candidates for active surveillance, and that follow-up protocol biopsies can be omitted for men with a PRECISE score of 1 or 2.

**MRI-BASED AS PROGRAM**

In a study involving 211 patients with grade 1, it was found that 27.5% of patients advanced to radical therapy within an average follow-up period of 4.2 years, as indicated by the MRI-based AS program [41]. Regardless of the MRI results, all patients were offered a confirmatory biopsy following their initial MRI. If patients continued on AS after this biopsy, a repeat MRI was scheduled for 2 years later. However, the MRI was conducted earlier if there were signs of clinical progression, such as an increase in PSA. Visible lesions were linked to higher progression rates compared to a negative MRI result (37.6% vs. 12.8%; OR, 4.1; 95% CI, 2.0–8.5). Additionally, PSA velocity was significantly related to subsequent progression in patients with an initially negative MRI (AUC, 0.85; 95% CI, 0.75–0.94; p<0.001). The researchers suggested that patients with a highly suspicious lesion on the initial MRI, who continue on AS after an MRI-targeted biopsy, should be offered an early repeat MRI (at 1 year or sooner) regardless of PSA dynamics. However, patients with a negative MRI result can delay a repeat MRI for 2 years, unless there is a rise in PSA or changes in digital rectal exam findings.

In the United Kingdom, the National Institute for Health and Care Excellence (NICE) guidelines suggest AS for men diagnosed with Cambridge Prognostic Group (CPG) 1 disease, which is equivalent to low-risk. They also selectively recommend it for men with CPG2 disease, which is comparable to the favorable intermediate-risk status [42]. A team of researchers from the University of Cambridge introduced a practical three-tier STRAtified CANcer Surveillance (STRATCANS) program, which is based on CPG and PSAD [43, 44]. Moreover, the scheduling of MRI scans was risk-based within the STRATCANS group, determined by the initial MRI Likert score. For instance, follow-up MRI examinations were scheduled every 3 years for PI-RADS 1–2, every 18 months for PI-RADS 3, and annually for PI-RADS 4–5 cases. Routine rebiopsies were not conducted for men in the STRATCANS group 1. However, protocol biopsies were offered at 3-year intervals for men in groups 2 or 3. If any changes were detected, triggered rebiopsies were carried out according to the protocol. The median follow-up periods were 4 years and 1.5 years on STRATCANS. Overall, 135 out of 156 men (86.5%) continued with AS. As the STRATCANS tier increased, progression rates to CPG ≥3 and any progression events were 0% and 4.6%, 3.4% and 8.6%, and 7.4% and 22.2%, respectively (p=0.019). The findings indicated potential reductions in appointments by 22% and MRI scans by 42% compared to the current NICE guideline protocol.

Actual MRI and MRI-targeted biopsies are currently
used for the selection and ongoing monitoring of men on AS. Modifications to the follow-up protocol-based on MRI features, as well as rescheduling of protocol biopsies, are currently being evaluated in several cohorts. We are awaiting evidence from larger, prospective cohorts to confirm these changes in clinical practice.

SUPER-PC-AS

The SUPER-GUC (Seoul National University Prospectively Enrolled Registry for Genitourinary Cancer) is a forward-looking, multidisciplinary cohort linked to a biobank. It focuses on prostate, kidney, and urothelial cancers and was initiated in March 2016 [45]. By February 2023, the registry had enrolled over 10,000 patients. The registry is comprehensive, comprising 11 subcohorts based on disease status and treatment methods. Men undergoing AS are registered in the Seoul National University Prospectively Enrolled Registry for Prostate Cancer – Active Surveillance (SUPER-PC-AS) (ClinicalTrials.gov Identifier: NCT02971085) [46].

In the past, the Korean Urological Oncology Society Prostate Cancer Research Group (KUOS-PCRG) carried out a multicenter study to establish safe selection criteria for AS. This was necessary because Korean patients with PCa often exhibit a more aggressive form of the disease than their Western counterparts [9]. SUPER-PC-AS employs these stringent criteria but also permits the enrollment of patients following standard protocols [4-7, 46]. In addition to the KUOS-PCRG selection criteria, we exclude patients with PI-RADS 5 lesions on mpMRI during screening. This exclusion is based on our previous study’s strict criteria [16]. The final strict selection criteria include: men under 80 years old, pathologically confirmed adenocarcinoma of the prostate by TRUS biopsies of 10 or more cores, prebiopsy PSA levels of 10 ng/mL or less, PSAD less than 0.15 ng/mL², clinical stage T1-2a, biopsy grade 1, no more than 2 positive cores, maximum cancer involvement in any one core of 20% or less, and no PI-RADS 5 lesion. Moreover, we conduct mpMRI annually to assess the role of MRI during AS. If indicated, we also include MRI-targeted biopsy at the time of the protocol biopsy.

During a median follow-up period of 2 years, 24.0% of men enrolled under the strict criteria and 51.7% of men enrolled under the nonstrict criteria (i.e., the usual AS criteria) experienced clinicopathological progression (p=0.025). This outcome indicates a higher risk of reclassification for Korean men enrolled under the expanded criteria recommended by Western standards. We recently assessed the effectiveness of the PRECISE score in predicting pathologic progression in SUPER-PC-AS. The analysis included a total of 116 men with 173 biopsies (unpublished data). Out of 173 follow-up mpMRI, 17% showed radiological regression (PRECISE 1%–7% and PRECISE 2%–10%), 43% remained radiologically stable (PRECISE 3), and 40% exhibited radiological progression (PRECISE 4%–35% and PRECISE 5%–5%). A PRECISE score of 4 or 5 was significantly associated with pathological progression, even after adjusting for other confounding factors (OR, 3.151; 95% CI, 1.323–7.502). Notably, no pathological progression was observed in individuals with a PRECISE score of 1. Therefore, we can postpone protocol biopsy in men with PRECISE scores of 1–3, considering other clinical risk factors (e.g., PSAD <0.15 ng/mL²), without negatively impacting oncologic outcomes. Moreover, for patients with PRECISE scores of 4 or 5 on follow-up mpMRI and other risk factors, we should contemplate additional MRI-targeted biopsies, even if it is not scheduled.

CONCLUSIONS

In conclusion, both MRI and MRI-targeted biopsies may prove beneficial in the selection and monitoring of men with low-risk PCa undergoing AS. An MRI-targeted biopsy during AS could potentially identify significant cancer. Therefore, mpMRI and/or MRI-targeted biopsies should be considered during the screening phase or shortly thereafter for men who have only undergone a random TRUS biopsies to minimize initial misclassification. On the other hand, a considerable number of pathological progressions were only diagnosed through systematic TRUS biopsies. Therefore, systematic biopsy, in conjunction with MRI-targeted biopsy and protocol-based TRUS biopsy, should not be omitted when no visible lesion is detected on mpMRI. The use of MRI features during active surveillance, particularly the PRECISE score, appears promising as it provides a more
accurate risk restratification during follow-up.

However, there remain unresolved questions. The suitable selection criteria for men following an MRI-targeted biopsy for AS have not been thoroughly examined. In particular, the quantity of positive cores and the characteristics of MRI-based lesions should be assessed in this scenario. We also require long-term results from larger prospective cohorts that utilize MRI and MRI-targeted biopsies for selection and monitoring with risk-adjusted protocols. We anticipate that these protocols will minimize misclassification and eliminate unnecessary follow-up biopsies.

NOTES

• Conflicts of Interest: The author has nothing to disclose.
• Funding/Support: This research was supported by a grant from the Patient-Centered Clinical Research Coordinating Center funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI19C0481, HC19C0164).
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