Active Surveillance for Prostate Cancer: Expanding Role of MRI and Use of PRECISE Criteria

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Synopsis

Multiparametric magnetic resonance imaging (mpMRI) has had an expanding role in active surveillance (AS) for prostate cancer. It can improve the accuracy of prostate biopsies, assist in patient selection, and help monitor cancer progression. The PRECISE recommendations standardise reporting of serial MRI scans during AS. We summarise the evidence on MRI-led AS and provide a clinical primer to help report using the PRECISE criteria. Some limitations to both serial imaging and the PRECISE recommendations must be considered as we move towards a more individualised risk-stratified approach to AS.

Key Words

Prostate cancer, active surveillance, mpMRI, MRI, PRECISE, biopsy

Key Points

- AS enrolment criteria and protocols differ between institutions and guidelines.
- Multiparametric MRI during AS improves the accuracy of prostate biopsies, assists in the selection of eligible patients, and can be used to monitor cancer progression.
- The PRECISE recommendations standardise reporting of serial MRI scans during AS.
- We include a clinical primer to help clinicians navigate the PRECISE case report form.
- There is increasing evidence to support MRI-led AS programmes and the need for an individualised risk-stratified approach to AS.
- Iimportant limitations to mpMRI and the PRECISE recommendations should be addressed in future updates

Active surveillance (AS) is a conservative management approach increasingly used for patients with low- and favourable intermediate-risk prostate cancer (PCa).[1] It is an alternative to active treatment, where patients are closely followed up to identify if and when cancer progression occurs, avoiding unnecessary treatment for clinically localised disease and identifying progression to trigger deferred procedures without losing the window of curability. AS differs from watchful waiting, which is a less aggressive system of PCa monitoring that does not involve frequent testing or biopsies for patients who do not want or cannot have treatment therapies, and is now the preferred management option for low-risk disease.[1,2]

Multiparametric magnetic resonance imaging (mpMRI) of the prostate can detect clinically significant cancer and has emerged as a non-invasive method to monitor AS patients for PCa progression.[3,4] The Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) recommendations[5] were published in 2016 to standardise reporting of serial mpMRIs during AS and have been applied in different MRI-led AS cohorts.[6-11]

The aim of this article is four-fold: i) discuss current AS protocols; ii) look at the expanding role of mpMRI in AS protocols; iii) describe the PRECISE criteria, providing a clinical primer to help report using these recommendations; and iv) synthesise the literature on MRI-led AS cohorts, examining the current limitations and offering suggestions on future directions for research.

Active Surveillance

From 1990 to 2010, more than 90% of patients diagnosed with low-risk prostate cancer (PCa) by prostate-specific antigen (PSA) and biopsy were treated radically according to a study on 11,892 patients from 36 sites across the US.[12] Yet definitive treatments such as radical prostatectomy (RP) and radiotherapy, have significant morbidity and serious side effects including urinary and sexual function problems.[13]

Active surveillance (AS) was first described explicitly in a 2002 report for a trial on 250 low-risk PCa patients of expectant management with periodic biopsies and treatment only for those reclassified as high-risk.[14,15] Following substantial evidence on the indolent nature of low-grade PCa and favourable outcomes with conservative management, there has been increasing consensus about the value and benefits of AS. This approach has now become widely adopted internationally with the percentage of low-risk PCa patients managed conservatively increasing from about 10% in 2000 to over 90% in a few regions.[16-18]

Randomised controlled trials comparing definitive therapy and conservative management have found similar long-term survival rates.[19,20] In the PIVOT trial,[19] 731 men with localised PCa were randomly assigned to either RP or observation, and after 19.5 years of follow-up (median=12.7), RP did not significantly reduce overall, or cancer-specific mortality compared with the observation arm. Further, the ProtecT trial,[13] a large, randomised UK study that compared RP, radiotherapy, and 'active monitoring' for localised PCa, recently reported its 15-year follow-up results and demonstrated no significant difference in overall or cancer-specific survival between the three cohorts. It should be noted that the conservative arm in both trials lacked the rigorous follow-up of modern AS protocols with no imaging or mandated biopsies and that both had a degree of cross-over between treatment arms.

Currently, there is significant inter-centre heterogeneity in AS enrolment criteria and protocols (Table 1). While AS is largely accepted for low-risk PCa, this is not the case for

intermediate-risk patients. Results from large, prospective studies that included patients with intermediate-risk PCa have been positive,[21-23] and the DETECTIVE study[24] demonstrated good outcomes for patients with favourable Grade Group (GG) 2 disease (PSA<10ng/ml, Stage ≤ T2, and few positive cores on biopsy). The UK National Institute for Health and Care Excellence (NICE) guidelines[1] were the first to support AS for GG2 patients in 2015, and now others support this approach for 'selected' intermediate-risk patients.[25,26] Protocols usually include monitoring PSA kinetics, digital rectal examinations, magnetic resonance imaging (MRI), and biopsies. Prostate biopsies, which are commonly used to assess changes in cancer grade, can be transrectal ultrasound scan-guided or transperineal and may be a random systematic biopsy (usually 12 cores) and/or targeted at specific lesions found on MRI. Protocol-based biopsies can be performed at different prespecified time points throughout AS, whereas confirmatory biopsies, if carried out, are usually performed within 12 months from diagnosis or AS inclusion.

However, biopsies are also a major barrier to the uptake, adherence, and tolerability of AS, with the PRIAS study[27] demonstrating lower compliance rates when protocol-based biopsies are utilised. These concerns must be weighed against the risk of delays in detecting PCa progression and missing the window of opportunity for curative treatment. Currently, there is no accepted consensus on the recommended frequency or timing of biopsies.

Magnetic Resonance Imaging in Active Surveillance

Multiparametric MRI consists of a combination of anatomical and functional sequences (Figure 1) and has played an expanding role in AS. Increasing availability, improved image quality, growing expertise in the interpretation of scans, and more data on MRI accuracy and limitations are all influencing its use.[15] Indeed, 90% of academic centres in the US and 72% of healthcare services in the UK now perform MRI of the prostate, with an additional 24% offering biparametric MRI (i.e., without the injection of intravenous contrast) [30,31] although the rates of pre-biopsy MRI for patients on AS ranges from 1.9% to 28.2% in studies on US populations.[32-34] MRI has several roles in AS and can assist with the selection of eligible patients, directing prostate biopsies, and monitoring for cancer progression.

A prerequisite for the repeated use of MRI during AS include good quality image acquisition. The Prostate Imaging-Reporting and Data System (PI-RADS)[35] guidelines indicate that both 1.5- and 3T magnets can provide adequate and reliable scans when acquisition parameters are optimised. The same acquisition protocol would ideally be used for baseline and follow-up scans but this is not always practical for patients on AS for significant periods since protocols and technology evolve over time.

Adequate reporting expertise and consistency are also extremely important. Traditionally, PCa lesions have been measured using a 1-to-5 Likert scale, which was highly influenced by reporter expertise and implied subjective assessment of the whole prostate gland. However, the Prostate Imaging and Reporting Data System (PI-RADS) scoring system was introduced in 2012 to standardise MRI reporting,[36] and this was followed by the Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) recommendations in 2016 for reporting serial MRI during AS.[5] The importance of reporting scan quality has been further emphasised by the introduction of the Prostate Imaging Quality System (PI-QUAL) scoring system in 2020.[37]

Selection of AS Patients at Baseline

MRI can improve risk stratification and improve patient selection for AS. Turkbey et al.[38] compared MRI with current clinicopathological criteria such as Cancer of the Prostate Risk Assessment (CAPRA), Einstein, and D'Amico to retrospectively determine AS eligibility for 133 patients undergoing RP. They found MRI was the most accurate (sensitivity=93%, positive predictive value =57%, overall accuracy=92%, $p<0.005$), and when used in combination, the sensitivity and accuracy of each clinic-pathological criterion improved. Moreover, correlations between pathology results from template-mapped biopsies with the gland sampled every 5mm, which is considered the gold standard for PCa detection, and RP specimens show that MRI has a good sensitivity (~90%) for the detection and localisation of GG≥2 cancers.[39,40] A 2019 meta-analysis comparing MRI with template-mapped biopsies in biopsy-naive and repeat-biopsy settings, demonstrated that MRI had a pooled sensitivity and specificity of 91% and 37% for GG≥2 cancers and 95% and 35% for GG≥3 cancers, indicating its clinical potential for ruling out high-grade disease.[40] Hence the use of MRI before the first biopsy has become widespread to aid prognostic assessment.[4,41]

MRI Prior to Confirmatory Biopsy

MRI-targeting can also improve reclassification on confirmatory biopsies and identify AS patients who had PCa under-sampled at the initial biopsy. A study demonstrated that an MRI-based nomogram could be used to help exclude patients from AS.[42] Another study on the use of MRI-targeted confirmatory biopsy reclassified 59% of patients initially selected for AS by systematic biopsy.[43] A meta-analysis of MRI confirmatory biopsies on 1,028 patients found the pooled sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio were 69%, 78%, 3.1 and 0.4 respectively.[44] A study to determine the prognostic implications of confirmatory biopsy results found that no cancer on targeted biopsy was associated with a reduced risk of GG progression (Hazard Ratio=0.41, $p<0.01$), as well as an increased median time to progression (74.3 vs. 44.6 months, $p<0.01$).[45] In the ASIST trial,[46] patients with a recent diagnosis of GG1 who were referred for confirmatory biopsy were randomised

to either MRI or non-MRI arms. Although initial results found no difference in the upgrading rates between the two groups,[46] which was attributed to the learning curve for MRI-targeted biopsies with higher volume centres performing better, after 2 years of follow-up, MRI before confirmatory biopsy resulted in 50% fewer AS failures (19% vs. 35%, p=0.017) and less progression to higher-grade cancer (10% vs. 23%, p=0.048).[47] Finally, a systematic review on the added value of MRI and MRI-targeted biopsies to confirmatory biopsies during AS found that 27% had cancer upgrading (to GS≥3+4) using a combined approach of i) MRI-targeted and systematic, ii) MRI-targeted and iii) standard confirmatory biopsies alone would have missed cancer upgrading in 10% and 7% of cases respectively, and 35% of MRI-positive patients were upgraded compared to only 12% of MRI-negative patients.[48]

MRI for AS Monitoring

While correctly identifying AS candidates is essential, monitoring for PCa progression is equally as important. Growth of a lesion, change in lesion parameters, or the development of new lesions can be equated with true pathological progression, which raises the possibility of MRI-led AS with triggers for biopsies based solely on imaging findings. This approach may limit the number of biopsies required, if a stable MRI can reduce the need for time-based biopsies and improve AS compliance, however, this remains controversial. Fujihara et al.[49] demonstrated if surveillance biopsy was triggered based only on MRI progression, 63% of initially scheduled biopsies would be postponed. Although this approach missed histological progression (GG2) in 12% of patients with no radiological progression, no high-grade (GG≥3) cancers were missed. The MRIAS trial[50] followed AS patients for 3 years with annual MRI, 6-month PSA, and exit biopsy at 3 years. Protocol-driven biopsies were performed for pre-defined targets, such as a new persistent lesion or rising PSA kinetics, and most patients (71%) avoided biopsy before 3 years, the progression rate was relatively low (21%), and the incidence of high-risk cancer missed by MRI was only 1%. In the UK, two major London hospitals, University College London Hospital (UCLH) and Guy's Hospital both use MRI for

AS, but while Guy's utilises protocol-based biopsies, UCLH does not, and the drop-out rate for stable disease is greater than 20% and less than 1% respectively.[51,52]

The PRECISE Recommendations

A 2015 systematic review found no consistency across reporting of serial MRI scans during AS, which prevented meaningful analysis and comparison of the data between studies.[53] This inspired the European School of Oncology Task Force to meet and discuss 394 statements on the topic, which resulted in the publication of the PRECISE recommendations.[5] Key recommendations included the adoption of a case report form (Figure 2) and reporting of a PRECISE score (Figure 3) as well as a checklist for investigators working on MRI-led AS cohorts.

The PRECISE score is a 1-to-5 scale that has been shown to be reproducible with agreement levels comparable to other scoring systems such as PI-RADS v.2.[54] It is intended to lead to the identification of AS patients who progress (i.e., PRECISE score 4-5) in a timely manner and thereby prompt rebiopsy or treatment, as well as the avoidance of repeat biopsy and lower surveillance intensity in case of radiological stability (i.e., PRECISE score 1-3) thereby reducing the burden of surveillance on the individual patient and the broader healthcare system. A retrospective analysis of 80 patients on AS,[54] where two expert radiologists assessed scans from two different cohorts independently, found high interobserver reproducibility, with agreement per patient and per scan for each PRECISE score of 79% and 81%, respectively. However, further work is needed to confirm these results with multiple readers of differing experience, in a variety of healthcare settings and incorporating different MR systems and vendors.

PRECISE Clinical Primer

We provide a practical guide on reporting MRI using the PRECISE case report form and to familiarise radiologists with the PRECISE scoring system. We present a variety of cases and images to demonstrate the difference between scores. We divide the case report form into three sections corresponding to the boxes on the page and discuss each step that should be followed.

Clinical Details and Overall Likelihood of Clinically Significant Prostate Cancer

1. The first box requires the necessary clinical and patient details including the scan and report date, the name of the reporting radiologist, and the date and result of the most recent serum PSA level.
2. The prostate volume on T2-weighted imaging should be measured either by planimetry (i.e., using manual slice-by-slice segmentation of the prostate or with automated segmentation algorithms)[55] or using the ellipsoid formula (i.e. [anteroposterior X transverse X longitudinal diameter] * π/6), with PSA density subsequently derived as PSA (ng/ml) /prostate volume (cc).
3. Record details about the MR scanner including the magnet field strength (either 1.5 or 3T) and the coils used (e.g., with/without an endorectal coil).
4. A rating of the *overall* likelihood of clinically significant disease is required using a Likert scale (where 1 = very low likelihood and 5 = very high likelihood), the *maximal* PI-RADS score for any lesion seen on the scan, as well as the TNM staging including 1-5 Likert scores for the likelihood of extraprostatic extension (T3a) and seminal vesicle invasion (T3b).

Description of the Current Lesion/s

1. The reporter is then required to comment on the three most conspicuous lesions with the most significant “index” lesion being number one. For each lesion, they are required to note whether they appeared since the last scan, if they remain visible,

and their volumes. Assessment of the likelihood of clinically significant PCa should be performed using the PI-RADS score and a more subjective Likert scale. PI-RADS recommends the use of the dominant sequence for reading prostate lesions (i.e., diffusion-weighted imaging for the peripheral zone and T2-weighted imaging for the transition zone).[35] Likert uses similar interpretation principles to PI-RADS but is less didactic in the use of a dominant sequence and is more experienced-based.[56] This section also includes a figure where the reporter can draw and number each lesion.

2. In accordance with PI-RADS recommendations, lesion size should be measured on the apparent diffusion coefficient (ADC) map for lesions within the peripheral zone and on T2-weighted imaging for transition zone lesions.[35] However, if lesion measurement is difficult or compromised on these sequences, the measurement should be made on the sequence that best depicts the lesion. Lesion volume can be determined using one of four different techniques (Figure 4). Planimetry or the ellipsoid formula are considered the most accurate, but single plane or biaxial measurements may also be used when the quality of sequences is compromised by artefacts or when lesions are very small and only seen on one or two slices. It is recommended that the volume of the lesion is recorded using the same method for serial studies, as this will prevent errors from inconsistent measurements and, ideally, radiologists should be blinded to the previous lesion measurements at this point.

PRECISE Scores

1. This section requires reporters to review previous MRI scans, and therefore is not reported for the baseline study. The date of the last MRI is recorded, a PRECISE score for the likelihood of radiological change compared to prior imaging should be provided, and a comment included on any parameters which have changed. Images should be compared to both the previous imaging and baseline study when determining the PRECISE score, with the recommended parameters for assessing

any change being lesion size, conspicuity (i.e., visibility), change in the PI-RADS score (indicating upgrade of existing lesions or new lesions), and any features of extraprostatic disease (including extracapsular extension, seminal vesicle invasion, nodal involvement, and metastasis). The final PRECISE score reflects either resolution (PRECISE 1, Figure 5) or reduction (PRECISE 2, Figure 6) of features suspicious for tumour such as conspicuity or size of the lesion compared to previous scans, overall radiological stability (PRECISE 3, Figure 7), or radiological progression in lesion size/conspicuity (PRECISE 4, Figure 8) or stage progression (PRECISE 5, Figure 9).

Synthesis of Available Evidence on MRI-led AS

Two recent systematic reviews have synthesised the literature on MRI-led AS**.**[57,58] The first study included 15 studies with 2,240 patients and provided pooled diagnostic estimates of serial MRI for PCa progression during AS.[57] The PRECISE recommendations were used in six studies (Table 2) and nine used institution-specific definitions. The pooled sensitivity, specificity, and accuracy of serial MRI for progression were 59%, 75%, and 73% respectively. The positive predictive value ranged from 37% to 50% with a negative predictive value of MRI for progression ranging from 81% to 88%. There was also a non-significant trend towards improved performance of the cohorts using the PRECISE recommendations. In the second analysis, only seven studies (including 800 patients) were assessed.[58] The pooled sensitivity and specificity of MRI for disease progression were 61% and 78%, respectively. These studies concluded that serial MRI alone is not enough to reliably exclude PCa progression and suggest that blood markers and clinical factors must also be used to determine the timing of follow-up biopsies.

At least another three MRI-led AS cohort studies have been published since these systematic reviews. Chu et al.[59] showed that both consistently visible and increasingly suspicious lesions on imaging were associated with GG≥2 detection and definitive treatment in 125 patients. Castillo et al.[60] reported on 90 patients who underwent serial imaging and observed radiological progression in 29% of patients with a suspicious baseline scan (PI-RADS = 3) and 25% with a non-suspicious baseline scan (PI-RADS ≤ 2). Additionally, Thankapannair et al.[61] investigated a tailored-risk monitoring strategy and enrolled 156 patients into a prospective stratified three-tier follow-up programme based on Cambridge Prognostic Group, PSA density, and MRI Likert score at entry. Rates of pathological progression, AS dropout, and patient choice for treatment were assessed. Overall, 86.5% of patients remained on AS or converted to watchful waiting by the end of the evaluation period and modelling suggested a potential 22% reduction in the need for outpatients appointments and 42% less MRI use compared to the current NICE guidelines. They concluded that the

early outcomes of their study supported a risk-stratified follow-up intensity, but the study is limited by a short follow-up period, a relatively small cohort, and only a single centre's experience.

Limitations

Systematic reviews have highlighted that the literature on MRI-led AS is predominantly retrospective, single-centre, cohort studies, currently lacking in high-quality evidence or randomised controlled trials. The literature is heterogenous with variability in the populations enrolled, protocols employed, and the infrastructure and image acquisition within and between studies. Most studies have taken place in high-volume, academic centres, where imaging is analysed and reviewed by a small number of expert genitourinary radiologists, limiting the generalisability of the results. Moreover, due to the need for long-term follow-up in AS populations and the relatively recent introduction of PRECISE in 2016, the system has typically been applied retrospectively. In addition, there are currently several limitations in the use of MRI for AS and also within the PRECISE recommendations (Figure 10).

Limitations of mpMRI in AS

- *False positives and false negatives*

A positive predictive value for MRI of 17%, 46% and 75% has been reported for lesions with a PI-RADS score of 3, 4, and 5 respectively,[62,63] with false positives resulting from non-malignant processes that mimic cancer,[64] technical issues such as artefacts from rectal air, improperly positioned endorectal coils or patient movement, iatrogenic causes (e.g., post-biopsy changes), and unusual appearance of otherwise normal anatomical structures. These false positives can lead to interpretation errors and unnecessary biopsies. MRI also misses lesions, some of which are genuinely MRI occult, but there is a variation in negative predictive valye,[65] which may also result from quality issues in patient preparation or acquisition.

- *Optimal scan timing and growth thresholds to prompt additional biopsy or treatment are uncertain.*

The decision of when to perform imaging is not straightforward and ideally should be based on both baseline risk and biological changes during follow-up, as well as an assessment of

the patient's suitability for treatment, taking into account co-morbidities that may have developed over the surveillance period.[66] Moreover, the natural growth rate of PCa lesions and the threshold to rebiopsy or start active treatment is also unclear. Rais-Bahrami et al.[67] reviewed 153 patients with MRI and biopsies and recommended MRI to monitor small lesions at least once every two years. It has been demonstrated that 11.6% of patients with no visible lesion on initial MRI develop a suspicious focus over a median follow-up of 3.6 years.[68] Morgan et al.[69] reported on 151 patients undergoing mpMRI at two-time points (median interval 1.9 years) and found that tumour volume increased measurably in 34.4% of patients after 2 years. While a cut-off of a 20% increase in maximum tumour diameter (on T2-weighted imaging) from baseline, and a minimum absolute increase in diameter with a minimum size threshold of 3 mm has been proposed as a more objective definition of radiological progression.[57]

- *Interscan variability debases quantitative measurements.*

The ADC has been proposed as a useful quantitative measure for lesion progression. Baseline ADC has also been shown to be strongly predictive of both adverse histology and time to deferred radical treatment in a prospective AS cohort with 9-year follow-up monitoring.[70] Further, a change in ADC could be used to identify tumours with measurable growth and a decreased ADC has been associated with pathological progression.[69,71] A recent study demonstrated high interreader reproducibility of different ADC calculations from serial MRI scans of thirty AS patients, as well as a correlation between ADC values and radiologic changes.[72] However, interscan variability including different magnets, vendors, and coils as well as the differences in diffusion-weighted imaging pulse sequences used by vendors, *b* values, and patient factors (e.g. the presence of artefacts) can all impact results and ADC values should preferably be normalised, for example, to non-cancerous tissue or urine in the bladder (Figure 11).[72,73]

- *Resource availability, cost-effectiveness, and contrast risks.*

Expert genitourinary radiologists, MRI scanners, and contrast are not always available. Although a cost-effectiveness analysis suggests that an MRI-guided PCa diagnostic pathway would result in fewer patients needing biopsies, it was shown to be only 86% cost-effective if applied to all low-risk cases.[74] Potential solutions to reduce the cost include same-day MRI,[75] where imaging and biopsy are performed in the same visit, or the use of biparametric MRI. [76] There is still debate over the need for the dynamic contrast-enhanced sequences and the PI-RADS committee position is that " *in men at persistent (higher) risk [...] under AS who are being evaluated for fast PSA doubling times or changing clinical or pathologic status, contrast-enhanced MRI is also preferred."* [77] Different AS studies have compared the use of biparametric MRI and multiparametric MRI.[78-80] One study, assessing whether biparametric MRI missed suspicious lesions, re-examined 101 patients with multiparametric MRI following biparametric MRI,[80] and found that 4% of the population had PCa (≥ GG2) initially missed, although the difference was not significant (p=0.13). A secondary analysis from the PROMIS study [3] has demonstrated that dynamic contrast-enhanced sequences do not improve accuracy over T2-weighted imaging and diffusion-weighted imaging in detecting clinically significant PCa (defined as GS≥4+3 or a maximum length of ≥6mm), with an MRI sensitivity of 95% and 94% and specificity of 38% and 37% with and without contrast, respectively (p>0.05). Although these results suggest that biparametric MRI could simplify scanning and reduce healthcare costs, more evidence (in particular level 1 evidence) is required,[81] and studies such as the PRIME trial[82,83] are attempting to answer this question in the detection setting. Additionally, the minor risk of gadolinium deposits in the brain or toxicity from multiple scans may concern patients.[84,85]

Limitations of PRECISE

- *Difficulties in assessing lesion growth.*

Although PRECISE aims to standardise scan interpretation and reporting, recommendations are qualitative and do not include standardised thresholds for changes in lesion size or conspicuity. Tumour size and volume are important prognostic factors in prostate cancer,

however, variations in the size of prostatic lesions can occur due to interobserver and intraobserver variability in the visual grading of lesions as well as interscan variability. Additionally, there is also an expected or natural rate of tumour growth, which is rarely considered, but is expected as part of the natural history of low-grade tumours on AS. These variations make it difficult to distinguish between fluctuations due to technical factors and true radiological progression during AS.

- *Variability in measuring lesions.*

In its current form, PRECISE offers no suggestions on the most accurate measurement for monitoring lesion size across serial MRI. It allows for lesion volume to be reported using several methods including planimetry, the ellipsoid formula, or with one or two diameters, which in turn permits inconsistencies and variability in reporting. We know that planimetry is the most accurate but time-consuming method. A recent study using a single, experienced genitourinary radiologist to report lesion volume for 196 AS patients found that the ellipsoid formula had the highest correlation with planimetry.[86] However, as acknowledged in PRECISE, a single diameter is likely to be the most reproducible, although no studies have been designed to confirm this. There is also debate about which sequence to measure the lesion on and Le Nobin et al.[87] used radical prostatectomy samples to demonstrate that diffusion-weighted imaging may lead to tumour volumes being underestimated.

- *Difficulties in assessing lesion conspicuity.*

Similarly, the current assessment of lesion conspicuity according to PRECISE is problematic. An increase or reduction in conspicuity will result in a change of PRECISE score. Although, the visibility of lesions is also affected by interobserver and interscan variability as well as image quality, and certain conditions, as well as medications, can also have an impact. Lesion conspicuity is always assessed with reference to the prostate background, and in patients with prostatitis or benign prostatic hyperplasia diffuse changes can make the delineation of tumour edges difficult.[88-91] Indeed, reporting background

changes has been recommended to convey the potential for diagnostic uncertainty to clinicians.[92] Additionally, the use of 5α -reductase inhibitors (e.g., dutasteride) can impact lesion conspicuity. Using forty patients randomised to dutasteride or placebo, the MAPPED study [93] demonstrated that dutasteride can decrease the conspicuity on diffusion-weighted but not necessarily on T2-weighted imaging (Figure 12). Therefore, the size of a lesion could increase over time on T2-weighted imaging, but its conspicuity could decrease on diffusion-weighted imaging obfuscating the assessment of the PRECISE score for patients on 5α-reductase inhibitors. This issue is particularly important for lesions in the peripheral zone, where diffusion-weighted imaging is the dominant sequence.

- *Redundancy and points of confusion within the current scoring system.*

Presently, extremes in the PRECISE score are rarely reported. Caglic et al.[8] noted that the PRECISE scores of 1 and 5 were only assigned in 1.6% of their cohort of 295 AS patients. This effectively turns PRECISE into a three-point scoring system (i.e., radiological improvement, stability, and progression). Additionally, the overreporting of PRECISE 3 and PI-RADS 3 lesions by inexperienced radiologists to avoid missing clinically significant cancer may result in unnecessary biopsies and increased healthcare costs. There are also some areas of uncertainty within the current scoring system, for example, the growth of a lesion past the midline or appearance of a new lesion is classified as stage progression (e.g., T2a to T2b or T2c), which under the current system is strictly defined as PRECISE 5, but in practice is often labelled as PRECISE 4. Moreover, the appearance of new lesions is not defined separately, and in practice, these are often scored as PRECISE 4 (Figure 13). However, this potentially leads to confusion if they are only PI-RADS 3 or possibly inflammatory “lesions” as well as if larger lesions on the same scan are stable or regress over time.

- *Increased reporting time.*

Finally, reporting according to the PRECISE recommendations can be time-consuming in clinical practice, and this may be unfeasible given the increasing burden in prostate MRI reporting that radiologists face. One possible answer is to shorten the case report form but this solution risks losing important clinical information. Technology and auto-populating template reports may also be a useful adjunct here and a study on a dedicated PRECISE software system, which provided a workflow to report step-by-step according to the recommendation, found a significant reduction in the reporting time at 6 months using the program.[94]

Future Directions

Moving forward there is a need for better evidence on the use of MRI in AS to inform guidelines and clinical practice. Randomised controlled trials and multicentre studies are required to determine the threshold for radiological progression, appropriate intervals for MRI, and optimal triggers to start treatment before the widespread acceptance of fully MRI-based AS protocols. Our group at University College London are currently leading a multi-centre validation of the PRECISE scoring system at an international level and data will be available in the near future.

- *Improvements in MRI acquisition.*

We must continue improving the diagnostic ability of MRI. Preliminary studies on 7T MRI have demonstrated higher spatial resolution than 1.5T and 3T,[95] and can detect cancer in both the peripheral and transitional zone[96] however further research is required to determine its clinical utility.[9] We should also work to limit interscan variability by utilising standardised and optimised acquisition protocols, and anthropomorphic imaging phantoms may soon help to improve calibrating scanners.[97]

- *Uniform standards for MRI reporting.*

Interreader variability could also be improved by teaching radiologists to report according to PRECISE. Studies have demonstrated a learning curve and that prognostic assessment of PCa is highly dependent on a radiologist's expertise. Indeed, higher rates of agreement have been found among expert reporters in prostate MRI and teaching has been shown to improve performance.[98] A significant improvement in the accuracy of reporting and assessment of radiological change was demonstrated after 11 radiologists took part in a single dedicated teaching course on PRECISE.[99] Moreover, the widespread adoption of the PI-QUAL score (and its future iterations) for image quality should promote and standardise reporting of image acquisition quality to ensure a basic standard has been met for all MRI scans.

- *Adoption of artificial intelligence and radiomics.*

There is potential for artificial intelligence (AI) to assist in reporting serial prostate MRI. It may reduce the amount of time for evaluation of MRI scans and help less experienced radiologists achieve similar PCa detection performance to experts.[100] A recent systematic review revealed an average sensitivity of 84% and specificity of 61.5% for AI detecting PCa on MRI.[101] While Cacciamani et al.[102] pooled the results of five studies comparing the performance of radiologists and AI alone versus a combination of radiologists aided by a computer-aided diagnosis (CAD). The pooled sensitivity (89.1% vs 79.5%), specificity (78.1% vs 73.1%), and diagnostic odds ratio (29% vs 11%) were higher for the radiologists plus CAD than for radiologists alone. Deep learning AI systems, which use an algorithm to learn the underlying features of a given image and undergo a training process to provide a classification label as output, are also promising. Song et al.[103] used a deep-learning algorithm on 195 localised PCa patients and was able to detect PCa with a sensitivity of 87%, specificity of 90.6%, positive predictive value of 87%, and negative predictive value of 90.6%. However, further research is needed before before AI tools can be adopted into clinical practice.

As an extension of AI, radiomics is a growing field where many MRI features are analysed and used to predict histopathology and genetic signatures.[104] Hectors et al. found 14 radiomic features that correlated imaging with RP samples from 64 patients.[105] Sushentsev et al. developed a time series radiomics predictive model that analysed longitudinal changes in tumour-derived radiomic features across 297 scans from 76 patients, combining time series radiomics and serial PSA density (AUC 0.86 [95% CI: 0.78–0.94]) that achieved comparable performance to expert-performed serial MRI analysis using the PRECISE scoring system (0.84 [0.76– 0.93])[106].Moreover, a recent systematic review found 57 papers on MRI radiomic features and concluded that there are good- to high-performance radiomics models for PCa detection and GS discrimination.[107]

- *An individualised risk-stratified approach to AS.*

A recent international consensus meeting identified developing a personalised risk-stratified approach as the most important priority in AS research.[108] Guidelines that recommend the same follow-up regime for all can result in over-investigation and morbidity (i.e. from repeat biopsy) and there is now a widely acknowledged need to risk stratify AS follow-up events based on the evolution of a patient's disease characteristics and parameters rather than prespecified intervals. Following promising early outcomes, this approach is likely to continue evolving.

- *Update and improve the PRECISE recommendations.*

Some limitations of the current PRECISE criteria should be addressed, and the recommendations should be updated. Standardising the definitions of radiological progression, tumour volume measurement and normal expected growth or fluctuations in the size of lesions should be a major focus of the next consensus meeting.

One suggestion could be to adopt a simplified three-point PRECISE score (where 1 = radiological improvement, 2 = radiological stability, and 3 = radiological progression) since studies have found higher interobserver reproducibility when reporting the absence or presence of radiological stability than the current PRECISE score.[54] Another aspect that should be addressed in the next iteration of PRECISE is the difference between visible and non-visible prostate cancer on mpMRI, as these are known to have different rates of progression during AS.[52] Finally, we encourage training courses and software to aid radiologists in adopting the updated recommendations.

In summary, the role of MRI in AS has recently been expanding. Studies suggest that it can improve the targeting accuracy of prostate biopsies, assist in the selection of eligible patients, and help to monitor PCa progression. The PRECISE recommendations standardise reporting of serial MRI scans for patients on AS and their suggested case report form can be easily implemented into clinical practice. There is increasing evidence to support MRI-led AS and the need for an individualised risk-stratified approach to AS has been identified. However, despite the promising results, there are some limitations to the current PRECISE criteria, which will be addressed in a future update.

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Figure Legend

Figure 1. An example of the sequences included in multiparametric magnetic resonance imaging.

A 1.5T scan of a 74-year-old patient with 10mm GS 4+3 on biopsy and a lesion (arrow) in the left peripheral zone between 4 and 6 o'clock. The following sequences should be included in mpMRI: (A) T2-weighted image (T2-WI), to look at the anatomy of the prostate; (B-C) diffusion-weighted image (DWI) including a sequence of multiple *b* values, a dedicated high *b* value sequence (shown in B) and an apparent diffusion coefficient (ADC) map (shown in C) to examine the cellularity of the lesion; (D) a dynamic contrast-enhanced (DCE) sequence, which requires the injection of an intravenous contrast medium, to assess the vascularity of a lesion. Prostate cancer usually appears hypointense on T2-WI (A), hyperintense on the high *b* value sequence (B) and hypointense on the ADC map (C) and demonstrates early wash-in (D) and early wash-out on DCE sequences.

Figure 2. Case report form for reporting of magnetic resonance imaging at baseline and during follow-up in patients on active surveillance.

MRI=magnetic resonance imaging; PI-RADS=Prostate Imaging Reporting and Data System; PRECISE=Prostate Cancer Radiological Estimation of Change in Sequential Evaluation; PSA=prostate-specific antigen; T2-WI=T2-weighted image.

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Figure 3. Breakdown of the PRECISE scoring system as shown in the original recommendations.

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Figure 4. The various methods for measuring lesion size on multiparametric magnetic resonance imaging.

A 1.5T scan of a 56-year-old patient with 5mm GS 3+3 in the right peripheral zone on targeted biopsy. The lesion between 7 and 9 o'clock (arrow) is clearly visible on (A) *T2*-WI, (B) ADC map, and (C) DCE sequences. (D) The lesion volume by planimetry is obtained contouring the lesion slice by slice on the axial image, while the volume using the ellipsoid formula is obtained using the three diameters from the (E) axial and (F) coronal acquisition according to the formula: (ab X cd X ef) * π/6. The size of a lesion can also be measured using a single maximum diameter or by the biaxial measurement of maximum diameters (i.e., estimated square area), as per the original case report form shown in Figure 2.

Figure 5. Case of resolution in suspicious features for prostate cancer on magnetic resonance imaging (PRECISE 1).

(A-D) A 1.5T MR scan of a 69-year-old patient showing a wedge-shaped focus (arrow) in the right peripheral zone (Likert 3/5). The patient had only 1mm Gleason 3+3 disease at targeted biopsy. A subsequent 1.5T scan (E-H) demonstrated no focal lesions (Likert 2/5). The PRECISE score was 1 (i.e., resolution of previous features suspicious on magnetic resonance imaging).

Figure 6. A case of reduction in suspicious features for prostate cancer on magnetic resonance imaging (PRECISE 2).

(A-D) A 1.5T MR scan of a 61-year-old patient showing diffuse patchy T2 signal associated with mildly restricted diffusion and diffuse enhancement (Likert 3/5). Systematic biopsy showed 3.5mm Gleason 3+4 disease in the left peripheral zone at mid-gland. A subsequent 3T scan demonstrated improvement of the diffuse changes with no focal lesions (Likert 2/5). The PRECISE score was 2 (i.e., reduction in conspicuity of previous features suspicious on MRI).

Figure 7. A case of a stable lesion on serial magnetic resonance imaging (PRECISE 3).

(A-D) A 1.5T MR scan of a 73-year-old patient showing a focal lesion (arrow) within the left mid-apical peripheral zone (Likert 4/5). Targeted biopsy showed 8 mm Gleason 3+4 disease and the patient opted for AS.

A subsequent 1.5T scan (E-H) showed a stable lesion (Likert 4/5). The PRECISE score was 3 (i.e., stable MR features over time).

Figure 8. A case of radiological progression on magnetic resonance imaging (PRECISE 4).

(A-D) A 1.5T MR scan of a 64-year-old patient showing a 6mm wedge-shaped lesion in the right peripheral zone (Likert 4/5). Targeted biopsy revealed 3mm Gleason 3+4 disease and the patient opted for AS.

(E-H) A subsequent 3T scan demonstrated increased size and conspicuity of the lesion (Likert 5/5) but no measurable extraprostatic extension. The PRECISE score was 4 (i.e., MR features suggesting disease progression). A targeted biopsy revealed 3.5mm Gleason 4+3 disease and the patient was treated with high-intensity focal ultrasound.

Figure 9. A case of definitive stage progression on magnetic resonance imaging (PRECISE 5).

(A-D) A 1.5T MR scan of a 70-year-old patient on AS for Gleason 3+4 disease showing a suspicious lesion (arrow) in the left peripheral zone in the mid-gland at 5 o'clock (Likert 4/5). A subsequent 1.5T scan (E-H) demonstrated progression in both the size and conspicuity of the tumour (Likert 5/5) as well as early macroscopic extracapsular disease extension. The PRECISE score was 5 (i.e., MR features suggesting definitive stage progression). A radical prostatectomy was performed and histology demonstrated Gleason 4+3 disease (pT3a).

Figure 10. Limitations of the current PRECISE recommendations and possible solutions.

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Figure 11. Method for the normalisation of apparent diffusion coefficient values.

Multiparametric magnetic resonance imaging of a 71-year-old patient with biopsy-proven prostate cancer in the left peripheral zone between 4 and 5 o'clock. (A) T2-weighted (B) diffusion-weighted and (C) dynamic-contrast enhanced imaging confirms the presence of the lesion (arrows). Three different regions of interest (of the same size and area) from the apparent diffusion coefficient map (D-E) were drawn on the lesion (orange circle) and normal prostatic tissue (blue circle) (D) and on the urine (green circle) in the bladder (E). These additional values were recorded and used to generate two parameters: the normalised prostatic ADC (npADC) and the normalised urinary ADC (nuADC) ratios, according to the formula: ADC (tumour)/ADC (reference).

Figure 12. A case of a patient with a focal lesion visible on MRI before and after starting a 5 alpha-reductase inhibitor.

(A-C) A 3T MR scan demonstrating a focal lesion (arrow) in the right peripheral zone between 7 and 8 o'clock extending towards the apex (Likert 4/5).

The patient opted for AS and started daily dutasteride (0.5mg) for 6 months as part of a trial. A 3T MR scan after 6 months (D-F) shows that the lesion is less conspicuous and has reduced in size on the T2-weighted image (D), diffusion-weighted image (E), and dynamic contrast-enhanced (F) images.

Figure 13. A case of a new focal lesion appearing on magnetic resonance imaging.

(A-D) A 1.5T MR scan of a 62-year-old patient on active surveillance for non-visible 1mm Gleason 3+4 disease in the left posterior base (Likert 2/5).

A subsequent 3T MR scan (E-H) demonstrated a 13 x 6mm lesion (measured on the ADC map) in the left peripheral zone between 3 and 5 o'clock (arrow) (Likert 4/5). The PRECISE score was 4 (i.e., MR features suggesting disease progression) and a targeted biopsy of the lesion demonstrated 6mm Gleason 3+4 disease.