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Systematic Review of Active Surveillance for Clinically Localised Prostate Cancer to Develop Recommendations Regarding Inclusion of Intermediate-risk Disease, Biopsy Characteristics at Inclusion and Monitoring, and Surveillance Repeat Biopsy Strategy

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1. Introduction

Active surveillance (AS) has been proved to be an appropriate alternative to radical treatment options for low-risk prostate cancer (PCa) [1] with equivalent oncological outcomes [2–4]. Nevertheless, there is significant heterogeneity in terms of AS protocols. To address this, a multidisciplinary project (DETECTIVE study) [5] aimed to develop consensus statements and recommendations. It successfully achieved consensus in >70% of statements pertaining to the conduct of AS [5]. Certain key issues failed to achieve consensus, including inclusion of patients with intermediate-risk disease; optimal thresholds regarding biopsy characteristics and how they should influence inclusion, exclusion, and reclassification; and nature and frequency of repeat prostate biopsy during monitoring.

The objective of this study was to perform a further analysis of exploratory data from a systematic review (SR) incorporating all studies on AS published from 1990 until October 2020 focusing exclusively on the above key areas of controversy, in order to develop clinical practice recommendations.

2. Evidence acquisition

2.1. Search strategy and review elements

This protocol has been published previously [6]. The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [7], including all prospective and retrospective studies incorporating AS or any deferred active treatment. The main outcome measures are summarised in Table 1. Specifically,
the SR focused on the following: (1) criteria for inclusion; (2) thresholds of prostate biopsy characteristics (ie, core positivity and core involvement [CI]) for inclusion, monitoring, and reclassification; and (3) strategies for repeat biopsy (ie, per protocol and/or triggered, and use of transrectal ultrasound [TRUS] or multiparametric magnetic resonance imaging [mpMRI] for targeted and/or systematic biopsies).

As the aim was to summarise criteria and thresholds in AS protocols only, including prospective study protocols published a priori, clinical effectiveness data were not assessed.

### 2.2. Data extraction, data analysis, and risk of bias assessment

Data extraction and risk of bias (RoB) assessment were performed as described previously [6,8–10]. Results were summarised qualitatively. Sensitivity and subgroup analyses were planned based on the year of publication (2010 onwards), studies recruiting ≥240 patients (median of all included studies), studies with a follow-up duration of ≥39.5 mo (median of all included studies), studies with a low RoB across all domains, thresholds of core positivity, CI, and International Society of Urological Pathology (ISUP) grade group for inclusion and reclassification.

### 3. Evidence synthesis

#### 3.1. Quantity of evidence identified

The study selection process is outlined in Figure 1. Out of 17 011 articles screened, 333 studies recruiting 264 582 patients were included.

#### 3.2. Characteristics of the included studies

Supplementary Table 1 presents the baseline characteristics of all included studies, consisting of 17 randomised controlled trials, 27 prospective nonrandomised comparative studies (NRCS), 24 retrospective NRCS, 158 prospective noncomparative case series (NCCS), and 107 retrospective NCCS. There were 375 protocols in total, with some studies assessing multiple AS protocols in different databases. Data regarding recruitment, inclusion, and exclusion were
available from 371 protocols, whereas data for monitoring and follow-up, and reclassification were available from 343 protocols.

3.3. RoB assessment

Figure 2 shows the results of RoB assessment of included studies. Most studies (75%) adhered to an a priori protocol. However, >87% of studies were judged to have a high or an unclear RoB for recruitment and follow-up.

3.4. Summary of results

Tables 2–4 present a summary of thresholds used across studies for inclusion, monitoring, and reclassification.

3.4.1. Inclusion and exclusion criteria

Of the protocols, >50% included patients with intermediate-risk disease, based on Prostate-specific antigen (PSA) ≤20 ng/ml (25%), ISUP 2 or 3 (28%), clinical stage cT2b/c (42%), and/or direct use of D’Amico risk grouping of intermediate-risk or above (51%). PSA density was not used often (26%); mpMRI was used as an inclusion tool in only 17 studies (5.1%). Regarding biopsy characteristics, 44% of protocols excluded patients with more than three positive cores, and 39% excluded patients with CI >50% per core.

3.4.2. Monitoring and follow-up criteria

The majority of protocols tested PSA ≤6 monthly (83%) and performed digital rectal examination (DRE) ≤12 monthly (60%). Only 34 protocols (9.1%) described the use of mpMRI during monitoring, and the majority (68.0%) used it only if triggered clinically. Of the protocols, 85% (n = 233) mandated a confirmatory untriggered TRUS biopsy, with 55% of protocols performing this within 1 yr and 24% within 2 yr; 72% of protocols (n = 189) mandated per-protocol surveillance repeat biopsies after the confirmatory biopsy, with 50 protocols performing the repeat biopsies annually, 69 performing this within every 2 yr, and 70 having other biopsy frequencies. Only 27 protocols (10%) performed triggered biopsies, triggered only in 4.6% and combined with per protocol in 5.7%. Of the triggered biopsy protocols, 74% were only based on MRI progression or changes. Of the protocols using MRI-based triggers of repeat biopsies (n = 20), 50% used a combination of systematic and targeted biopsies (n = 4) or either systematic and/or targeted biopsies (n = 6). Other triggers of repeat biopsies included PSA progression (n = 6), PCA3 changes (n = 1), or a combination (n = 2). The majority of protocols (70%) did not specify the number of biopsy cores that should be taken during repeat biopsies.

3.4.3. Reclassification criteria

For reclassification, the commonest trigger (87%) was histological upgrading. An increase in the number of positive cores was also a reason for reclassification in 136 studies (50%). Of these, 56 studies (41%) defined a cut-off of three or more positive cores, 33 studies (24%) defined a cut-off of four or more positive cores, and 47 studies (35%) used other cut-off values. Changes in serum PSA and PSA dou-

![Fig. 2 – Risk of bias assessment of included studies.](image-url)
blinding time may have triggered further evaluation, but were rarely (n = 2) the only cause for reclassification. The majority of studies (90%) did not specify patient preference as a reason for reclassification. MRI was used to define reclassification in 26 studies (7.8%).

3.4.4 Sensitivity and subgroup analyses
Sensitivity analyses based on studies recruiting from 2010 onwards (n = 50), studies recruiting >240 patients (n = 156), studies with a follow-up duration of ≥39.5 mo (n = 120), studies with a low RoB across all domains (n = 34), subgroup analysis on thresholds of disease extent based on biopsies for inclusion, and reclassification based on ISUP 1 (n = 245 for inclusion; n = 196 for reclassification) and ISUP 2 (n = 51 for inclusion; n = 41 for reclassification) did not significantly alter the main findings regarding inclusion and progression thresholds, and monitoring and follow-up criteria.

3.5 Discussion

3.5.1 Principal findings
The results of this SR should be juxtaposed with those of the DETECTIVE study [5]. This report focused on addressing the remaining areas of uncertainty in order to issue recommendations based on a combination of expert opinion by a multidisciplinary panel underpinned by exploratory data from an SR. Only a minority of included studies (14%) described the use of mpMRI in their protocols; consequently, the recommendations derived from this SR should apply only to AS protocols where the use of mpMRI is either not mandatory or absent.

3.5.1.1 Should intermediate-risk localised disease be considered for AS? Since >50% of AS studies have included patients with intermediate-risk localised disease, we believe that AS can be considered in selected patients with single elements of intermediate-risk disease, but excluding ISUP 3 disease.
From the SR, the majority of candidates with intermediate-risk disease had only one intermediate-risk characteristic. The monitoring schedule should be more intensive, given the significantly higher risk of progression, development of regional or distant metastases, and death compared with low-risk disease [11]. In the future, tissue-based genetic risk scores may be helpful in stratifying these patients [12].

3.5.1.2. What is the maximum biopsy tumour extent appropriate for inclusion into AS? A total of 202 AS protocols (67%) used histological biopsy core information as a threshold for inclusion. Biopsy tumour extent expressed as the number of positive cores, proportion of positive cores, or maximum cancer CI is a strong predictor of grade reclassification [1,3,10,13,14], adverse pathological outcomes [13,15], biochemical progression [13], and biochemical recurrence following delayed radical treatment [10]. In our SR, 164 protocols (44%) used a maximum threshold of three positive cores as an inclusion criterion; another 144 protocols (39%) used a maximum threshold of CI >50% as an inclusion criterion. Consequently, we conclude that the most suitable maximum threshold for inclusion in systematically obtained biopsies is either three positive cores or 50% cancer involvement per core of ISUP 1 PCa; beyond these thresholds, patients could still be included, but they should be monitored closely due to a higher risk of adverse oncological outcomes. Patients with ISUP 2 and high core positivity (more than three positive cores) and/or cancer involvement (>50% CI per core) should be excluded.

3.5.1.3. What is the most appropriate strategy of repeat prostate biopsies during monitoring? The DETECTIVE study reached consensus on several issues regarding confirmatory and repeat biopsies during monitoring. However, there was no consensus on the role of per-protocol repeat biopsies. We found that more than half of included studies (55%) performed confirmatory biopsy within 1 yr of starting AS, and 79% performed it within 2 yr. The purpose of initial repeat biopsy is to account for understaging and undersampling at diagnosis, especially in the absence of mpMRI [16–18], and to detect potentially missed high-grade cancers. The vast majority of included studies (86%) did not report the use of MRI, where the risk of undergrading is approximately 20% on initial biopsy. Patients who are likely to progress are usually detected within the first 2 yr [19]. With the introduction of new and more accurate diagnostic modalities such as mpMRI at the outset of AS, the risk of undergrading at inclusion is likely to have decreased. However, this risk is not insignificant, as such per-protocol confirmatory biopsy may still be important [20,21]. Consequently, we recommend per-protocol confirmatory biopsies within 2 yr of commencing AS for non–mpMRI-based protocols.

The increasing use of mpMRI in contemporary AS protocols is leading to new standards. A recent SR and meta-analysis on the reliability of serial prostate MRI to detect PCa progression during AS [22] showed significant heterogeneity on MRI progression between included studies, and the pooled measured positive and negative predictive values were 0.50 and 0.85, respectively. The authors concluded that MRI progression alone should not be used as the sole trigger for repeat biopsy. This underlines the importance of frequent PSA and DRE measurements as well as per-protocol surveillance repeat biopsies during the entire duration of AS.

Regarding the per-protocol surveillance repeat biopsies in non–mpMRI-based AS protocols, >70% of included studies performed surveillance repeat biopsies after the initial confirmatory biopsy. Almost 60% of included protocols performed surveillance repeat biopsies at least once every 3 yr throughout the duration of AS. We therefore recommend per-protocol surveillance repeat biopsies at least every 3 yr for the first 10 yr, if mpMRI is not available.

3.5.1.4. What histological characteristics on repeat systematic biopsies should lead to a change in management?. The DETECTIVE study issued recommendations on the use of histological characteristics for reclassification. However, no consensus was reached regarding whether tumour extent on repeat biopsies should lead to reclassification, nor on the thresholds. We found that 67% of included studies used ISUP 2 or 3 on repeat systematic biopsies as a reclassification criterion. Of the protocols, 21% and 12% used, respectively, three or more and four or more positive cores as a reclassification criterion. Of the protocols, 27.3% defined CI >50% as a reclassification criterion. Results from the PRIAS study showed that 17% of patients had an increase in tumour volume, with the increasing number of baseline positive cores being an independent predictor (odds ratio [OR] 2.2; 95% confidence interval [CI] 1.67–2.81; p < 0.001) for reclassification [12] on multivariate analysis. Similar results have been shown by Klotz et al [11]. Tosoian et al [23] have also shown that the number and percentages of positive cores are predictors of pathological upgrading. The appropriate thresholds to guide management however remain unclear, whilst several retrospective studies provide compelling evidence. Truong et al [13] analysed clinical and pathological variables, and built a nomogram for recruiting patients with low-risk disease into an AS protocol. The authors found that the number of positive cores >3 (OR 1.23; 95% CI 1.05–1.45; p = 0.01) and % maximum CI >30% (OR 1.02; 95% CI 1.005–1.035; p = 0.009) were significantly associated with histological upgrading at radical prostatectomy on multivariate analysis. Other studies showed that a higher number of positive cores (more than three) were associated with higher rates of progression to treatment [24], whilst a lower number of cores at diagnostic biopsy showed a significant association with reduced need for active treatment [25]. An increase in the percentage of CI in low-risk PCa significantly increases the progression rate (adjusted hazard ratio 1.6; 95% CI 1.2–2.4; p = 0.02) for Cl >38% during a median follow-up of 2.2 yr [26]. Half of men with CI >25% were reclassified within 2 yr. The percentage of needle biopsy cores and surface area positive for cancer were the strongest predictors of pathological stage and tumour volume in 207 consecutive patients who subsequently underwent radical prostatectomy [27]. The percentage of core positivity has also been associated with pathology progression [28,29].

In summary, there is sufficient evidence indicating that biopsy characteristics from repeat systematic biopsies
should drive future management if certain thresholds are exceeded, although the data are insufficient to make conclusions regarding reclassification for low-risk disease. Consequently, we recommend that thresholds of more than three positive cores or CI >50% per core obtained via repeat systematic biopsy (ie, when no MRI-targeted biopsies have been performed) for low-risk disease from previously low core positivity and/or low CI at diagnosis should be used as the criteria to monitor closely for evidence of adverse characteristics, including intermediate-risk disease, especially when no mpMRI is available. For patients with ISUP 2 disease recruited into AS, increase in core positivity and/or CI to such thresholds based on systematic repeat biopsies should be considered as a marker of reclassification.

Our SR did not find sufficient data on mpMRI to address whether mpMRI use could potentially supersede other clinical triggers of change in management during monitoring, such as changes in PSA, DRE, and histological characteristics of repeat biopsies. However, data from other studies may potentially be useful. The SR and meta-analysis by Rajwa et al [32] found that the incorporation of serial mpMRI scans does not reduce the importance of clinical and pathological staging during AS, primarily because MRI is not yet accurate enough to exclude disease progression during AS. Therefore, the thresholds identified in our SR including clinical T stage and core positivity and CI from repeat systematic biopsies are all likely to remain relevant, even for protocols involving mpMRI. However, the role of per-protocol repeat systematic biopsies and how they should be incorporated into AS protocols involving regular use of mpMRI during monitoring remain unclear.

3.5.3. Strengths and limitations
The work is strengthened by utilising robust methods based on an a priori, PRISMA-adhering protocol. It is the largest and most comprehensive SR on AS to date, including 333 studies (375 protocols). Lastly, the study findings were interpreted in conjunction with those from the DETECTIVE study [5]. The main limitation is the lack of reported data on the role mpMRI. However, the fact that mpMRI may improve the identification of intermediate- and high-risk disease on biopsy should be taken into account, since many of them may have been included in historic cohorts. We emphasise that the recommendations from this study are based on low levels of evidence, being derived from a qualitative SR that did not have any clinical effectiveness data and instead relied on exploratory data from the literature, and interpreted using expert opinion from the panel. Consequently, we stress the interim nature of the guidance provided by the recommendations, being subject to a review when higher levels of evidence emerge.

4. Conclusions
Based on our SR, we are able to formulate the following recommendations for AS protocols in which the use of mpMRI is either not mandatory or absent: (1) AS can be considered in selected patients with low-volume ISUP 2 disease or other single intermediate-risk features (except ISUP 3, which is strictly excluded), only if strict monitoring is followed due to the higher risk of progression; (2) at recruitment, patients with low-risk but more extensive disease based on systematic biopsies, defined as more than three positive cores or maximum CI >50% per core, should be monitored closely, whereas patients with ISUP 2 but similarly high core positivity and/or CI should be excluded; (3) per-protocol confirmatory prostate biopsies should be performed within 2 yr, and per-protocol surveillance repeat biopsies should be performed at least once every 3 yr for the first 10 yr; and (4) patients with low-volume, low-risk disease at recruitment in whom repeat systematic biopsies have revealed an increase in core positivity to three or more positive cores or maximum CI >50% per core, especially when no MRI-targeted biopsies are performed and/or no
Table 5 – Summary of additional recommendations for active surveillance for localised prostate cancer based on SR

| Domain                  | Current EAU PCa 2020 guideline recommendations | Additional recommendations based on SR | Strength of recommendation |
|-------------------------|-------------------------------------------------|---------------------------------------|-----------------------------|
| Inclusion criteria      | 1. Perform mpMRI prior to inclusion to ensure that appropriate biopsies have been taken and to stage disease | 1. Favourable ISUP 2 grade group disease (ie, PSA <10 ng/ml, clinical stage ≤ CT2a, and a low number of positive cores [ie, ≤ 3 positives cores, or maximum CI <50% per core]), or any single element of intermediate-risk disease (eg, PSA 10–20 ng/ml accompanied by other favourable features (eg, ISUP 1 grade group, CT2a), can be included; however, ISUP 3 is excluded | Weak                        |
|                         | 2. ISUP 1 disease                               | 2. ISUP 2 with high core positivity (>3 cores) and/or high CI (>50% per core) should be excluded | Weak                        |
|                         | 3. PSA <10 ng/ml                                | 3. Patients with low-risk disease but ≥3 positive cores or maximum CI >50% per core should be monitored more closely than those with smaller disease extent | Weak                        |
|                         | 4. T1 and T2a disease                           | 4. If repeat biopsies are needed, mpMRI should be performed prior to repeat biopsies | Weak                        |
|                         | 5. Offer AS to highly selected patients with ISUP grade 2 disease (ie, <10% pattern 4, PSA <10 ng/ml, <CT2a, low disease extent on imaging and biopsy) accepting the potential increased risk of metastatic progression | 5. For AS protocols not using mpMRI, per-protocol confirmatory biopsies should be performed within the first 2 yr | Weak                        |
| Monitoring criteria     | 1. PSA at least every 6 mo                      | 1. For AS protocols not using mpMRI, per-protocol confirmatory biopsies should be performed within the first 2 yr | Weak                        |
|                         | 2. DRE at least every 6 mo                      | 2. For AS protocols not using mpMRI, repeat systematic biopsies should be performed at least once every 3 yr for 10 yr | Weak                        |
|                         | 3. There is no need for confirmatory biopsies if upfront mpMRI followed by systematic and targeted biopsies have been performed | 3. For protocols not using mpMRI, patients with low-volume, low-risk disease at recruitment, if repeat systematic biopsies reveal >3 positive cores or maximum CI >50%/core, should be monitored closely for evidence of adverse features (eg, upgrading), especially in the absence of surveillance mpMRI | Weak                        |
|                         | 4. If repeat biopsies are needed, mpMRI should be performed prior to repeat biopsies | 4. Patients with low-volume ISUP 2 disease at recruitment with increased core positivity (>3 cores) and/or core involvement (>50% per core) on repeat systematic biopsies should be reclassified | Weak                        |

CI = cancer involvement; DRE = digital rectal examination; EAU = European Association of Urology; ISUP = International Society of Urological Pathology; mpMRI = multiparametric magnetic resonance imaging; PCa = prostate cancer; PSA = prostate-specific antigen; SR = systematic review.

mpMRI is available, should be monitored closely for adverse features, including presence of intermediate-risk disease; patients with ISUP 2 disease with increased core positivity and/or CI to similar thresholds should be reclassified. Although important, we acknowledge the strength of recommendations as weak, being based on data with low levels of evidence; consequently, these are subject to some uncertainty and must be interpreted accordingly.

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