Platinum Priority – Review – Prostate Cancer

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


* Corresponding author at: Department of Urology, Cancer Center, University Medical Center Utrecht, Utrecht, The Netherlands.
E-mail address: p.m.willems-3@umcutrecht.nl (P.-P.M. Willemsen).

https://doi.org/10.1016/j.eururo.2021.12.007
0302-2838 © 2021 The Authors. Published by Elsevier B.V. on behalf of European Association of Urology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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 NCs. 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-

Table 2 – Summary of thresholds used by studies for inclusion and recruitment.

<table>
<thead>
<tr>
<th>Inclusion criterion</th>
<th>Threshold</th>
<th>No. of protocols using threshold (N; n = 371)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum PSA</td>
<td>≤10 ng/ml</td>
<td>193 (52)</td>
</tr>
<tr>
<td></td>
<td>&lt;20 ng/ml</td>
<td>94 (25)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>13 (3.5)</td>
</tr>
<tr>
<td>NR</td>
<td></td>
<td>71 (19)</td>
</tr>
<tr>
<td>Gleason sum score</td>
<td>≤3 + 3</td>
<td>259 (70)</td>
</tr>
<tr>
<td></td>
<td>&lt;3 + 4</td>
<td>73 (20)</td>
</tr>
<tr>
<td></td>
<td>≤4 + 3</td>
<td>30 (8.1)</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>9 (2.4)</td>
</tr>
<tr>
<td>Clinical T stage</td>
<td>≤T1c</td>
<td>47 (13)</td>
</tr>
<tr>
<td></td>
<td>≤T2a</td>
<td>130 (35)</td>
</tr>
<tr>
<td></td>
<td>≤T2b</td>
<td>57 (15)</td>
</tr>
<tr>
<td></td>
<td>≤T2c</td>
<td>98 (26)</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>39 (11)</td>
</tr>
<tr>
<td>Number of positive</td>
<td>≤2</td>
<td>125 (34)</td>
</tr>
<tr>
<td>cores</td>
<td>≥3</td>
<td>39 (11)</td>
</tr>
<tr>
<td>Cancer involvement</td>
<td>≤30%</td>
<td>24 (6.5)</td>
</tr>
<tr>
<td>per core</td>
<td>≤50%</td>
<td>120 (32)</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>227 (61)</td>
</tr>
<tr>
<td>PSA density</td>
<td>≤0.15 ng/ml^2</td>
<td>42 (11)</td>
</tr>
<tr>
<td></td>
<td>≤0.20 ng/ml^2</td>
<td>55 (15)</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>274 (74)</td>
</tr>
<tr>
<td>D’Amico risk group</td>
<td>Low risk</td>
<td>92 (25)</td>
</tr>
<tr>
<td></td>
<td>Intermediate risk</td>
<td>70 (19)</td>
</tr>
<tr>
<td></td>
<td>High risk</td>
<td>120 (32)</td>
</tr>
<tr>
<td></td>
<td>Missing value</td>
<td>89 (24)</td>
</tr>
<tr>
<td>Use of mpMRI</td>
<td></td>
<td>17 (4.6)</td>
</tr>
</tbody>
</table>

* The total number of studies was 276, with studies having multiple protocols; hence, the total number of protocols included in our SR was 375; 371 protocols reported on thresholds for inclusion and recruitment. Most studies with multiple protocols within the same study had different inclusion criteria.

mpMRI = multiparametric magnetic resonance imaging; NR = not reported; PSA = prostate-specific antigen; SR = systematic review.

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 \( \geq 39.5 \) 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.

---

Table 3 – Summary of thresholds used by studies for monitoring.

| Monitoring criterion | Threshold | No. of protocols using threshold \( (\% ; n = 263) \)
|----------------------|-----------|--------------------------------|
| PSA testing frequency | Every 3–4 mo | 130 \( (50) \)
|                      | Every 6 mo | 88 \( (34) \)
|                      | Every 12 mo | 9 \( (3.4) \)
|                      | NR         | 36 \( (14) \)
| DRE examination frequency | Every 3–4 mo | 42 \( (16) \)
|                      | Every 6 mo | 100 \( (38) \)
|                      | Every 12 mo | 15 \( (5.7) \)
|                      | NR         | 106 \( (40) \)
| Nature of TRUS biopsy | Pre-protocol biopsy (ie, untriggered) | 208 \( (79) \)
|                      | Triggered biopsy | 12 \( (4.6) \)
|                      | Combined untriggered and triggered biopsy | 15 \( (5.7) \)
|                      | NP         | 28 \( (11) \)
| Type of untriggered biopsy | Only confirmatory | 34 \( (13) \)
|                      | Confirmatory and then surveillance biopsies | 189 \( (72) \)
|                      | NP         | 40 \( (15) \)
| Timing of confirmatory biopsy | Within 6 mo | 13 \( (5.0) \)
|                      | At 12 mo | 132 \( (50) \)
|                      | At 18 mo | 23 \( (8.7) \)
|                      | At 24 mo | 40 \( (15) \)
|                      | At 36 mo | 9 \( (3.4) \)
|                      | At 48 mo | 1 \( (0.4) \)
|                      | NP         | 45 \( (17) \)
| Frequency of surveillance biopsies | Every year | 50 \( (19) \)
|                      | Every 1–2 yr | 30 \( (11) \)
|                      | Every 18 mo | 10 \( (3.8) \)
|                      | Every 2 yr | 29 \( (11) \)
|                      | Once after 2 yr | 6 \( (2.3) \)
|                      | Every 3 yr | 10 \( (3.8) \)
|                      | After 4 and 7 yr | 18 \( (6.8) \)
|                      | After 4, 7, and 10 yr | 4 \( (1.5) \)
|                      | Other frequency | 32 \( (12) \)
|                      | NP         | 74 \( (28) \)
| Type of triggered biopsy | MRI triggered | 18 \( (6.8) \)
|                      | PSA density triggered | 3 \( (1.1) \)
|                      | PSA density & MRI | 2 \( (0.8) \)
|                      | Other | 4 \( (1.6) \)
|                      | NP         | 236 \( (90) \)
| Number of cores taken on biopsy | 6–10 | 29 \( (11) \)
|                      | 12 | 28 \( (11) \)
|                      | Other (ie, \(<6 or >12) | 21 \( (8.0) \)
|                      | NR         | 185 \( (70) \)

---

Table 4 – Summary of thresholds used by studies for reclassification.

| Reclassification criterion | Threshold | No. of protocols using threshold \( (\% ; n = 271) \)
|-----------------------------|-----------|--------------------------------|
| Serum PSA                   | \( \geq 10 \) ng/ml | 35 \( (13) \)
|                            | \( \geq 20 \) ng/ml | 9 \( (3.3) \)
|                            | Other | 9 \( (3.3) \)
|                            | NR | 218 \( (80) \)
| Gleason sum score           | \( \geq 3 + 4 \) | 179 \( (66) \)
|                            | \( \geq 4 + 3 \) | 40 \( (15) \)
|                            | \( \geq 4 + 4 \) | 15 \( (5.5) \)
|                            | NR | 37 \( (14) \)
| Clinical T stage            | \( \geq T2a \) | 6 \( (2.2) \)
|                            | \( \geq T2b \) | 24 \( (8.9) \)
|                            | \( \geq T3a \) | 47 \( (17) \)
|                            | Other | 4 \( (1.5) \)
| PSA doubling time           | \( \leq 2 \) yr | 15 \( (5.5) \)
|                            | \( \leq 3 \) yr | 51 \( (19) \)
|                            | Other | 4 \( (1.5) \)
| Number of positive cores    | \( \geq 3 \) | 56 \( (21) \)
| Number of surveillance biopsies | Only confirmatory | 189 \( (72) \)
| Type of untriggered biopsy | Confirmatory and then surveillance biopsies | 189 \( (72) \)
| Timing of confirmatory biopsy | Within 6 mo | 13 \( (5.0) \)
| Frequency of surveillance biopsies | Every year | 50 \( (19) \)
| PSA testing frequency       | Every 3–4 mo | 130 \( (50) \)
| DRE examination frequency   | Every 3–4 mo | 42 \( (16) \)
| Nature of TRUS biopsy       | Pre-protocol biopsy (ie, untriggered) | 208 \( (79) \)
| Nature of TRUS biopsy       | Triggered biopsy | 12 \( (4.6) \)
| Nature of TRUS biopsy       | Combined untriggered and triggered biopsy | 15 \( (5.7) \)
| Type of untriggered biopsy  | Only confirmatory | 34 \( (13) \)
| Type of untriggered biopsy  | Confirmatory and then surveillance biopsies | 189 \( (72) \)
| Timing of confirmatory biopsy | Within 6 mo | 13 \( (5.0) \)
| Frequency of surveillance biopsies | Every year | 50 \( (19) \)
| PSA testing frequency       | Every 3–4 mo | 130 \( (50) \)
| DRE examination frequency   | Every 3–4 mo | 42 \( (16) \)
| Nature of TRUS biopsy       | Pre-protocol biopsy (ie, untriggered) | 208 \( (79) \)
| Nature of TRUS biopsy       | Triggered biopsy | 12 \( (4.6) \)
| Nature of TRUS biopsy       | Combined untriggered and triggered biopsy | 15 \( (5.7) \)
| Type of untriggered biopsy  | Only confirmatory | 34 \( (13) \)

DRE = digital rectal examination; MRI = magnetic resonance imaging; NP = not performed; NR = not reported; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

* The total number of protocols which reported on monitoring thresholds was 263.
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 [13,10,13,14], 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 Klotez et al [11]. Tossoin 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 CI >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 [22] 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.

3.5.2. Implications of study findings for clinical practice and research

Table 5 summarises the additional recommendations on AS derived from our SR. These findings can be compared with those of other studies with similar or overlapping aims. Kinsella et al [30] aimed to report on contemporary worldwide AS practices for PCa and what clinical triggers were important in recommending radical treatment. Only studies with a minimum of 18 mo of follow-up were included (n = 13). The authors found consistency amongst the studies to include patients with only localised low- or intermediate-risk disease. Monitoring protocols reported only on PSA surveillance, DRE, and rebiopsy strategies. Triggers for intervention across studies were inconsistent and not universally applied. Additionally, Bruinsma et al [31] demonstrated that AS protocols varied widely, but stated that the patients most suitable for AS were those with pretreatment cT1c or cT2 tumours, serum PSA levels <10 ng/ml, biopsy ISUP 1, a maximum of two tumour-positive biopsy core samples, and/or a maximum CI of 50% per core. Komisarenko et al [32] systematically summarised the current literature on AS strategies published by international guidelines and major institutions. They found minimal consensus on inclusion criteria, surveillance schedules, and intervention thresholds. Unlike our study, none of those reviews were protocol driven or PRISMA adherent, covering all essential domains, including inclusion/exclusion, monitoring, and reclassification thresholds. Recently, a new randomised trial of AS in PCa (PCASTt/SPCG-17) was designed to evaluate the safety of an MRI-based AS protocol and PSA testing, comparing standardised triggers for repeat biopsy and curative treatment [33], in order to reduce the number of biopsies, improve quality of life, and reduce overtreatment of PCa without compromising oncological outcomes. Basic follow-up consists of biannual PSA testing, annual clinical examination and MRI scan, and quality of life questionnaire every 2nd year. Biopsies are taken only if standardised triggers are reached, including increase in PSA density and MRI progression. Curative intent is recommended only if standardised triggers are reached (ie, MRI progression of lesions with confirmed Gleason pattern 4 and pathological progression). It is worth noting that less invasive and less stringent follow-up protocols such as Protect appear not to disadvantage patients significantly, with cancer-specific mortality of 1% over 10 yr [34].

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-protoctor 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
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.

**Author contributions:** Peter-Paul M. Willemse had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Willemse, MacLennan, Mason, Cornford, Mottet, Lam.

**Acquisition of data:** Willemse, Davis, Grivas, Zattoni, Lardas, Dell’Oglio, Donaldson, Gandaglia, Liew, Pang, Paterson, Yuan.

**Analysis and interpretation of data:** Willemse, Davis, Grivas, Zattoni, Lardas, Lam.

**Drafting of the manuscript:** Willemse, Davis, Grivas, Lam, Mottet, Cornford.

**Critical revision of the manuscript for important intellectual content:** Briers, Cumberbatch, De Santis, Fossati, Gillessen, Grummet, Henry, Moris, O’Hanlon, Omar, Oppera-Lager, Ploussard, Rouvière, Schoots, Tilki, van den Bergh, van den Broeck, van der Kwast, van der Poel, Wiegel, Yuan, Cornford, Mottet, Lam.

**Statistical analysis:** Willemse, MacLennan, Lam.

**Obtaining funding:** None.

**Administrative, technical, or material support:** Willemse, Plass, Yuan.

**Supervision:** Cornford, Mottet, Lam.

**Other:** None.

**Financial disclosures:** Peter-Paul M. Willemse certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Professor Dr. Nicolas Mottet is a company consultant for Janssen, GE, BMS, Sanofi, and Astellas; has received speaker honoraria from Astellas, Pierre Fabre, Steba, Janssen, and Ferring; and has received fellowships and travel grants from Astellas, Ipsen, Sanofi, Janssen, and Roche. Professor Dr. Philip Cornford is a company consultant for Astellas, Ipsen, and Ferring; has received speaker honoraria from Astellas, Ipsen, and Pfizer; has participated in trials run by Ferring; and has received fellowships and travel grants from Astellas and Janssen. Dr. Erik Briers has received grants and research support from Janssen, and Ferring; and has received fellowships and travel grants from Astellas and Janssen. Professor Dr. Philip Cornford is an ex officio board member for Europe UOMO; is an ethics committee and advisory group member for REQUITE; is a patient advisory committee member for PAGMI; is a member of SCA and EMA PCWP. Professor Dr. Maria De Santis is a company consultant for AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Dendreon, Eisai Inc., ESSA, Ferring, GSK, Incyte, Ipsen, Janssen Cilag, Merck, MSD, Novartis, Pfizer, Pierre Fabre Oncologie, Roche, Sanofi Aventis, SeaGen, Shionogi, Syn-
Funding/Sponsor and role of the sponsor: None.

Peer Review Summary

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euro.2021.12.007.

References


[8] Dalziel K, Round A, Stein K, Garside R, Castelnuovo E, Payne L. Do the findings of case series studies vary significantly according to methodological characteristics? Health Technol Assess 2005;9:


[14] Soeretik TFW, van Melick HHE, Dijksman LM, Biesma DH, Witjes JA, Schoots, Dr. Michael Lardas, Mr. Matthew Liew, Dr. Giorgio Gandaglia, Professor Dr. Thomas Van den Broek, Dr. Derya Tilki has received speaker honoraria from Amgen and Novartis; and participates in multiple trials sponsored by different companies. Professor Dr. Jeremy P. Grummet has received a speaker honorarium from Mundipharma, a travel grant from Astellas, and a research grant from Cancer Australia; and is the owner of MBI Pro Pty Ltd., an online training platform. Professor Dr. Ann M. Henry is a company consultant for Nucletron-Elektara; participates in trials by Cancer Research UK and the National Institute of Health Research (UK); has received travel grants from the Medical Research Council, the National Institute of Health Research (UK), and Cancer Research UK; and has received research grants from Cancer Research UK and the Sir John Fisher Foundation. Dr. Thomas B.L. Lam is a company consultant for and has received company speaker honoraria and travel grants from Pfizer, GSK, Astellas, IPSEN, and Consilient Health. Professor Dr. Malcolm D. Mason is a company consultant for Elipsis Pharma and Oncotherics. Professor Dr. Shane O’Hanlon received travel grants from SIOG and ESMO, and research support from Slaintecare. Professor Dr. Guillaume Ploussard is a company consultant for Janssen, Takeda, Ferring, Ipsen, Astellas, and Koeltis; received company speaker honorarium from Janssen, Takeda, Ferring, Ipsen, Astellas, and Bayer; and received research support from Ferring. Professor Dr. Derya Tilki has received speaker honoraria from Astellas and a travel grant from Janssen. Olivier Rouvière received speaker honorarium from EDAP-TMS, travels grants and research support from Philips, and participated in clinical trials by EDAP-TMS and Vermon. Theodoros van der Kwant received research support from Google Inc. Professor Dr. Henk G. van der Poel is a company consultant for Intuitive Surgical; has participated in trials for Astellas and Steba Biotech; and has received grant and research support from Astellas. Professor Dr. Thomas Wiegel is an advisory board member for Ipsen; receives company speaker honoraria from Ipsen and Hexal; is a member of the Janssen Steering Committee; and has participated in the ATLAS/AUO trial. Dr. Thomas Van den Broek, Dr. Ivo G. Schoots, Dr. Michael Lardas, Mr. Matthew Liew, Dr. Giorgio Gandaglia, Dr. Nicola Fossati, Mr. Marcus Cumberbatch, Dr. Roderick C.N. van den Bergh, Dr. D. Oprea-Lager, Dr. Lisa Moris, Dr. Andrea Farolfi, Dr. Peter-Paul M. Willemsen, Dr. Nikos Grivas, Dr. Y. Yuan, Mr. N.F. Davis, Dr. C.C. Paterson, Dr. P. Dell'Oglio, Dr. M.I. Omar, and Dr. S. MacLennan have nothing to disclose.


