Systematic review of active surveillance for clinically localized 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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ABSTRACT

Context: There is uncertainty regarding the most appropriate criteria for recruitment, monitoring and reclassification in active surveillance (AS) protocols for localized prostate cancer (PCa). ***Objective:*** To perform a qualitative systematic review (SR) to issue recommendations regarding inclusion of intermediate-risk disease, biopsy characteristics at inclusion and monitoring, and repeat biopsy strategy. ***Evidence acquisition:*** A protocol-driven, PRISMA-adhering SR incorporating AS protocols published from January 1990 to October 2020 was performed. The main outcomes were criteria for inclusion of intermediate-risk disease, monitoring, reclassification, and repeat biopsy strategies (per-protocol and/or triggered). Clinical effectiveness data were not assessed. ***Evidence synthesis:*** Of 17,011 articles identified, 333 studies incorporating 375 AS protocols, recruiting 264,852 patients were included. Only a minority of protocols included use of MRI for recruitment (n=17), follow-up (n=47) and reclassification (n=26). More than 50% of protocols included patients with intermediate or high-risk disease, whilst 44.1% of protocols excluded low-risk patients with >3 positive cores, and 39% of protocols excluded patients with core involvement (CI) >50%/core. ≥80% of protocols mandated a confirmatory TRUS biopsy. 72% (n=189) of protocols mandated per-protocol repeat biopsies, with 20% performing this annually, and 25% every 2 years. Only 27 protocols (10.3%) mandated triggered biopsies, with 74% of these protocols defining progression or changes on MRI as triggers for repeat biopsy. ***Conclusions:*** For AS protocols in which use of MRI is not mandatory or absent, we recommend the following: (1) AS can be considered in patients with low-volume ISUP 2 (≤3 positive cores and cancer involvement ≤50% CI/core) or another single element of intermediate-risk disease; patients with ISUP 3 should be excluded; (2) Per-protocol confirmatory prostate biopsies should be performed within 2 years, and per-protocol surveillance repeat biopsies should be performed at least once every 3 years for the first 10 years; and (3) For patients with low-volume, low-risk disease at recruitment, if repeat systematic biopsies reveal >3 positive cores or maximum CI>50%/core, they should be monitored closely for evidence of adverse features (e.g. upgrading); patients with ISUP 2 disease with increased core positivity and/or CI to similar thresholds should be reclassified. ***Patient summary:*** We examined the literature to issue new recommendations on active surveillance (AS) for managing localized prostate cancer. The recommendations include setting criteria for including men with more aggressive disease (intermediate-risk disease), thresholds for close monitoring of men with low-risk but more extensive disease, and when to perform repeat biopsies (within 2 years and 3 yearly thereafter).

Key words: Systematic review, active surveillance, localized prostate cancer, consensus statements, criteria for inclusion and eligibility, monitoring and reclassification, positive cores, core involvement, per-protocol or untriggered repeat biopsies, clinical practice guidelines and recommendations.

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1.0 INTRODUCTION

Active surveillance (AS) has proven to be an appropriate alternative to radical treatment options for low-risk prostate cancer (PCa)[1] with equivalent oncological outcomes[2, 3, 4]. Nevertheless, there is significant heterogeneity in terms of AS protocols. To address this, a multi-disciplinary project (DETECTIVE Study)[5] aimed to develop consensus statements and recommendations. It successfully achieved consensus in more than 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 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.

2.0 EVIDENCE ACQUISITION

2.1 Search Strategy and review elements

This protocol has been previously published[6]. The review was performed according to 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: (1) Criteria for inclusion; (2) Thresholds of prostate biopsy characteristics (i.e. core positivity and core involvement [CI]) for inclusion, monitoring and reclassification; and (3) Strategies for repeat biopsy (i.e. per-protocol and/or triggered, and use of TRUS or mpMRI for targeted and/or systematic biopsies). As the aim was to summarize 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 (RoB) assessment

Data extraction and RoB assessment were performed as previously described[6,8,9,10]. Results were summarised qualitatively. Sensitivity and subgroup analyses were planned based on year of publication (2010 onwards), studies recruiting ≥240 patients (median of all included studies),

studies with duration of follow-up ≥39.5 months (median of all included studies), studies with low RoB across all domains, thresholds of core positivity, core involvement and ISUP grade group for inclusion and reclassification.

3.0 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 4 presents the baseline characteristics of all included studies, consisting of 17 RCTs, 27 prospective non-randomised comparative studies (NRCS), 24 retrospective NRCS, 158 prospective non-comparative 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 Risk of bias (RoB) assessment

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

3.4 Summary of results

Table 2 presents a summary of thresholds used across studies for inclusion, monitoring and reclassification.

3.4.1 Inclusion and exclusion criteria

≥50% of protocols included patients with intermediate-risk disease, based on 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 >3 positive cores, and 39% excluded patients with core involvement (CI) of >50%/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. 85% of protocols (n=233) mandated a confirmatory untriggered TRUS biopsy, with 55% of protocols performing this within 1 year and 24% within 2 years. 72% of protocols (n=189) mandated per-protocol surveillance repeat biopsies after the confirmatory biopsy, with 50 performing the repeat biopsies annually, 69 performing this within every 2 years and 70 protocols had other biopsy frequencies. Only 27 protocols (10%) performed triggered biopsies; triggered only in 4.6%, and combined with per-protocol in 5.7%. 74% of triggered biopsy protocols were only based on MRI progression or changes. For protocols using MRI-based triggers of repeat biopsies (n=20), 50% of them 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 which 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 ≥3 positive cores, 33 studies (24%) defined a cut-off of ≥4 positive cores, and 47 studies (35%) used other cut-off values. Changes in serum PSA and PSA doubling 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%) only.

3.4.4 Sensitivity and subgroup analyses

Sensitivity analyses based on studies recruiting from 2010 onwards (n=50), studies recruiting more than 240 patients (n=156), studies with duration of follow-up ≥39.5 months (n=120) and studies with low RoB across all domains (n=34), and 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.

4.0 Discussion

4.1 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.

4.1.1 Should intermediate-risk localized disease be considered for AS?

Since >50% of AS studies have included patients with intermediate-risk localized disease, we believe 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].

4.1.2 What is the maximum biopsy tumour extent appropriate for inclusion into AS?

202 AS protocols (67%) used histological biopsy core information as a threshold for inclusion. Biopsy tumour extent expressed as number of positive cores, proportion of positive cores or maximum cancer CI are a strong predictor of grade reclassification[1,10,13,14,15], adverse pathological outcomes[14,16], biochemical progression[14], and biochemical recurrence following delayed radical treatment [10]. In our SR, 164 protocols (44%) used a maximum threshold of 3

positive cores as an inclusion criteria; another 144 protocols (39%) used a maximum threshold of CI>50% as an inclusion criterion. Consequently, we conclude that the most suitable maximum thresholds for inclusion in systematically obtained biopsies are either 3 positive cores or 50% cancer involvement per core of ISUP 1 prostate cancer; 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 (>3 positive cores) and/or cancer involvement (>50%CI/per core) should be excluded.

4.1.3 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 more than half of included studies (55%) performed confirmatory biopsy within one year of starting AS, and 79% performed it within 2 years. The purpose of initial repeat biopsy is to account for understaging and undersampling at diagnosis especially in the absence of mpMRI[17,18,19], 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 in the first 2 years[20]. With the introduction of new and more accurate diagnostic modalities like 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[21,22]. Consequently, we recommend per-protocol confirmatory biopsies within 2 years 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 prostate cancer progression during AS[23] showed significant heterogeneity on MRI progression between included studies, and the pooled measured PPV and NPV 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, more than 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 years throughout the duration of AS. We therefore recommend per-protocol surveillance repeat biopsies at least every three years for the first 10 years, if mpMRI is not available.

4.1.4 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 67% of included studies used ISUP 2 or 3 on repeat systematic biopsies as a reclassification criterion. 21% and 12% of protocols used ≥3 positive cores and ≥4 positive cores as a reclassification criterion, respectively. 27.3% of protocols defined CI>50% as a reclassification criterion. Results from the PRIAS study showed that 17% of patients had an increase in tumour volume, with increasing number of baseline positive cores being an independent predictor (OR 2.2; 95%CI 1.67-2.81; p<0.001) for reclassification[12] on multivariate analysis. Similar results have been shown from Klotz et al [10]. Tosoian et al. have also shown that number and percentages of positive cores are predictors of pathologic upgrading[24]. The appropriate thresholds to guide management however remain unclear, while several retrospective studies provide compelling evidence. Truong et al. analysed clinical and pathological variables and built a nomogram for recruiting patients with low-risk disease into an AS protocol[13]. The authors found that 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 RP on multivariate analysis. Other studies showed a higher number of positive cores (>3) was associated with higher rates of progression to treatment[25], whilst a lower number of cores at diagnostic biopsy showed significant association with reduced need for active treatment[26]. An increase in the percentage of CI in low-risk PCa significantly increases the progression rate (adjusted HR 1.6; 95% CI 1.2-2.4; p=0.02) for CI >38% during a median follow-up of 2.2 years[27]. Half of men with CI >25% were reclassified within 2 years. 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[28]. The percentage of core positivity has been also associated with pathology progression[29,30].

In summary, there is sufficient evidence indicating 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 >3 positive cores or CI>50% per core obtained via repeat systematic biopsy (i.e. when no MRI-targeted biopsies have been performed) for low-risk disease from a previously low core positivity and/or low CI at diagnosis, should be used as 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 mpMRIs does not reduce the importance of clinical and pathologic 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 core involvement 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 remains unclear.

4.2 Implications of study findings on clinical practice and research

Table 3 summarises the additional recommendations on AS derived from our SR. These findings can be compared with other studies with similar or overlapping aims. Kinsella et al. aimed to report on contemporary worldwide AS practices for PCa and what clinical triggers were important in recommending radical treatment[31]. Only studies with a minimum of 18 months follow-up were included (n=13). The authors found consistency amongst the studies to include only patients with localized low-risk or intermediate-risk disease. Monitoring protocols reported only on PSA surveillance, DRE and re-biopsy strategies. Triggers for intervention across studies were inconsistent and not universally applied. Additionally, Bruinsma et al.

demonstrated that AS protocols varied widely, but stated that the most suitable patients for AS were those with pre-treatment 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 core involvement of 50% per core[32]. Komisarenko et al. systematically summarized the current literature on AS strategies published by international guidelines and major institutions[33]. They found minimal consensus on inclusion criteria, surveillance schedules and intervention thresholds. Unlike our study, none of those reviews were protocol-driven nor PRISMA-adherent covering all essential domains, including inclusion/exclusion, monitoring and reclassification thresholds. Recently, a new randomised trial of AS in prostate cancer (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[34], 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 second year. Biopsies are only taken if standardised triggers are reached, including increase in PSA density and MRI progression. Curative intent is only recommended if standardised triggers are reached (i.e. 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 years[35].

4.3 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 the recommendations from this study are based on low levels of evidence, being derived from a qualitative SR which 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 review when higher levels of evidence emerge.

5.0 Conclusions

Based on our SR, we are able to formulate the following recommendations for AS protocols in which 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), but only if strict monitoring is followed due to the higher risk of progression; (2) At recruitment, patients with low-risk but more extensive disease extent based on systematic biopsies, defined as >3 positive cores or maximum CI>50% per core should be monitored closely, whereas patients with ISUP 2 but similarly high core positivity and/or core involvement should be excluded; (3) Per-protocol confirmatory prostate biopsies should be performed within 2 years, and per-protocol surveillance repeat biopsies should be performed at least once every 3 years for the first 10 years; and (4) Patients with low-volume, low-risk disease at recruitment in whom repeat systematic biopsies have revealed an increase in core positivity to >3 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 core involvement 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 they are subject to some uncertainty and must be interpreted accordingly.

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