REVIEW PAPER

UROLOGICAL ONCOLOGY

Reclassification of prostate cancer on first confirmatory prostate biopsy in men under active surveillance: A systematic review and meta-analysis

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Introduction Prostate cancer is typically diagnosed following prostate biopsy. In low-risk and selected favourable intermediate-risk disease, active surveillance is the treatment strategy of choice. In these men, a confirmatory biopsy performed. We report on the rates of risk upgrading at biopsy confirmatory that may represent a need to pursue further treatment in lieu of active surveillance.

Material and methods We performed a systematic review and meta-analysis of pooled reclassification rates of men on active surveillance at first confirmatory biopsy, in line with PRISMA recommendations. PubMed, EMBASE, and Cochrane central registry for clinical trials were searched until June 2024. Stata was used to pool reclassification rates at first confirmatory biopsy.

Results Seventeen studies from 9 countries comprising 6,039 patients were included. Transrectal biopsy was the most common biopsy method for confirmatory biopsy. Weighted pooled rates of upgrading on first confirmatory biopsy were 20% with a 95% confidence interval of 19–21%.

Conclusions Approximately 20% of men undergoing active surveillance were upgraded at confirmatory biopsy. This may alter the management of these patients, and it highlights the importance of a confirmatory biopsy.

Key Words: prostate cancer ‹› prostate biopsy ‹› active surveillance ‹› Gleason score

INTRODUCTION

Prostate cancer (PC) is the most commonly diagnosed cancer in men and is the sixth most common cause of cancer mortality. It has been reported that 359,000 men died as a result of PC in 2018 [1]. Worldwide PC diagnoses are expected to increase from 1.5 million to 2.9 million per year by 2040 [2].

A relevant clinical history, an abnormal digital rectal examination (DRE), or elevated prostate-specific antigen (PSA) levels may raise clinical suspicion of PC. Multiparametric magnetic resonance imaging (MRI) of the prostate is commonly used to further stratify patients who warrant a biopsy. If MRI is not available, nomogram based risk calculators can be used to

help select patients who require further stratification [3]. Pre-biopsy MRI increases the likelihood of diagnosing significant PC and decreases the likelihood of diagnosing clinically insignificant PC [4, 5]. It has also been shown to be beneficial prior to performing a confirmatory biopsy in MRI-naïve patients [6, 7].

The adoption of active surveillance (AS) aims to identify patients who can avoid or defer intervention and reduce the risk of overtreatment in men with low-risk or favourable intermediate-risk disease [8]. It consists of monitoring patients at pre-determined timepoints with a combination of clinical examination, PSA testing, MRI, and biopsy. Curative treatment may be prompted if there is an indication of clinical progression [3].

Men deemed appropriate for AS will typically undergo a confirmatory biopsy at a per protocol determined timepoint to reduce the risk of missing clinically significant disease [9]. Despite being recommended by the EAU, AUA, and NICE, there is no clear consensus on inclusion criteria or follow-up protocol for patients undergoing AS with discrepancies between guidelines [10–12].

Patients selected for AS typically undergo confirmatory prostate biopsies within 18 months of initial diagnosis. This is to evaluate the appropriateness of AS and the potential need for intervention. The purpose of this review is to summarise the findings of repeat/confirmatory biopsies reported in the literature, with particular attention to a change in Gleason score/ISUP grade. We aim to evaluate the rate of disease reclassification at confirmatory biopsy and review it's role in PC surveillance.

MATERIAL AND METHODS

Registration and search strategy

Our search was conducted in line with the most recent Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) recommendations [13]. The study was registered on PROSPERO under CRD42024551202. An electronic search was conducted of the PubMed, EMBASE, and Cochrane Central Register of Controlled Trials databases utilising the search algorithms provided below. The search was completed on June 5, 2024: ("gleason score" OR "gleason grade") AND (change OR increase OR decrease OR reclassification) AND ("active surveillance") AND ("repeat biopsy" OR "confirmatory biopsy" OR "confirm* biopsy" OR "rebiopsy" OR "re biopsy" OR "re-biopsy" OR "subsequent biopsy").

A complete breakdown of the analysed studies can be viewed in the PRISMA diagram (Figure 1). The bibliographies of included publications were also searched for any relevant studies.

Inclusion criteria

- Reports the rates of upgrade on confirmatory biopsy in men undergoing AS for PC.
- English language or translation available.
- Prospective studies or prospectively maintained database studies.
- Full text available.
- Studies reporting upgrading based on pathological diagnosis and not radiology were included.
- Must include Gleason score as a criterion for reclassification.

Exclusion criteria

- Studies that utilised datasets of patients from studies previously included were excluded so as not to include the same data twice.
- Case reports, conference abstracts, retrospective studies.
- Not fulfilling inclusion criteria.
- MRI or PSA prompt to re-biopsy outside of a predefined confirmatory biopsy timepoint.
- If histopathological reclassification figures were not available.
- Not first confirmatory biopsy.
- Studies examining the effect of a medication on PC progression were excluded.
- Studies reporting targeted confirmatory biopsy only based on PIRADs score >3 or excluding some cohort of patients to be generalisable to patients in a non-targeted cohort.

Identification of studies and outcomes of interest

Studies that satisfied the inclusion and exclusion criteria were included. The following PICO elements were used as the basis for selecting studies [14]:

- Population: Patients under AS for PC.
- Intervention: Confirmatory prostate biopsy.
- Comparison: PC grade post confirmatory biopsy versus original diagnostic grade.
- Outcome: Rates of grade upgrading on reclassification post confirmatory biopsy.

Studies were independently reviewed by three separate authors (BMC, KD, HT) using Rayyan [15]. If there was any disagreement between authors, an alternative author (GC) was used to mediate the discussion, and consensus was reached.

The primary outcome of interest was the rate of Gleason score reclassifications post first confirmatory prostate biopsy.

Secondary outcomes of interest were biopsy method, targeted or systematic biopsy, primary and confirmatory biopsy Gleason score/histology, and confirmatory biopsy timing.

Data extraction

Study demographics and biopsy variables of interest were transcribed using Google Sheets (Mountain View, California, United States). Five independent authors (WQ, AD, BMC, AOM, RMC) were involved in the data extraction due to the large number of studies included.

Study selection

Prospective studies including randomised trials were included in this systematic review and meta-analysis. Both the rates and definition of reclassification were used as the primary criterion for inclusion, and the rates provided the metric of interest in our meta-analysis. Secondary outcomes of interest as reported above were included in our systematic review, as were study demographics.

Risk of bias assessment

Assessment of potential biases for non-randomised studies was assessed using a modified Newcastle-Ottawa scale risk of bias tool [16], with the results tabulated in Suppl. Table 1. This assessment tool grades each study as being "satisfactory" or "unsatisfactory" across various categories. We assigned stars to evaluate study quality: 7 stars – "very good", 5–6 stars "good", 3–4 stars "satisfactory", and 0–2 stars "unsatisfactory". The critical appraisal was completed by 2 reviewers independently (EC and AOM), where once again a third reviewer (HCT) was asked to arbitrate in cases of discrepancies in opinion.

Statistical analysis

We performed a proportional meta-analysis as part of this review [17]. Statistical analysis was run using Stata 17 (StataCorp., 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC). Proportions were pooled using the "metaprop" function within Stata [18]. 95% confidence intervals were employed, and $p \leq 0.05$ was considered statistically significant. Heterogeneity was reported using I^2 [18]. It has been put forward that I^2 values of 25%, 50%, and 75% can be used to assess the degree of heterogeneity [19]. We considered there to be a notable degree of heterogeneity if I^2 was greater than 50%. A random effects model was used due to evidence of significant statistical heterogeneity as well as evidence of study design heterogeneity [20]. Qualitative bias assessment was conducted as proposed by Barker et al. [17] because this was a proportional meta-analysis.

RESULTS

Study and patient demographics

Included studies and patient characteristics are outlined in Table 1. Overall, 783 studies were identified in the database search. After 129 duplicates and non-English texts were removed, 654 articles remained. Titles, abstracts, and full texts were then reviewed, and 637 were excluded. Exclusion criteria are summarised in the PRISMA flow diagram (Figure 1).
In total, data was collected from 17 studies (n = 6,039) for the systematic review [21–37]. The mean age of patients at initial diagnosis was 65 years.

Confirmatory biopsy disease reclassification rate

Biopsy and reclassification details are presented in Table 2. Twelve studies detailed the original biopsy type used, with 10 studies utilising TRUS-guided biopsy [21–27, 29, 35, 36], one study utilising TP bi-

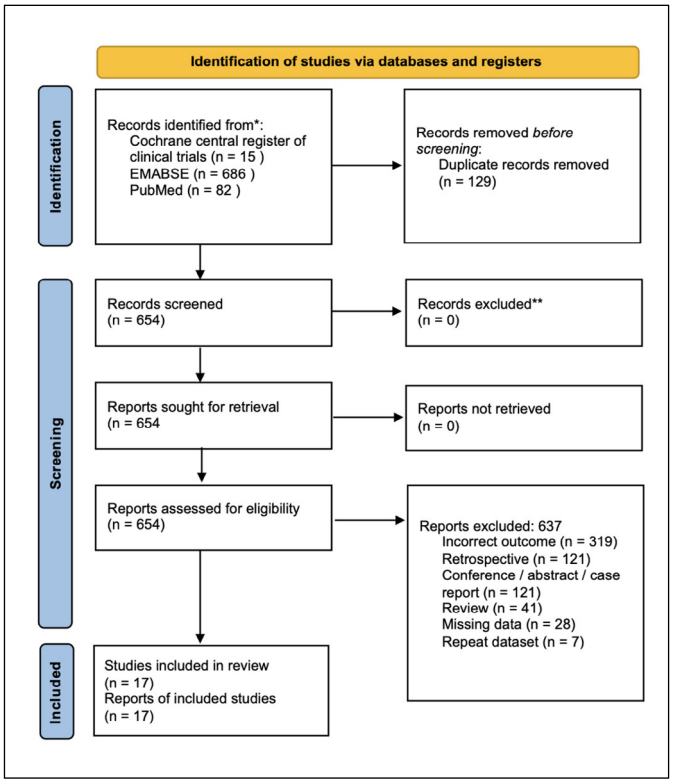


Figure 1. *PRISMA Flowchart.*

opsy [30], and one study utilising TRUS and TP biopsies [37]. Choo et al. [36] also included TURP samples. Five studies did not outline the biopsy method [28, 31–34].

For confirmatory biopsy, 7 studies utilised transrectal biopsy alone [21–23, 25, 26, 29, 36] and 3 utilised TP biopsy alone [24, 27, 30]. One study utilised both TRUS and TP biopsy [37]. One study used a combination of systematic TRUS and MRI assisted targeted biopsy [35]. The 5 remaining studies did not outline the method of confirmatory biopsy [28, 31–34].

Five studies specifically reported patients undergoing MRI pre biopsy, as seen in Table 2 [26, 27, 29, 30, 32].

The primary outcome examined was disease reclassification after confirmatory biopsy. Disease reclassification included cases of upgrade or downgrade. Studies differed in their definition of upgrade; with Kato et al. [37] we used Gleason upgrade alone due to lack of data granularity.

Confirmatory biopsies were performed at various time intervals across the included studies, ranging from 4 to 24 months. From the 6039 patient cases included across all studies, 1454 patients (24.1%) had diagnosis reclassification based on their initial confirmatory biopsy. When examining the rate of upgrading, a total of 1,115 patients had an upgrade after confirmatory biopsy. The pooled rate of upgrade at confirmatory biopsy was 20% (95% CI: 19–21%). The Forest plot displaying this pooled reclassification rate is demonstrated in Figure 2.

Gleason score change was then analysed based on the score itself and not the overall rate of change. Of note, in the study by Venkitaraman et al. [21] and Barnett et al. [33], grouped Gleason scores into categories of no cancer, 6 or less, 3 + 4, 4 + 3, 4 + 4 or greater, and as such the 6 or less group were included in the 3 + 3 forest plot, and the 4 + 4 or greater were included in the 4 + 4 forest plot. Choo et al. [36] and Voss et al. [27] reported Gleason 7 changes and did not report 3 + 4 or 4 + 3 individually. This study was excluded from the meta-analysis regarding Gleason 7 changes as seen in Suppl. Figures 1 and 2 [27, 36]. Because data were included in the 4 + 4 cohort as 4 + 4 or greater, Voss et al.'s [27] patients who were Gleason 9 or 10 were also included in this plot. Pessoa et al. [35] also grouped patients into 4 + 4 or greater.

Overall, there was no cancer observed in 32% (95% CI: 30–34%) of patients who were enrolled in AS, as observed in Figure 3. At confirmatory biopsy, 44% (95% CI: 42–46%) were found to have Gleason 3 + 3 disease (Figure 4). Suppl. Figure 1 shows Gleason 3 + 4 rates of 6% (95% CI: 5–7%) at confirmatory biopsy. Suppl. Figure 2 shows Gleason 4 + 3 rates of 3% (95% CI: 2–3%) at confirmatory biopsy, and Suppl. Figure 3 shows rates of change on confirmatory biopsy of Gleason 4 + 4 or higher of 2% (95% CI: 1–2%). These are the pooled proportions of all studies that reported Gleason score on confirmatory biopsy. It does not imply that all these results were upgrades,

Table 1. *Study demographics*

Study	Journal	Country	Study type	Number of patients	Age
Venkitaraman et al. 2007 [21]	The Journal of Urology	UK	Prospective	119	66 (median)
Choo et al. 2007 [36]	The Prostate	Canada	Prospective	105	70 (median)
Porten et al. 2011 [22]	Journal of Clinical Oncology	USA	Prospective	377	61 (mean)
Whitson et al. 2011 [23]	The Journal of Urology	USA	Prospective	241	61 (mean)
Ayres et al. 2012 [24]	BJU International	Denmark	Prospective	95	68 (median)
Selkirk et al. 2015 [25]	Urology	USA	Prospective	200	66 ±6.9
Pessoa et al. 2017 [35]	BJU International	Brazil	Prospective	105	65 ±24
Elkjaer et al. 2018 [26]	Scandinavian Journal of Urology	Denmark	Prospective	50	65.6 ±5.3
Voss et al. 2018 [27]	BJU International	UK	Prospective	208	63.5 (mean)
Kearns et al. 2018 [28]	European Urology	USA	Prospective	657	63 (median)
Kortenbach et al. 2021 [29]	Scandinavian Journal of Urology	Denmark	Prospective	127	65 (mean)
Kato et al. 2021 [37]	Prostate Cancer and Prostatic Diseases	Japan	Prospective	135	68 (median)
Pepe et al. 2024 [30]	In vivo	Italy	Prospective	30	63 (median)
Bul et al. 2013 [31]	European Urology	Netherlands	Prospective	1,480	65.8 (median)
Jung et al. 2023 [32]	The World Journal of Men's Health	Korea	Prospective	148	68.7 (mean)
Barnett et al. 2018 [33]	Cancer	USA	Prospective	1,370	66 (mean)
Jain et al. 2015 [34]	The Journal of Urology	Canada	Prospective	592	66 ±13

Table 2. *Biopsy details and upgrading rates.*

Study	Original biopsy type	MRI?	Targeted or systematic	Original Gleason score/Benign	Timing of confirmatory biopsy	Confirmatory biopsy mode	Targeted or systematic	Reclassified Gleason score/Benign	Number upgraded	Definition of upgrade utilised
Venkitaraman et al. 2007 [21]	TRUS	No	–	GS ≤6: 104 (87%), GS 3 + 4: 15 (13%)	18–24 months	TRUS	–	No cancer: 25 (21%), GS 3 or less + 3: 68 (57.1%), GS 3 + 4: 18 (15.1%), GS 4 + 3: 6 (5%), GS 4 or greater + 4: 2 (1.7%)	33 (28%) upgraded	Increase in Gleason score, Increase in number of involved cores
Choo et al. 2007 [36]	98 TRUS, 7 TURP	No	–	Gx: 1 (1%), GS 4: 2 (1.9%), GS 5: 14 (13.3%), GS 6: 67 (63.8%), GS 7: 21 (20%)	12–18 months	TRUS		No cancer: 27 (25.7%), GS 5: 4 (3.8%), GS 6: 29 (27.6%), GS 7: 37 (35.2%), GS 8: 8 (7.6%)	37 (35%) upgraded, 34 (32%) downgraded, 33 (31%) unchanged	Increase in Gleason Score only
Porten et al. 2011 [22]	TRUS	No	–	GS 2-6: 356 (94%), GS 7 (3 + 4): 17 (5%), GS 7 (4 + 3): 3 (1%), GS 8-10: 1 (<1%)	12–24 months	TRUS	–	–	81 (21%) upgraded	Increase in Gleason Score only
Whitson et al. 2011 [23]	TRUS	No	–	–	10 months (median)	TRUS	–	–	55 (23%) upgraded	Increase in Gleason Score, Increase In number of involved cores and % core involvement
Ayres et al. 2012 [24]	TRUS	No	Systematic	GS 3 + 3: 101	12 months	TP	Systematic	GS 3 + 4: 20%, GS 4 + 3: 4%, GS >7: 2%, increase vol: 5%, stable 3 + 3: 51%, No cancer: 18%	29 (31%) upgraded	Increase in Gleason score and Increased % core involvement
Selkirk et al. 2015 [25]	TRUS	No		GS ≤6: 200	6 months	TRUS	–	3 + 3 31 (48.4%) 3 + 4 19 (29.7%) 4 + 3 8 (12.5%) 4 + 4 4 (6.3%) Unknown 2 (3.1%)	64 (32%) upgraded	Increase in Gleason Score, Increase In number of involved cores and increased % core involvement
Pessoa et al. 2017 [35]	TRUS	MRI before confirmatory biopsy.	Systematic	GS ≤6: 105	4 to 6 months	Combination of systematic TRUS and MRI assisted targeted biopsy	Both	Gleason 3 + 4 34 (32.38%) Gleason 4 + 3 11 (10.47%) Gleason ≥8 2	58 (total) (55%) upgraded	Increase in Gleason Score, Increase In number of involved cores and increased % core involvement
Elkjaer et al. 2018 [26]	TRUS	MRI at baseline and pre confirmatory biopsy	Systematic	GS ≤6: 25	12 months	TRUS		GS 6 = 20, GS 7 = GS 8 =1	7 (total) (14%) upgraded	Increase in Gleason Score, Increase In number of involved cores
Voss et al. 2018 [27]	TRUS	MRI before confirmatory biopsy	Systematic	GS 3 + 3 (196) GS 3 + 4 (12)	9.9 months	TP	Systematic	Benign = 23 GS 6 = 99 GS 7 = 77 GS 8 = 6 GS 9 = 3	83 (39.9%) upgraded	Increase in Gleason Score, does not state if other metrics used or not.

Table 2. *Continued*

Study	Original biopsy type	MRI?	Targeted or systematic	Original Gleason score/Benign	Timing of confirmatory biopsy	Confirmatory biopsy mode	Targeted or systematic	Reclassified Gleason score/Benign	Number upgraded	Definition of upgrade utilised
Kearns et al. 2018 [28]	–	Variable – data not given	–	GS 3 + 4: 657	11.58 ±4.4 months 1st biopsy	–	–	–	165 (25%) at 1 year	Increase in Gleason score and Increased % core involvement
Kortenbach et al. 2021 [29]	TRUS	50% of patients had a pre initial biopsy MRI	Systematic	–	12 months	TRUS	50% targeted, 50% non-targeted	–	7 (6%) upgraded (targeted) 25 (20%) non targeted and no pre MRI	Increase in Gleason Score Only
Kato et al. 2021 [37]	TP and TRUS	Variable – data not given.	–	G3 + 2 = 1 (0.7%), 3 + 3 = 129 (95.6%), 3 + 4 = 5 (3.7%)	12 months	Both	–	3 + 2 = 0 (0%), 3 + 3 96 (97%), 3 + 4 3(3%)	30 Gleason only (83.3% of reclassified) upgraded	Increase in Gleason Score Only
Pepe et al. 2024 [30]	TP	All men pre confirmatory biopsy	Targeted	G3 + 4: 30	12 months	TP	Targeted	4 + 3 3	3 (10%) upgraded	Gleason Score, Increase In number of involved cores and increased % core involvement
Bul et al. 2013 [31]	–	No	–	–	12 months	Systematic (volume based)	-	-	415 (28%) upgraded – 89 demonstrated GS upgrading, 212 reclassified based on # of positive cores, 114 combination of both	Increase in Gleason Score, Increase In number of involved cores
Jung et al. 2023 [32]	–	96% of patients had MRI with 33% of these being pre initial biopsy and 66% post initial biopsy	–	G3 + 3 = 268 (94.4%), G3 + 4 = 16 (5.6%)	9.5 months mean	–	–	Upgrading of ISUP grade 20 (13.5%), but GG not specified	41 upgraded	Increased % positive cores or ISUP grade
Barnett et al. 2018 [33]	–	No	–	GS ≤6: 1488 (99.7%), NA: 5 (0.3%)	13 months (mean)	–	–	No cancer: 568 (41.5%), GS ≤6: 670 (48.9%), GS 7: (3 + 4) 78 (5.7%), GS 7: (4 + 3): 30 (2.2%), GS ≥8: 18 (1.3%), NA: 6 (0.4%)	126 (9.2%) upgraded	Increase in Gleason Score only
Jain et al. 2015 [34]	–	No	–	–	16 months (median)	–	–	–	136 upgraded (22.9%), 242 (40.8%) no change, 19 downgrade (3.2%), 198 (33.3%) negative	Increase in Gleason Score only

TRUS – transrectal ultrasound; TP – transperineal; TURP – transurethral resection of the prostate; GS – Gleason score

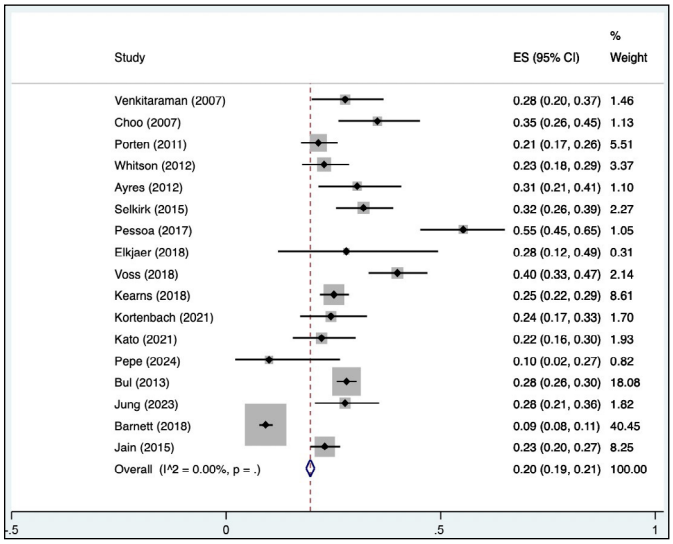


Figure 2. *Pooled rates of prostate cancer upgrade at confirmatory biopsy.*

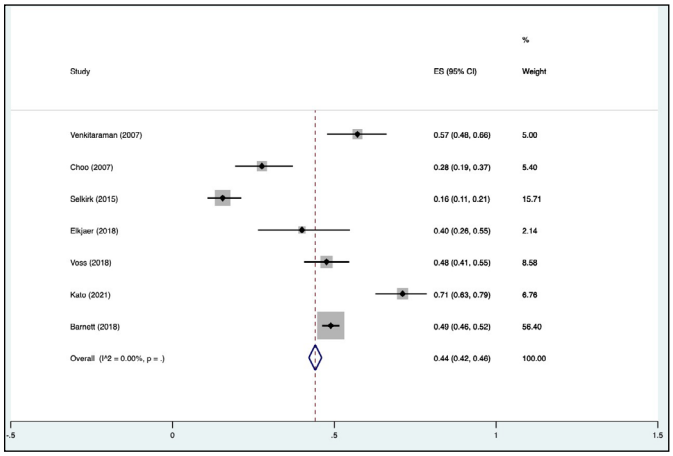


Figure 3. *Proportion of no cancer at confirmatory biopsy.*

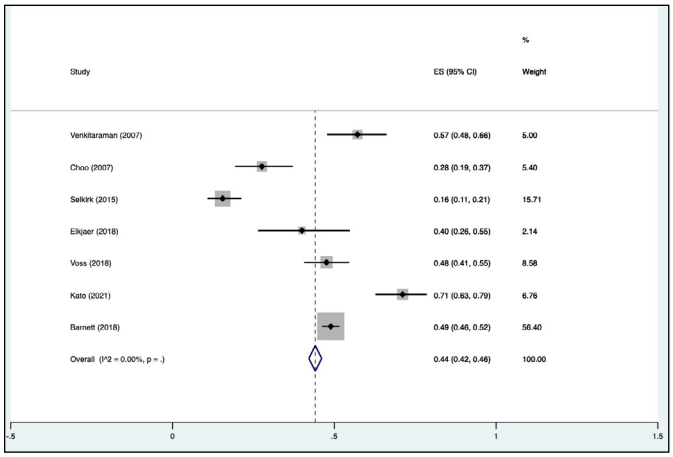


Figure 4. *Proportion of Gleason 3 + 3 at confirmatory biopsy.*

and of course, because no cancer was found in some samples, some were downgrades.

Risk of bias assessment

Fourteen studies received a score of 9 [21–34], while 2 received an 8 [35, 36] and one a 7 [37].

DISCUSSION

In this systematic review and meta-analysis, we have synthesised evidence in relation to AS of PC and the rate of reclassification at confirmatory biopsy. We report on the pooled rate of upgrade reclassification at first confirmatory biopsy.

Our calculated rate of 20% is in line with other previous individual studies on the topic, which interestingly found that the timing of first confirmatory biopsy did not influence the rates of upgrading observed [38]. Furthermore, immediate repeat biopsy has shown similar rates of upgrading [39]. This may imply that the sampling as well as disease progression may account for disease reclassification typically associated with repeat biopsies. This may alter our approach and care when taking initial prostate biopsies. Overall, we observed a considerable amount of initial confirmatory re-biopsy to be clinically insignificant. While this study does not take into account disease volume, 32% of repeat biopsies were observed to show no cancer and 44% were Gleason 3 + 3 disease or less. Of course, Gleason 7 and above disease was picked up on confirmatory biopsy, which may have ultimately prompted further management. Also, some patients with Gleason 3 + 3 disease on initial confirmatory biopsy may have ultimately opted for further management if they had a higher volume disease.

We observed that just one study, by Pepe et al. [30], included only transperineal prostate biopsy. All other studies either did not report on the biopsy type used or used TRUS. One study reported using a mix of TRUS and TP [37].

One such way to ensure adequate sampling is perhaps to employ a targeted as well as a systematic approach [40]. The use of targeted biopsy alone has also been seen to eliminate the risk of finding clinically insignificant disease, which must be weighed against the risk of undersampling [41]. A previous meta-analysis has demonstrated the value of prebiopsy MRI in improving diagnostic accuracy [42]. Previous studies have suggested that MRI use may defer the need for confirmatory biopsy [43]; however, our results, including some studies from the MRI era, indicate that there is still utility in confirmatory biopsy demonstrated by the significant rate of PC

reclassification [44]. We acknowledge that this was not the main aim of this study, however, we excluded studies with targets solely on MRI prior to confirmatory biopsy. This was done to examine the rate of upgrade in our patient cohorts in which they may or may not have had an MRI, or there was no target on MRI, for example in a PIRADS 2 MRI with a PSA density >0.2. There is a paucity of data detailing if the biopsies were targeted or systematic; however, Kortenbach et al. [45] reported an upgrade rate of 6% for targeted and 20% for systematic. This may support the use of targeted biopsy alone in low-risk men as per the latest EAU guidelines; however, with the significant upgrade rate we report it also supports the use of systematic biopsy prior to very low-risk disease being included in AS protocols.

With the advent of improved diagnostic techniques, including pre-biopsy MRI and trans-perineal biopsy, the role of routine confirmatory biopsy has been brought into question [46].

There remains a significant rate (20%) of Gleason score reclassification at confirmatory biopsy. This suggests that undersampling remains a consideration even with modern diagnostic techniques; however, this should again be taken with the consideration that not all upgrades prompt treatment. The EAU defines confirmatory biopsy as taking place usually between 6 and 12 months post initial diagnosis, suggesting that if an MRI-targeted and systematic biopsy is performed, then a confirmatory biopsy can be omitted; however, they state that should a confirmatory biopsy be performed, then it should be MRI targeted and systematic [45].

There is significant heterogeneity regarding active surveillance protocols. Mean first confirmatory biopsy times of 6 months have been described in the literature [47]. However, as can be observed from our results, a wide range of timelines are followed in practice. Included in this review are studies from Europe, North America, South America, and Asia, and as such, a broad timing of biopsy protocols may be expected. Taking this into account, these figures should represent global practise.

Further implications are the impact of subsequent benign or unchanged biopsy results, which identify patients with an excellent prognosis [48]. The extra prognostic information provided by confirmatory biopsy must be weighed against the risk of complications of a biopsy and use of resources. Additionally, some men opt for radical treatment without evidence of progression, which illustrates the mental toll AS may have on some men [49].

This meta-analysis demonstrates a significant rate of reclassification to a higher Gleason score. While this may not necessitate treatment, histological grade is one of the mainstays of prognostication, and therefore accuracy is paramount. While this study is important and novel, several limitations are present. There is significant heterogeneity between studies in relation to the use of MRI, biopsy technique, and timing of confirmatory biopsy. These data also include significant data weighting towards the Johns Hopkin's data set, which included favourable-risk PC and older men with low-risk disease [33]. Percentage core volume involvement and core involvement amongst other metrics would be used in conjunction with a Gleason score upgrade in clinical practice, and as such some of these figures do not represent an entire decision-making tool, but they do represent a possible illustration of the usefulness of confirmatory biopsy. Porten et al. [22] also included a Gleason 8 or above disease cohort, illustrating the patient selection heterogeneity.

Based on this review, we conclude that confirmatory biopsy plays an important role in patients managed with AS who do not undergo pre-biopsy MRI or, who have no target on MRI and undergo systematic biopsy. This may represent patients with no lesion on 2 MRI with a high PSA density, for example. This is also in agreement with current EAU guidelines for low-risk men who undergo targeted and perilesional biopsy alone, i.e. that they require a repeat systematic biopsy prior to being enrolled in AS. This data change to "supports this" recommendation because the risk of upgrading may be as high as 20%; however, a limitation of this data is that targeted cohorts are lacking. The role of MRI to replace confirmatory biopsy remains unproven but warrants further evaluation. Further studies may be prudent to evaluate the effect of per protocol vs for cause biopsy in confirmatory biopsy, as well as the impact of initial MRI and biopsy targeting status on reclassification rates, which may inform further EAU guidelines.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

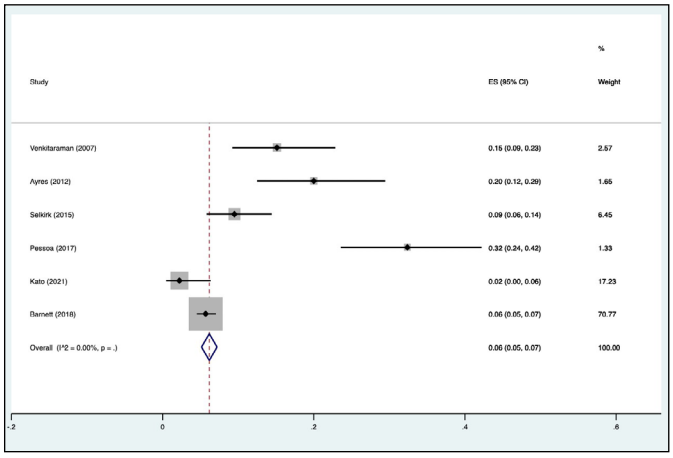
FUNDING

This research received no external funding.

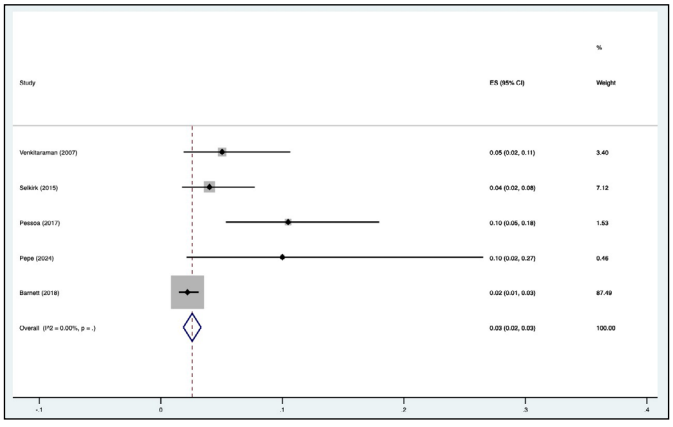
ETHICS APPROVAL STATEMENT

The ethical approval was not required.

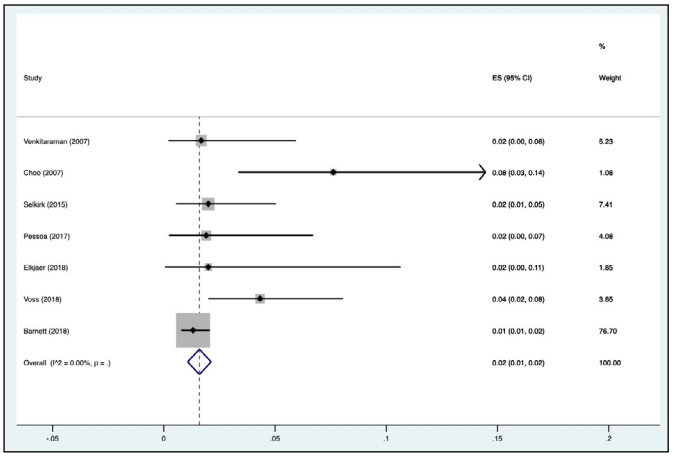
SUPPLEMENTARY MATERIALS



Suppl. Figure 1. *Proportion of Gleason 3 + 4 change at confirmatory biopsy.*



Suppl. Figure 2. *Proportion of Gleason 4 + 3 change at first confirmatory biopsy.*



Suppl. Figure 3. *Proportion of Gleason 4 + 4 or greater change at first confirmatory biopsy.*

Suppl. Table 1. *Risk of bias assessment*

Author	Selection				Comparability of cohorts on the basis of the design or analysis		Outcome			Total score
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that this outcome was not present at the start	Main factor	Additional factor	Assessment of outcome	Sufficient follow-up time for outcomes to occur (≥6 months)	Adequacy of follow-up	
Venkitaraman et al. 2007 [21]	*	*	*	*	*	*	*	*	*	9
Choo et al. 2007 [36]	*	*	*	*	*	*	*	*	/	8
Porten et al. 2011 [22]	*	*	*	*	*	*	*	*	*	9
Whitson et al. 2011 [23]	*	*	*	*	*	*	*	*	*	9
Ayres et al. 2012 [24]	*	*	*	*	*	*	*	*	*	9
Selkirk et al. 2015 [25]	*	*	*	*	*	*	*	*	*	9
Pessoa et al. 2017 [35]	*	*	*	*	*	*	*	*	/	8
Elkjaer et al. 2018 [26]	*	*	*	*	*	*	*	*	*	9
Voss et al. 2018 [27]	*	*	*	*	*	*	*	*	*	9
Kearns et al. 2018 [28]	*	*	*	*	*	*	*	*	*	9
Kortenbach et al. 2021 [29]	*	*	*	*	*	*	*	*	*	9
Kato et al. 2021 [37]	*	*	*	*	*	/	*	*	/	7
Pepe et al. 2024 [30]	*	*	*	*	*	*	*	*	*	9
Bul et al. 2013 [31]	*	*	*	*	*	*	*	*	*	9
Jung et al. 2023 [32]	*	*	*	*	*	*	*	*	*	9
Barnett et al. 2018 [33]	*	*	*	*	*	*	*	*	*	9
Jain et al. 2015 [34]	*	*	*	*	*	*	*	*	*	9

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