Is magnetic resonance imaging-targeted biopsy a useful addition to systematic confirmatory biopsy in men on active surveillance for low-risk prostate cancer? A systematic review and meta-analysis

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⭐ 1 BJUI Systematic Review Quality Score (based on AMSTAR-2)

Objective

To systematically review and meta-analyse evidence regarding the additional value of magnetic resonance imaging (MRI) and MRI-targeted biopsies to confirmatory systematic biopsies in identifying high-grade prostate cancer in men with low-risk disease on transrectal ultrasonography (TRUS) biopsy, as active surveillance (AS) of prostate cancer is recommended for men with Gleason 3 + 3 on standard TRUS-guided biopsy. Confirmatory assessment can include repeat standard TRUS-guided biopsy, and/or MRI with targeted biopsy when indicated.

Methods

A systematic review of the Embase, Medline, Web-of-science, Google scholar, and Cochrane library was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Identified reports were critically appraised according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 criteria. Studies reporting men with Gleason 3 + 3 prostate cancer who had chosen AS based on transrectal systematic biopsy findings and had undergone MRI with systematic ± targeted biopsy at confirmatory assessment were included. The primary outcome was detection of any Gleason pattern ≥4.

Results

Included reports (six) of men on AS (n = 1 159) showed cancer upgrading (Gleason ≥3 + 4) in 27% (95% confidence interval [CI] 22–34%) using a combined approach of MRI-targeted biopsies and confirmatory systematic biopsies. MRI-targeted biopsies alone would have missed cancer upgrading in 10% (95% CI 8–14%) and standard biopsies alone would have missed cancer upgrading in 7% (95% CI 5–10%). No pathway was more favourable than the other (relative risk [RR] 0.92, 95% CI 0.79–1.06). In all, 35% (95% CI 27–43%) of men with a positive MRI were upgraded, compared to 12% (95% CI 8–18%) of men with a negative MRI being upgraded (RR 2.77, 95% CI 1.76–4.38).

Conclusions

A pre-biopsy MRI should be performed before confirmatory systematic TRUS-guided biopsies in men on AS, together with MRI-targeted biopsies when indicated. A combined approach maximises cancer detection, although other factors within multivariate risk prediction can be used to aid the decision to biopsy in these men.

Keywords

active surveillance, biopsy, magnetic resonance imaging, diagnostic test accuracy, meta-analysis, #PCSM, #ProstateCancer

Introduction

Active surveillance (AS) for men with prostate cancer involves avoidance or postponement of radical treatment combined with continued surveillance, whereas definitive treatment is proposed only if disease progression is likely or if the patient chooses. AS is the recommended option for the initial management of most men with localised and low-burden disease of low- to intermediate-risk prostate cancer according to some guidelines [1,2], although the entry criteria

of AS varies both by country and between different centres [3]. Patients with true low-risk disease are likely to benefit from AS having 10- and 15-year cancer-specific survival rates of 98% and 94% [4], respectively, without the complications or side-effects from definitive treatment. Current strategies of AS are safe for the large majority of patients, but improvements regarding patient selection, monitoring, reducing unnecessary prostate biopsies, and improving quality of life of men on AS should be pursued.

Under-grading of prostate cancer in men with low-risk disease at initial biopsy is widely recognised, and confirmatory biopsies are advocated within the first year of diagnosis. Unfortunately, the sensitivity of standard TRUS-guided biopsy is known to be low, especially in the case of anterior tumours or large prostates [5,6]. Biopsies directed to MRI lesions can detect aggressive prostate cancer more reliably than standard TRUS-guided biopsies [7]. Whilst targeted biopsy clearly identifies significant cancer that is missed by concurrent systematic biopsy in men under consideration for AS, there is persistent concern about missed significant cancer on targeted biopsies alone [8]. Thus, performing concurrent systematic and targeted biopsy has been advised for optimal risk stratification in this population [9–11]. However, the additional value of MRI pathway (including targeted biopsies), and to what extent this MRI pathway misses high-grade prostate cancers has not been systematically reviewed.

In the present review, we systematically assess the evidence for the use of MRI and targeted biopsy in addition to systematic sampling at confirmatory biopsy in men with low-risk prostate cancer, who had Gleason score 3 + 3 at initial biopsy.

Patients and Methods
Objective

We aimed to systematically evaluate the additional value of MRI and targeted biopsies to standard TRUS-guided sampling at confirmatory biopsy, for the detection of Gleason ≥3 + 4 prostate cancer in men on AS for Gleason 3 + 3 disease.

Search Strategy

The search strategy is provided as Supporting Information; in summary, for each database the search terms used were ('prostate cancer') AND ('magnetic resonance imaging') AND ('active surveillance'), with a number of alternatives for each search term. A critical review of the Embase, Medline (OvidSP), Web-of-science, Google Scholar, and Cochrane library was performed. The search was updated to 30 March 2017.

Inclusion and Exclusion Criteria

Included studies focus on men on AS, with low-risk prostate cancer (Gleason score 3 + 3) based on the findings of standard TRUS-guided biopsies, and now scheduled for confirmatory (first re-biopsy) assessment with standard TRUS-guided biopsy and first pre-biopsy MRI, varying from 6 to 24 months after the initial biopsy. According to international consensus [12], interval confirmatory prostate biopsy is the one that is intended to check the absence of clinically significant prostate cancer or the progression of initially diagnosed clinically insignificant disease. It could also sample previously under-sampled areas.

We selected only studies providing individual patient data and applying a sequential sampling design of the two biopsy tests (direct comparison), MRI targeted and systematic sampling TRUS-guided biopsies, in the same man, according to the Standards of Reporting for MRI-targeted Biopsy Studies (START) criteria [13]. We included only those studies where the TRUS-guided biopsy results of men with negative (first pre-biopsy) MRIs were reported.

A positive (first pre-biopsy) MRI was determined by the identification of a suspicious lesion for prostate cancer on the prostate MRI scan. A suspicious lesion was defined as ≥3 on a 5-point scale (Likert or Prostate Imaging Reporting and Data System [PI-RADS]), from 1 (no suspicion) to 5 (high suspicion) according to the likelihood of significant prostate cancer being present.

The MRI-targeted biopsy was defined as any TRUS-guided biopsy technique where an MRI scan was used to determine the location of a suspicious target before biopsy. All transrectal approaches (visual registered (cognitive) fusion, software registered MRI-ultrasonography fusion, or 'in-bore' targeted biopsies) were included. Transperineal approaches were excluded, as they tend to be associated with a higher sampling density than transrectal approaches.

Studies on MRI and AS were excluded if MRI had previously been used (initial biopsies or previous negative biopsies) [8,14–17], if data on negative prostate MRI was excluded [18], if Gleason score 3 + 4 at initial TRUS biopsy was also included in the AS cohort [19], if sampled lesions with suspicion score of '2' on MRI could not be excluded from the results [20], when MRI suspicion scores (Likert or PI-RADS) were dichotomised as positive to a score ≥4 instead of a score ≥3 [20,21], if template biopsies (>20 cores) was used as the reference test [22,23], if data extraction to 2 × 2 contingency tables was not possible [10,20,24–27], if a transperineal biopsy approach [22], or unclear definition of index test was used [28]. We excluded double publications [29,30]. We excluded unpublished data or abstracts because

information to correctly assess study quality and results was not available.

Data Collection and Data Extraction

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [31] process for reporting included and excluded studies was followed, with the recommended flowchart showing the numbers of papers at each stage (Fig. 1). Titles and abstracts were reviewed for relevance to the defined review question. If it was not clear from the abstract whether the paper might contain relevant data, the full paper was assessed. The references cited in all full-text articles were also assessed for additional relevant articles. The search was carried out by two independent reviewers (I.S. and F.G.) at two separate institutions.

Data regarding study methodology, patient population, conduct of MRI, conduct of biopsy, and outcomes were extracted. Outcome data on detected prostate cancer by MRI with/without MRI-targeted biopsies and TRUS-guided biopsies were extracted in 3×2 contingency tables, according to the START criteria [13]. Histology outcome of sampled MRI-targeted areas and TRUS-guided biopsies were analysed at a per-patient (i.e. per-gland) level.

Assessment of Publication Bias and Study Quality

To study the presence of publication bias the log-transformed values of the relative sensitivity were plotted against the associated standard errors for graphical (funnel plot) inspection (Fig. S1). Funnel plots are presented for the analysis of all MRI (Fig. S1a) and for the analysis of positive MRI only (Fig. S1b). Identified reports were reviewed according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 criteria (Fig. S2) [32].

Fig. 1 PRISMA flow diagram showing the outcome of the searches resulting in the full studies included in the review.
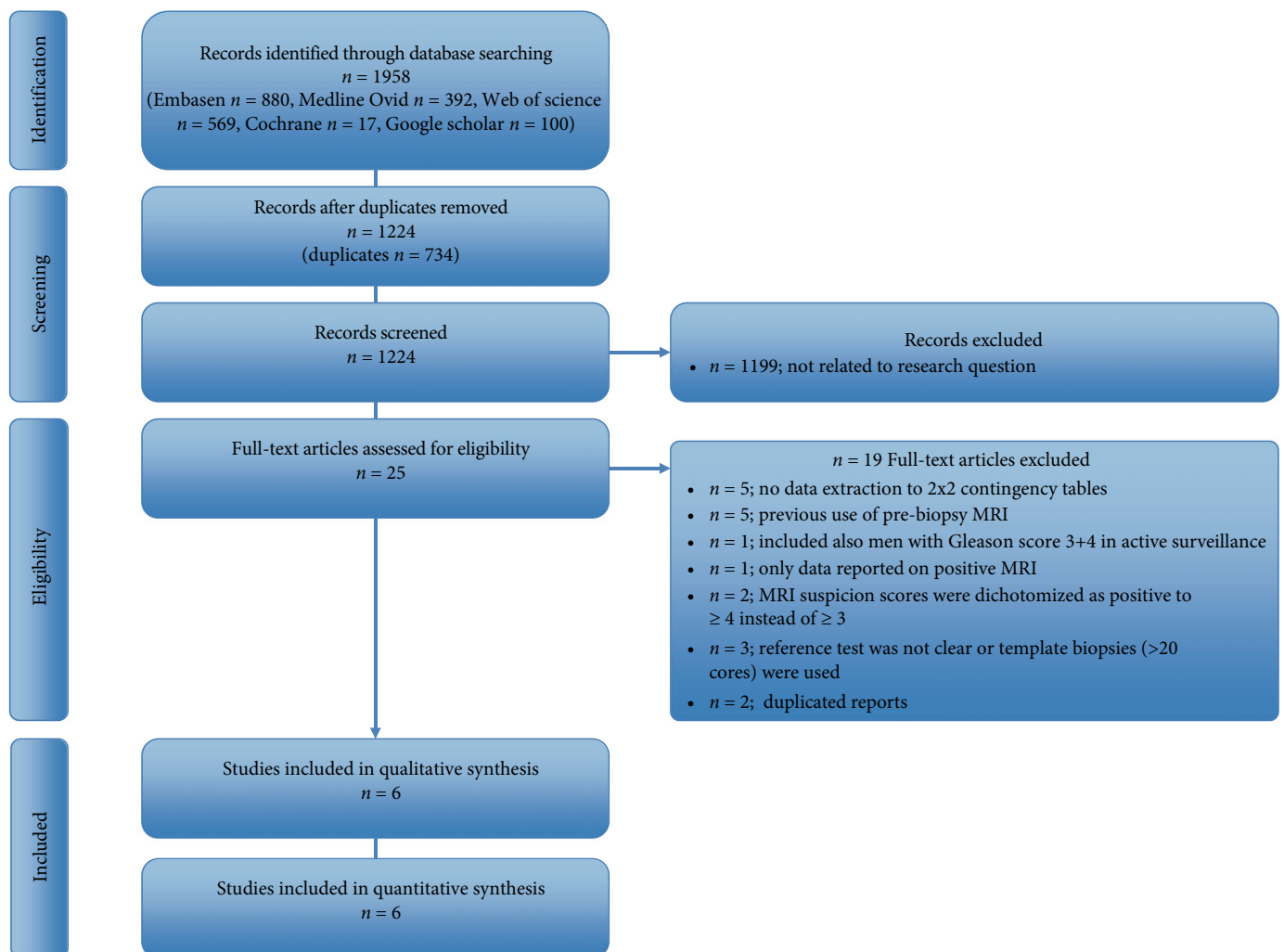
Table 1 Summary data table of included studies.

Reference	Year	Recruitment AS criteria	Patient population No. of patients	MRI Definition MRI positive	Biopsy Navigational system for TBx	Biopsy Comparator TRUS-Bx	Pathology Definition upgrading
Da Rosa et al. [33]	2015	Gleason score ≤6	72	Likert 3–5	MRI/US fusion	12-core	Gleason score ≥3 + 4
Walton Diaz et al. [34]	2015	≤cT1c PSAD ≤0.15 ng/mL/mL Gleason score ≤6 ≤2 positive cores <50% cancer core length	152	Moderate, high (3–5)	MRI/US fusion	12-core	Gleason score ≥3 + 4
Filson et al. [35]	2016	≤cT1c PSA level <10 ng/mL Gleason score ≤6	390	Likert 3–5	MRI/US fusion	≥10-core	Gleason score ≥3 + 4
Recabal et al. [9]	2016	Gleason score ≤6	208	Likert 3–5	MRI/US and cognitive fusion	14-core	Gleason score ≥3 + 4
Alberts et al. [37]	2017	≤cT2a PSA level ≤10 ng/mL Gleason score ≤6	56	PI-RADS 3–5	MRI/US fusion	8/12-core	Gleason score ≥3 + 4
Ma et al. [36]	2017	≤cT2a PSA level ≤10 ng/mL Gleason score ≤6	284	PI-RADS 3–5	MRI/US fusion	12-core	Gleason score ≥3 + 4

TBx, targeted biopsy; TRUS-Bx, TRUS-guided biopsy.

Data Syntheses and Analysis

For prostate cancer diagnosis there is not a perfect reference ('gold standard') test. Most published studies define standard TRUS-biopsies as a reference test, although investigators acknowledge that standard TRUS-biopsies can underestimate the burden of disease.

To synthesise the results, we performed a random-effects meta-analysis on proportional and relative risk (RR) analysis of MRI and targeted biopsies, and TRUS-guided biopsies. Heterogeneity was assessed using the chi-squared statistic and the I^2 statistic. A continuity correction was applied where necessary. All statistical analyses were performed using R version 3.4.3 using the 'metafor' package (R Foundation for Statistical Computing, Vienna, Austria).

Results

Six studies were eligible for inclusion in this review [9,33–37]. Table 1 shows summary data of each study on methodology, patient population, conduct of MRI, biopsy, and pathology. Comprehensive data is presented in a Table S1.

Prostate Cancer Upgrading at Confirmatory Biopsies

This review comprised a total of 1 159 men with low-risk prostate cancer on AS, 70% (95% CI 62–76%) having a positive pre-biopsy MRI. Pooled data showed 27% (95% CI 22–34%) cancer upgrading (from Gleason 3 + 3 to ≥3 + 4) with the combined approach of MRI-targeted biopsies and systematic biopsies (Table 2). In men with a positive MRI, 35% (95% CI 27–43%) of men were upgraded, compared to 12% (95% CI 8–18%) of men with a negative MRI being upgraded (Table 3). The RR was 2.77 (95% CI 1.76–4.38; Fig. 2), favouring a positive MRI over a negative MRI for cancer upgrading in men on AS.

Prostate Cancer Upgrading Using the Individual MRI or TRUS Biopsy Pathway

(Denominator = All 1 159 men who underwent confirmatory biopsies)

The combined biopsy approach of MRI-targeted and systematic TRUS-guided biopsies resulted in 27% (95% CI 22–34%) cancer upgrading. The individual pathway of MRI and MRI-targeted biopsy showed cancer upgrading in 17% (95% CI 10–26%), whilst the individual pathway of TRUS-guided biopsies showed cancer upgrading in 20% (95% CI 16–25%) (Table 2 and Fig. 3a). The RR of identifying cancer upgrading in men on AS at confirmatory biopsies, according to the MRI vs TRUS pathway, was 0.92 (95% CI 0.79–1.06), without favouring either biopsy pathway (Table 4). Both biopsy pathways were complementary to each other; some upgraded cancers were detected by both biopsy approaches; however, still a considerable proportion of upgraded cancers were only detected by either MRI and MRI-targeted biopsy or TRUS-guided biopsies (see below).

Additional Value of MRI-Targeted Biopsies to Systematic TRUS Biopsy

(Denominator = All 1 159 men who underwent confirmatory biopsies)
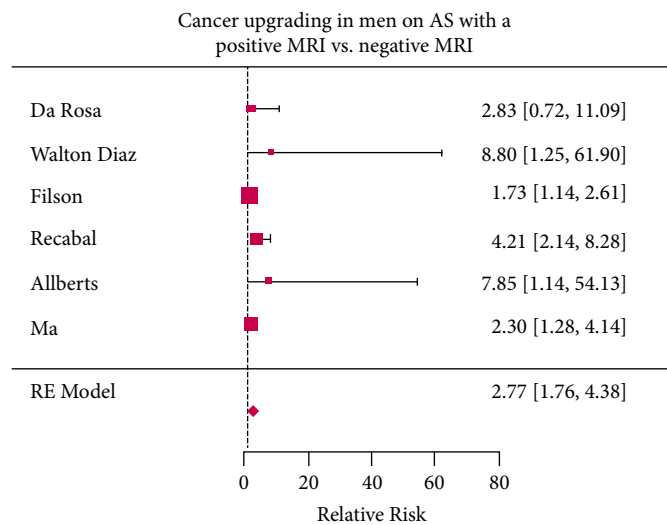
MRI-targeted biopsies identified an additional 7% (95% CI 5–10%) of men who were upgraded, in addition to the 20% (95% CI 16–25%) identified by TRUS-guided biopsies only (Table 2). Vice versa, TRUS-guided biopsies identified an additional 10% (95% CI 8–14%) of men who were upgraded, in addition to the 17% (95% CI 10–26%) identified by MRI-targeted biopsies only (Table 2 and Fig. 3a).

Relative Additional Value of MRI-Targeted Biopsies to Systematic TRUS Biopsy

(Denominator = All 317 men who were upgraded at confirmatory biopsies)

Starting from all men who were identified with cancer upgrading, we may better understand the relationship between each diagnostic pathway by using the 'relative' additional value. MRI-targeted biopsies identified an additional 25% (95% CI 20–31%) cancer upgrading (Fig. 4), in addition to the 75% identified by TRUS-guided biopsies only. Vice versa, TRUS-guided biopsies identified an additional 36% (95% CI 20–56%) cancer upgrading, in addition to the 64% identified by MRI-targeted biopsies only. This 36% additional cancer upgrading resulted from men with a negative MRI (40%), but also from men with a positive MRI (60%) without cancer upgrading on targeted biopsies.

Fig. 2 Forest plot analyses of the RR of cancer upgrading in men on AS at confirmatory biopsies with a positive MRI vs a negative MRI, showing an almost three-times increase (RR 2.77, 95% CI 1.76–4.38).

Cancer upgrading in men on AS with a positive MRI vs. negative MRI

	Relative Risk
Da Rosa	2.83 [0.72, 11.09]
Walton Diaz	8.80 [1.25, 61.90]
Filson	1.73 [1.14, 2.61]
Recabal	4.21 [2.14, 8.28]
Allberts	7.85 [1.14, 54.13]
Ma	2.30 [1.28, 4.14]
RE Model	2.77 [1.76, 4.38]

Prostate Cancer Upgrading at Confirmatory Biopsies in Men with a Positive MRI Only

The idea of avoiding further biopsy when the MRI is negative is an attractive one. Consequently, data of men with only a positive MRI would preferably be analysed separately. This review comprised a total of 792 men with low-risk prostate cancer and a positive MRI. In men with a positive MRI, the overall cancer upgrading was 35% (95% CI 27–43%) (Table 3 and Fig. 3b), compared to 27% (95% CI 22–34%) cancer upgrading in the group as a whole (Table 2 and Fig. 3a).

Table 2 Results of included studies according to prostate cancer upgrading in men on AS at confirmatory biopsies: the combined and the individual biopsy approaches of MRI-targeted biopsies and TRUS-guided biopsies, and additionally the 'added value' of each pathway.

Upgrading (Gleason score ≥3 + 4)			All (positive and negative) MRIs			
			Combined pathways		Individual pathways	
			Upgrading by MRI-TBx and TRUS-Bx pathways		Upgrading by MRI-TBx pathway	
Reference	Year	No. of patients (denominator)	No. of patients (numerator)	Proportion (95% CI)	No. of patients (numerator)	Proportion (95% CI)
Da Rosa et al. [33]	2015	72	19	0.26 (0.18–0.38)	17	0.24 (0.15–0.35)
Walton Diaz et al. [34]	2015	152	34	0.22 (0.16–0.30)	24	0.16 (0.11–0.22)
Filson et al. [35]	2016	389	123	0.32 (0.27–0.36)	67	0.17 (0.14–0.21)
Recabal et al. [9]	2016	206	72	0.35 (0.29–0.42)	47	0.23 (0.18–0.29)
Alberts et al. [37]	2017	56	19	0.34 (0.23–0.47)	15	0.27 (0.17–0.40)
Ma et al. [36]	2017	284	50	0.18 (0.14–0.22)	13	0.05 (0.03–0.08)
Pooled data		1 159	317	0.27 (0.22–0.34)	183	0.17 (0.10–0.26)

MRI-TBx, MRI-guided targeted biopsy; TRUS-Bx, TRUS-guided biopsy.

Prostate Cancer Upgrading Using the Individual MRI or TRUS Biopsy Pathway

(Denominator = All 792 men with a positive MRI and confirmatory biopsies)

In men with a positive MRI, targeted biopsy alone identified cancer upgrading in 24% (95% CI 16–35%), whilst TRUS-guided biopsies alone also identified cancer upgrading in 24% (95% CI 19–31%) (Table 3 and Fig. 3b). The RR of cancer upgrading in men with a positive MRI, according to the MRI vs TRUS pathway, was 0.98 (95% CI 0.87–1.09), without favouring either biopsy pathway (Table 4).

Additional Value of MRI-Targeted Biopsies to Systematic TRUS Biopsy

(Denominator = All 792 men with a positive MRI and confirmatory biopsies)

MRI-targeted biopsies identified an additional 10% (95% CI 8–13%) cancer upgrading, in addition to the 24% (95% CI 19–31%) identified by TRUS-guided biopsies only (Table 3 and Fig. 3b). Vice versa, TRUS-guided biopsies identified an additional 11% (95% CI 10–15%) of cancer upgrading, in addition to the 24% (95% CI 16–35%) identified by MRI-targeted biopsies only.

Prostate Cancer Upgrading in Different Biopsy Strategies (Benefit and Harms)

Table 5 shows eight different biopsy strategies, each with its potential proportion of missing cancer upgrading (harms) in relation to the benefits of reducing the number of biopsies. Furthermore, a one-step (combined MRI-targeted and TRUS-guided prostate biopsies) and a two-step biopsy approach were analysed. A two-step biopsy approach was defined as the performance of MRI-targeted or systematic TRUS-guided biopsies subsequently to the other, depending on the results of the first.

From these data, without missing any cancer upgrading, the one-step approach would save a second biopsy session in three in four men. Alternatively, an MRI-driven two-step approach of: (i) MRI-targeted biopsies, and (ii) additional TRUS-guided biopsies in those men without upgrading, would result in reducing one in four TRUS-guided biopsies. However, the 'harm' would be having two biopsy sessions in three in four men. A TRUS-driven two-step approach of: (i) TRUS-guided biopsies in all men, and (ii) only additional MRI-targeted biopsies in men without upgrading, would result in reducing about one in five MRIs and one in six MRI-targeted biopsies. The 'harm' would be having two biopsy sessions in almost four in five men.

The decision regarding which biopsy strategy is performed in daily practice depends on several factors. Most importantly, the risk of missing intermediate- or high-grade cancer must be balanced against saving biopsies and reducing harm on an individual basis. As MRI is nowadays more regularly performed upfront in primary diagnosis, the discussion during AS of which biopsy protocol is optimal will be less relevant.

Study Quality

All individual studies followed the START criteria of the Prostate [13]. Identified studies were reviewed according to the QUADAS-2 criteria [32]. We conclude that the overall methodological quality of the included studies was fair to good (Fig. S2). A detailed description and analysis is presented as a supplement (Table S2). Publication bias was assessed with funnel plot analysis (Fig. S1). We found

| Upgrading by TRUS-Bx pathway | | Added value of Individual pathways to another | | | |
| | | Added value of MRI-TBx to TRUS-Bx pathway | | Added value of TRUS-Bx to MRI-TBx pathway | |
No. of patients (numerator)	Proportion (95% CI)	No. of patients (numerator)	Proportion (95% CI)	No. of patients (numerator)	Proportion (95% CI)
12	0.17 (0.10–0.27)	7	0.10 (0.05–0.19)	2	0.03 (0.01–0.10)
22	0.14 (0.10–0.21)	12	0.08 (0.05–0.13)	10	0.07 (0.04–0.12)
92	0.24 (0.20–0.28)	31	0.08 (0.06–0.11)	56	0.14 (0.11–0.18)
57	0.28 (0.22–0.34)	15	0.07 (0.04–0.12)	25	0.12 (0.08–0.17)
14	0.25 (0.15–0.38)	5	0.09 (0.04–0.20)	4	0.07 (0.03–0.18)
43	0.15 (0.11–0.20)	7	0.02 (0.01–0.05)	37	0.13 (0.10–0.17)
240	0.20 (0.16–0.25)	77	0.07 (0.05–0.10)	134	0.10 (0.08–0.14)

Fig. 3 Cancer upgrading to Gleason score ≥3 + 4 in men on AS (with Gleason score 3 + 3) undergoing systematic TRUS-guided biopsy (TURS-Bx) and MRI-guided targeted biopsy (MRI-TBx); if the pre-biopsy MRI is positive: (**A**) cancer upgrading in all men, irrespective of whether the MRI was positive or negative, and (**B**) cancer upgrading in only those men with a positive MRI.
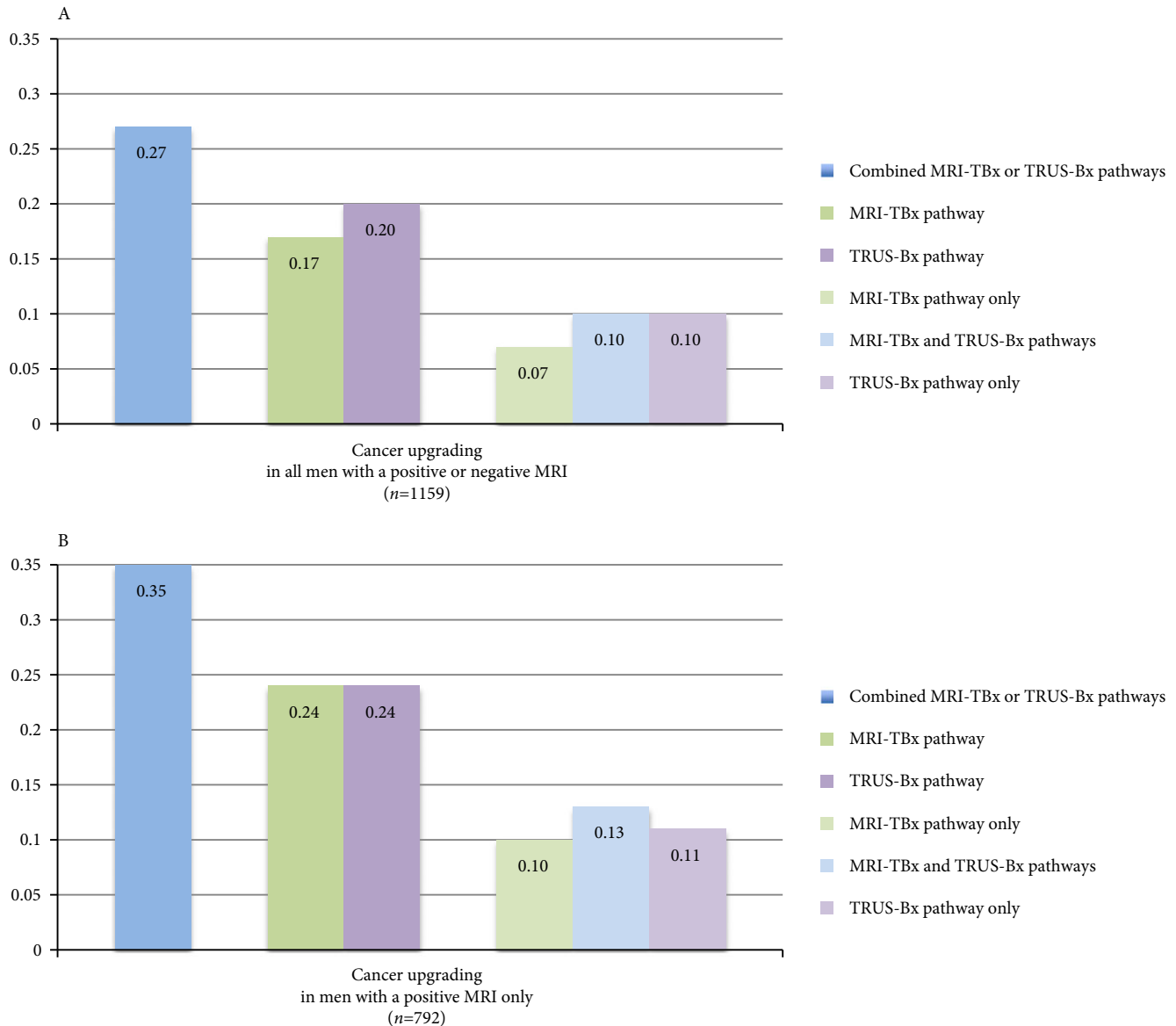
no strong evidence for publication bias by graphical inspection.

Discussion

Summary of Findings and Clinical Implications

Should We Incorporate MRI at Confirmatory Biopsy?

In men with low-risk prostate cancer on AS, based on Gleason 3 + 3 at TRUS-guided biopsy findings, MRI and MRI-targeted biopsies identified an absolute additional 7% of prostate cancer upgrading (≥3 + 4) to TRUS-guided biopsy only. Therefore, a pre-biopsy MRI should be performed before confirmatory biopsy, together with MRI-targeted biopsies in addition to systematic TRUS-guided biopsies.

Could We Reduce TRUS-Guided Biopsy at Confirmatory Biopsy?

Conversely reasoned, TRUS-guided biopsies identified an absolute additional 10% of cancer upgrading to MRI-targeted biopsies only. Furthermore, the RR of cancer upgrading in men on AS at confirmatory biopsies was 0.92, showing no superior results from one biopsy pathway over the other. Both pathways appear to be complementary to

each other, both missing a significant proportion of cancer upgrading, and therefore in general we tentatively recommend performing both diagnostic tests at confirmatory biopsies.

Could we Reduce TRUS-Guided Confirmatory Biopsy in Men with a Negative MRI?

If future management may focus on reducing the number of biopsies in AS, men with a negative MRI may not be biopsied anymore. In the present analysis, 30% of these low-risk men on AS had a negative MRI, which may show the potential reduction in TRUS-guided biopsies. However, it must be noted that on the basis of these series, still one in eight (12%) men with a negative MRI showed cancer upgrading, identified by TRUS-guided biopsies. Unfortunately, we were not able to further discriminate cancer upgrading in intermediate- or high-risk prostate cancer. Intermediate-risk or even high-risk prostate cancer may also qualify for AS according to some guidelines [12]. Furthermore, for some men with a negative MRI, omitting TRUS-guided biopsies would be acceptable considering the harms and benefits; for other men this would be unacceptable. This may argue for a multivariate risk-based approach comprehending and objectively weighing all relevant factors [11,38].

Could We Reduce TRUS-Guided Confirmatory Biopsy in Men with a Positive MRI?

In this analysis, 70% of these low-risk men on AS had a positive MRI, which may show the potential reduction in the number of TRUS-guided biopsies. However, based on these series, still additionally one in nine (11%) men with a positive MRI showed cancer upgrading by TRUS-guided biopsies only (Fig. 3b). Again, this further supports a multivariate risk-based approach weighing all relevant factors, not compromising the identification of all high-grade prostate cancers [11,38].

Do we need MRI–Targeted Biopsy in Men with a Positive MRI, or will Standard TRUS-Guided Biopsy be Sufficient?

MRI-targeted biopsies identified absolute cancer upgrading in one in 10 (10%) men with a positive MRI, in addition to TRUS-guided biopsies, which identified cancer upgrading in one in four (24%). Abovementioned arguments for reducing TRUS-guided biopsies in men with a positive MRI would also apply for omitting MRI-targeted biopsy in these men. The RR of cancer upgrading in men on AS at confirmatory biopsies was 0.98, without favouring any biopsy pathway. Both missed a significant proportion of cancer upgrading. Without the knowledge of which prostate cancers (low intermediate-, high intermediate-, or high-risk) will be missed by omitting either

biopsy test, we recommend performing both tests at confirmatory biopsies.

How Should we Biopsy Men at Confirmatory Biopsies: A One-Step or a Two-Step Strategy?

Local preferences, expertise, and capacity may play a role in the performance of a one-step or a two-step biopsy strategy. Based on the outcome of cancer upgrading (Table 5), neither strategy would be favoured over the other. In a two-step approach the total amount of biopsy core samples would be reduced; however, three in four men would still need a second biopsy session. Based on this argument a one-step biopsy approach at confirmatory biopsies would be preferable.

Should We Incorporate Multivariate Risk Prediction at Confirmatory Biopsy?

Patients and clinicians prefer to be guided by additional risk factors when considering repeat standard biopsy in AS such as adverse PSA kinetics, or a high PSA density. In this meta-analysis, cancer upgrading was identified almost three-times more often in men with a positive MRI in contrast to a negative MRI (RR 2.77, 95% CI 1.76–4.38). Hence, a positive MRI should be marked as a positive predictor for upgrading in men on AS at confirmatory biopsies. Subsequently, a negative MRI, in combination with other stable negative predictors (low PSA kinetics, low PSA density) may support the decision to omit additional TRUS-guided biopsies at routine repeat biopsies, at least on an individual basis with adequate counselling.

Although a significant number of additional cancer upgrading was identified by each of both biopsy pathways, future management strategies in AS may focus on reducing the number of biopsies, and subsequently reducing patient burden and complications of biopsies. The acceptable balance between benefits and harms should be established amongst all relevant stakeholders, and may differ from patient to patient.

Strengths and Limitations

The major strengths of the present meta-analysis are: (i) including the results of negative MRIs and (ii) its focus on reports applying a sequential sampling design in the same patient of the two biopsy tests, MRI with MRI-targeted biopsies and standard TRUS-guided biopsies (direct comparison). However, the present meta-analysis has several limitations that may reduce the strength of the conclusions.

First, we only identified six studies addressing the research question, including 1 159 men on AS for low-risk prostate cancer. These were all single-centre studies from expert institutions. All studies reported their data following the

Table 3 Results of included studies according to prostate cancer upgrading in men with only a positive MRI on AS at confirmatory biopsies: the combined and the individual biopsy approaches of MRI-targeted biopsies and TRUS-guided biopsies, and additionally the 'added value' of each pathway.

Upgrading (Gleason score ≥3 + 4)			Only positive MRIs					
			Combined pathways		Individual pathways			
			Upgrading by MRI-TBx and TRUS-Bx pathways		Upgrading by MRI-TBx pathway		Upgrading by TRUS-Bx pathway	
Reference	Year	No. of patients (denominator)	No. of patients (numerator)	Proportion (95% CI)	No. of patients (numerator)	Proportion (95% CI)	No. of patients (numerator)	Proportion (95% CI)
Da Rosa et al. [33]	2015	54	17	0.31 (0.21– 0.45)	17	0.31 (0.21–0.45)	10	0.19 (0.10–0.31)
Walton Diaz et al. [34]	2015	120	33	0.28 (0.20–0.36)	24	0.20 (0.14–0.28)	21	0.18 (0.12–0.25)
Filson et al. [35]	2016	287	102	0.36 (0.30–0.41)	67	0.23 (0.19–0.29)	71	0.25 (0.20–0.30)
Recabal et al. [9]	2016	135	64	0.47 (0.39–0.56)	47	0.35 (0.27–0.43)	49	0.36 (0.29–0.45)
Alberts et al. [37]	2017	39	18	0.46 (0.31–0.62)	15	0.38 (0.25–0.54)	13	0.33 (0.20–0.49)
Ma et al. [36]	2017	157	37	0.24 (0.18–0.31)	13	0.08 (0.05–0.14)	30	0.19 (0.14–0.26)
Pooled data		792	271	0.35 (0.27–0.43)	183	0.24 (0.16–0.35)	194	0.24 (0.19–0.31)

MRI-TBx, MRI-guided targeted biopsy; TRUS-Bx, TRUS-guided biopsy.

Table 4 Summary of results.

	No. of men	Outcome (95% CI)	Q	P	I^2, %
All men (with positive or negative MRI)	1 159				
Upgrading by MRI-TBx and TRUS-Bx	317	**0.27 (0.22–0.34)**	25.6	<0.001	79
Upgrading by MRI-TBx	183	0.17 (0.10–0.26)	36.8	<0.001	91
Upgrading by TRUS-Bx	240	0.20 (0.16–0.25)	18.1	0.003	72
RR upgrading MRI-TBx vs TRUS-Bx		0.92 (0.79–1.06)	13.2	0.022	66
Proportion upgrading missed by TRUS-Bx	77	**0.25 (0.20–0.31)**	7.0	0.218	19
Proportion upgrading missed by MRI-TBx	134	**0.36 (0.20–0.56)**	31.4	<0.001	89
Men with only positive MRI	792	0.70 (0.62 to −0.76)	36.9	<0.001	84
Upgrading by MRI-TBx and TRUS-Bx	271	**0.35 (0.27–0.43)**	23.0	<0.001	79
Upgrading by MRI-TBx	183	0.24 (0.19–0.31)	18.0	0.003	73
Upgrading by TRUS-Bx	194	0.24 (0.16–0.35)	34.0	<0.001	89
RR upgrading by MRI-TBx vs TRUS-Bx		0.98 (0.87–1.09)	8.5	0.13	39
Men with only negative MRI	367	0.30			
Upgrading by TRUS-Bx	46	**0.12 (0.08–0.18)**	9.0	0.108	45
RR positive MRI vs negative MRI		**2.77 (1.76–4.38)**	8.3	0.139	43

MRI-TBx, MRI-guided targeted biopsy; Q, Cochrane's Q; TRUS-guided biopsy.
The most important results (author's choice) are highlighted (in bold).

START criteria, with overall methodological quality from fair to good.

Publication bias and related types of small-study effects threaten the validity of systematic reviews. Meta-analyses are therefore subject to publication bias because studies with negative results are less likely to be published and, therefore, results from meta-analyses may overstate a beneficial effect. However, most studies included patients prospectively in an Institutional Review Board-approved protocol, with written informed consent. Furthermore, graphical funnel plot analysis did not show evidence for publication bias.

Demonstrated differences in some of the variables in conducting MRI and MRI-targeted biopsy may contribute to heterogeneity as depicted by the Quadas-2 evaluation. However, this heterogeneity provides relevant additional information on the topic of interest and offers opportunities for increasing our standards on prostate cancer imaging analysis such as the START and the Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) consortia [13,39], rather than threats to our efforts to synthesise the available evidence.

	Added value of Individual pathways				Only negative MRIs	
					Added value of TRUS-Bx to MRI-TBx pathway	
Added value of MRI-TBx to TRUS-Bx pathway		Added value of TRUS-Bx to MRI-TBx pathway				
No. of patients (numerator)	Proportion (95% CI)	No. of patients (numerator)	Proportion (95% CI)	No. of negative MRIs (denominator)	No. of patients (numerator)	Proportion (95% CI)
7	0.13 (0.06–0.25)	0	0.00 (0.00–0.13)	18	2	0.11 (0.03–0.35)
12	0.10 (0.06–0.17)	9	0.08 (0.04–0.14)	32	1	0.03 (0.00–0.19)
31	0.11 (0.08–0.15)	35	0.12 (0.09–0.17)	102	21	0.21 (0.14–0.30)
15	0.11 (0.07–0.18)	17	0.13 (0.08–0.19)	71	8	0.11 (0.06–0.21)
5	0.13 (0.05–0.27)	3	0.08 (0.03–0.21)	17	1	0.06 (0.01–0.32)
7	0.04 (0.02–0.09)	24	0.15 (0.10–0.22)	127	13	0.10 (0.06–0.17)
77	0.10 (0.08–0.13)	88	0.11 (0.10–0.15)	367	46	0.12 (0.12–0.18)

In using Gleason grade as the outcome parameter to evaluate the added value of MRI and targeted biopsies to systematic TRUS-guided biopsies, we accept an underlying potential methodological challenge. As proposed by the START consortium, Gleason grade is the most appropriate histological parameter to report in studies on MRI-targeted biopsy [13]. However, offering active treatment in men on AS is traditionally not only based on progression of Gleason grade alone, but also on a higher maximum percentage core involvement or an increase in the number of positive biopsies in a standard set of 10–12. Using a risk-classification system that is also based on the number of positive cores and/or the maximum cancer core length, the effect of targeted rather than standard systematic biopsies would result in a shift towards higher risk classification.

Furthermore, a prostate cancer that is stable may be more accurately sampled at MRI-targeted biopsy and found to include higher risk features than when it was sampled in a systematic manner. This can result in so called 'risk inflation' and patients and physicians may be falsely encouraged to more active treatment, because of an apparent increase in risk (reclassification) rather than a true change in their cancer [40]. Appropriate risk thresholds are not yet fully understood when MRI-targeted biopsies are used. Therefore, this comparison of MRI-targeted to standard systematic biopsy needs to be regarded with caution.

The upgraded proportion due to the TRUS-guided biopsies was 20% (95% CI 16–25%; Table 2), which is slightly higher than the ~15% in published reports at confirmatory assessment [41,42]. Part of the upgrading could be influenced by the unblinded study design in two reports [26,34], favouring the TRUS-guided biopsies. However, one study explicitly reported excluding areas that had been previously sampled with the MRI-targeted biopsy approach favour the MRI and targeted-biopsies approach [9].

Conclusion

MRI and subsequently MRI-targeted biopsies identified cancer upgrading in a significant number of men with low-risk prostate cancer on AS, not detected by TRUS-guided biopsies. Hence, a pre-biopsy MRI should be performed at the time of confirmatory systematic biopsy including MRI-targeted biopsies when indicated.

Reducing biopsy burden and biopsy complications, by avoiding TRUS-guided biopsies at confirmatory biopsies, may risk missing early intermediate- and high-grade prostate cancers, not detected by the MRI pathway.
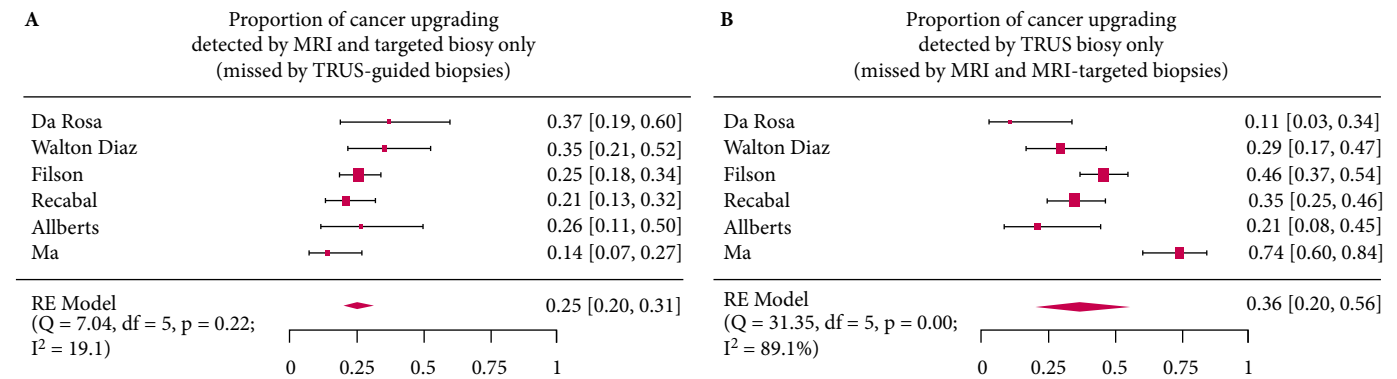
In the present meta-analysis, cancer upgrading occurred almost three-times more often in men with a positive MRI in contrast to a negative MRI. Combining negative predictors such as a negative MRI, low PSA kinetics, and PSA density should be further investigated to help safely counsel these men on AS in reducing repeat biopsies.

Table 5 Results of included studies, focussing on eight different biopsy strategies in men on AS at confirmatory biopsies.

Biopsy strategies in men on AS (*n* = 1 000)	Yield	Equipment			Savings (benefits)			Harms		
	Upgrading to Gleason score ≥3 + 4, *n*	MRI, *n*	MRI-TBx, *n*	TRUS-Bx, *n*	MRIs	MRI-TBx	TRUS-Bx	2 × Bx	Missing upgrades to Gleason score ≥3 + 4	
One-step biopsy approach										
MRI + MRI-TBx (in positive MRI) + TRUS-Bx	274	1 000	683	1 000	0	0	0	0	0	0%
MRI + MRI-TBx (in positive MRI) + only additional TRUS-Bx in men with a positive MRI	234	1 000	683	683	0	0	317	0	40	13%
MRI + MRI-TBx (in positive MRI) + only additional TRUS-Bx in men with a negative MRI	198	1 000	683	317	0	0	683	0	76	24%
MRI + MRI-TBx (in positive MRI)	158	1 000	683	0	0	0	1 000	0	116	37%
Only TRUS-Bx	207	0	0	1 000	1 000	683	0	0	67	21%
Two-step biopsy approach										
MRI-driven pathway										
MRI + MRI-TBx (in positive MRI) + only additional TRUS-Bx in men without upgrading in positive and in negative MRI	274	1 000	683	758	0	0	242	758	0	0%
MRI + MRI-TBx (in positive MRI) + only additional TRUS-Bx in men without upgrading in positive MRI	234	1 000	683	525	0	0	475	525	40	13%
TRUS-driven pathway										
TRUS-Bx in all men + only additional MRI + MRI-TBx (in positive MRI) in men without upgrading by initial TRUS-findings	274	793	516	1 000	207	167	0	793	0	0%

MRI-TBx, MRI-guided targeted biopsy; TRUS-Bx, TRUS-guided biopsy.

Fig. 4 Forest plot analyses of the additional proportion of cancer upgrading in men on AS at confirmatory biopsies: (**A**) additional proportion of MRI and MRI-targeted biopsies to TRUS-guided biopsies (0.25, 95% CI 0.20–0.31); (**B**) additional proportion of TRUS-guided biopsies to MRI and MRI-targeted biopsies (0.36, 95% CI 0.20–0.56).

A — Proportion of cancer upgrading detected by MRI and targeted biosy only (missed by TRUS-guided biopsies)

Da Rosa	0.37 [0.19, 0.60]
Walton Diaz	0.35 [0.21, 0.52]
Filson	0.25 [0.18, 0.34]
Recabal	0.21 [0.13, 0.32]
Allberts	0.26 [0.11, 0.50]
Ma	0.14 [0.07, 0.27]
RE Model (Q = 7.04, df = 5, p = 0.22; I² = 19.1)	0.25 [0.20, 0.31]

B — Proportion of cancer upgrading detected by TRUS biosy only (missed by MRI and MRI-targeted biopsies)

Da Rosa	0.11 [0.03, 0.34]
Walton Diaz	0.29 [0.17, 0.47]
Filson	0.46 [0.37, 0.54]
Recabal	0.35 [0.25, 0.46]
Allberts	0.21 [0.08, 0.45]
Ma	0.74 [0.60, 0.84]
RE Model (Q = 31.35, df = 5, p = 0.00; I² = 89.1%)	0.36 [0.20, 0.56]

Conflict of Interest

All authors declare they have no conflict of interest.

Take home message

A pre-biopsy MRI should be performed at confirmatory biopsies in men on AS, together with MRI-targeted biopsies in addition to systematic TRUS-guided biopsies. Both pathways appear to be complementary to each other, both missing a significant proportion of cancer upgrading.

Patient Summary

We found evidence to suggest that MRI should be performed before systematic confirmatory biopsy in men on AS, together with MRI-targeted biopsies when indicated.

Twitter

A pre-biopsy prostate MRI should be performed before confirmatory assessment to reduce misclassification of men on active surveillance: meta-analysis (150).

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Abbreviations: AS, active surveillance; PI-RADS, Prostate Imaging Reporting and Data System; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QUADAS, Quality Assessment of Diagnostic Accuracy Studies; RR, relative risk; START, Standards of Reporting for MRI-targeted Biopsy Studies.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Assessment of publication bias with funnel plot analysis, of the 6 included studies within the meta-analysis.
Figure S2. Graphical presentation of the QUADAS-2 assessment.
Table S1. Data table of included studies.
Table S2. Tabular presentation of the QUADAS-2 assessment.
Appendix S1. QUADAS-2 domains signalling questions.
Appendix S2. Literature search.