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Review

Regional Versus Systematic Biopsy in Addition to Targeted Biopsy: Results from a Systematic Review and Meta-analysis

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Abstract

Background and objective: Intensification of targeted biopsy (TBx) around a magnetic resonance imaging (MRI)-visible lesion with regional biopsy (RBx) could obviate the need for systematic biopsy (SBx). We aimed to compare the detection yields of clinically significant prostate cancer (csPCa)—defined as International Society of Urological Pathology (ISUP) grade group ≥2—between TBx + RBx and the reference standard (TBx + SBx).

Methods: RBx was defined as perilesional or ipsilateral biopsy. A literature search was conducted up to September 2023 using PubMed, Embase, and Web of Science databases. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed. Included studies were eligible when presenting data from SBx, TBx, and TBx + RBx cores and their detection yields. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria were used to assess the risk of bias of the included studies.

Key findings and limitations: Twenty-one studies were included for a meta-analysis. The overall detection yield of csPCa was not statistically different between TBx + SBX and TBx + RBx (46.1% vs 44.2%; odds ratio [OR] 1.07, 95% confidence interval [CI] 0.99–1.16, p = 0.07); similar findings were found also for ISUP grade group ≥3 prostate cancer (PCa; OR 1.06, 95% CI 0.92–1.22, p = 0.43) and in different subgroup analyses. TBx + SBx was associated with higher cancer detection of ISUP grade group 1 PCa (OR 1.16, 95% CI 1.04–1.30, p = 0.008). The main limitations

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include the retrospective nature of most of the selected studies, heterogeneity of RBx definition, and template.

Conclusions and clinical implications: Our study supports the use of the TBx + RBx template in the early detection pathway for the detection of csPCa. SBx can be omitted when targeting lesions visible on MRI.

Patient summary: A prostate biopsy strategy consisting of taking biopsy in and around an magnetic resonance imaging–visible lesion reduces the risk of detecting indolent prostate cancers without affecting the detection of aggressive tumours.

1. Introduction

The multiparametric magnetic resonance imaging (MRI)-driven pathway is the standard of care for the diagnosis of prostate cancer (PCa), by combining targeted biopsy (TBx) of MRI-visible lesions with systematic biopsy (SBx) [1–4]. The trade-off of the combination of SBx + TBx with respect to TBx alone leads to an increase of 5.8% detection of clinically significant prostate cancer (csPCa)— defined as International Society of Urological Pathology (ISUP) grade group (GG) ≥2—at the cost of 5% of more clinically insignificant prostate cancer (insignPCa)— defined as ISUP GG 1 [4,5]. Additionally, the increased number of biopsy (Bx) cores is associated with an increased procedure time, environmental burden, and risk of complications [1,6,7]. Furthermore, higher detection of insignPCa may lead to heightened patient anxiety regarding inclusion in an active surveillance protocol, potential further harm for repeated monitoring Bx, and higher health care costs [8].

In recent years, some investigators have questioned the need to combine TBx with SBx in patients with MRI-positive lesions because of the increased risk of histological downgrading, when testing the concordance between combined Bx and radical prostatectomy specimen. A recent systematic review showed that combining TBx with SBx resulted in an estimated net harm because of the two-fold increase risk of downgrading, suggesting a potential for overtreatments [9]. Nevertheless, the secondary analysis of the TRIO study showed that men with smaller lesion sizes and indeterminate lesions (Prostate Imaging-Reporting and Data System [PI-RADS] 3) benefited most from a combination Bx approach [10].

In the last few years, an alternative approach has variably been reported to optimise the benefits and harms of prostate Bx (ie, maintaining csPCa yields and grading concordance while reducing insignPCa detections and complications) consisting of intensifying the sampling of the MRI-defined region of interest (ROI) by adding extra cores in the proximity of the ROI, defined as regional biopsy (RBx) [11–13]. Indeed, different sampling definitions and templates have been described in literature regarding RBx, including perilesional biopsy (PLBx), extended TBx, ipsilateral SBx (ipsiSBx), or focal saturation Bx [14–26]. The 2024 version of the European Association of Urology (EAU) guidelines on PCa has been the first to issue a recommendation for undertaking a TBx + RBx combination instead of SBx after positive MRI [27]. Nevertheless, this recommendation is based on a single meta-analysis of a limited number of studies; hence, an updated meta-analysis of the evolving evidence is required by comparing the detection yields for csPCa of TBx + RBx versus TBx + SBx [13].

2. Methods

2.1. Search strategy

A literature search was performed in PubMed, Web of Science, and Embase databases, from inception to September 2023. This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [28]. References from selected studies were also retrieved. The mesh/search terms and strings are provided in the Supplementary Material.

Screening was performed independently by two investigators (C.L. and A.T.) based on the article titles and abstracts to identify ineligible reports. Potentially relevant reports were then read in full text. Reasons for exclusions were noted. Disagreements were resolved by discussion with a senior coauthor (F.S.). Missing data were requested via e-mails to the corresponding authors of the relevant papers.

The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number: CRD42023468572).

2.2. Studies' selection and main outcomes

We developed the study protocol in accordance with the Population, Intervention, Control, Outcomes, and Study type (PICOS) framework. Population consisted of patients diagnosed with at least one prostatic lesion defined as PI-RADS or Likert score ≥3 on MRI, who underwent TBx and SBx, irrespectively to the targeting approach used (ie, either transperineal or transrectal).

Intervention consisted of any RBx strategy, by including the data of PLBx (cores taken around the index lesion) and ipsiSBx (systematic cores from the same lobe of the index lesion), in addition to TBx.

Comparator is represented by the current standard of care (ie, TBx + SBx).

The primary outcome consisted of comparing the detection yields of csPCa (defined as ISUP GG ≥2) of TBx + RBx compared with those of TBx + SBx.

The secondary outcomes included the detection yields of insignPCa and higher-grade PCa (defined as ISUP GG ≥3) of TBx + RBx versus TBx + SBx. We also aimed to look at potential differences in complication rates between the intervention (TBx + RBx) and reference standard (TBx + SBx) strategies. Studies were considered eligible when involving patients undergoing intervention (TBx + RBx) and reference standard (TBx + SBx) approaches. Included studies portrayed Bx-naïve men as well as patients with previous prostate Bx. We included prospective and retrospective comparative studies, excluding letters, editorials, commentaries, unpublished studies, case reports, conference reviews, authors' replies, reviews, and meta-analyses.

2.3. Data extraction

Data extraction from the final pool of papers selected for the meta-analysis involved the following data: first author's name, publication year, journal name, study design, radiological score used (PI-RADS vs Likert), Bx approach, type of comparison, number of patients included, age, prostate-specific antigen, prostatic volume, lesion size, number of cores of TBx and SBx performed, and number of cores of RBx performed.

2.4. Risk of bias assessment

Two authors (C.L. and A.T.) independently assessed the studies' quality and the risk of bias (RoB) using the criteria outlined in the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) [29]. The domains assessed included patient selection, index test, reference standard, flow, and timing. The overall assessment of RoB was judged as "low", "high", or "unclear".

2.5. Subgroup analyses

Subgroup analyses were planned a priori. We sought for csPCa detection yields comparing TBx + RBx versus reference standard according to the sampling strategies (PLBx and ipsiSBx); by suspicious category according to PI-RADS or Likert systems (scores ≥3 or ≥4), Bx routes (transperineal vs transrectal), SBx template protocols (Ginsburg vs standard 12 cores), and lesion sizes (<10 vs >10 mm); and finally for Bx-naïve versus previously biopsied patients.

2.6. Statistical analysis

Given the small size of the studies, the Mantel-Haenszel method was used to determine the association between prostate Bx strategy (TBx + RBx vs TBx + SBx) and csPCa detection. When adjusted odds ratios (ORs) were unavailable, we used dichotomous data to calculate pooled ORs and corresponding 95% confidence intervals (CIs).

We assessed heterogeneity using the Cochrane Q test and quantified it using I^2 values. In the case of heterogeneity (Cochrane Q test $p < 0.05$ and $I^2 > 50\%$), we used a random-effect model, and attempted to investigate and further explain the heterogeneity by sensitivity analyses [30]. All statistical analyses were performed using Cochrane Collaboration Review Manager software (RevMan v.5.4; Cochrane Collaboration, Oxford, UK). Statistical significance was set at $p < 0.05$.

3. Results

3.1. Study selection and characteristics

Figure 1 shows the flowchart of the study selection criteria by employing the PRISMA guidelines.

Overall, 22 articles were eventually selected with 21 eligible for a quantitative analysis, accounting for 11 784 patients. One article was not included in the meta-analysis as data could not be extracted and no additional information from corresponding author could be obtained [31].

Seventeen studies were retrospective [14–16,18–24,26,31–36], four prospective [3,17,25,37] with one of these being a randomised trial [17], and one combined prospective and retrospective cohort populations [38].

Table 1 shows the studies' characteristics regarding the main variables in observation. A detailed description of MRI, fusion system characteristics, vendors, and radiological scores is provided in Supplementary Table 1. Nine studies utilised the transrectal Bx approach [3,15,20,21,24,25,31,36,37], nine used the transperineal Bx approach, and two used both techniques [22,38]; two studies did not report the approach.

The majority of studies had TBx with a median of 2 (interquartile range [IQR] 2–4) cores. Only three studies [16,32,34] performed a higher number of TBx cores with a median of 5 (IQR 4–7) cores. The number of cores obtained from TBx + RBx depended on the definition of the latter from the included studies (median range from two to 20 cores). Most patients underwent systematic 12-core Bx, except for seven studies [17,19,26,33–35,37], with a median of systematic cores of 23 (IQR 19–29) by applying the Ginsburg template.

3.2. RoB and study heterogeneity

RoB evaluation is shown in Supplementary Figure 1, with no evidence of major biases identified that would prevent the quantitative analysis. Proportions of studies with a low RoB were as follows: 90% of articles for what concerns patient selection, 75% for flow and timing, and 25% for reference standard and index test. Although the studies showed expected heterogeneity in methodology, the individual and overall quality was considered acceptable.

3.3. Primary outcome: detection yields of csPCa

The overall csPCa detection yield of the intervention group (TBx + RBx) was 44.2% versus the 46.1% of the reference standard (TBx + SBx). As shown in the forest plot (Fig. 2A), nonstatistically significant difference was observed in the detection yields of csPCa between the reference standard and intervention groups (OR 1.07, 95% CI 0.99–1.16, $p = 0.07$). No significant heterogeneity was found at Cochrane Q test.

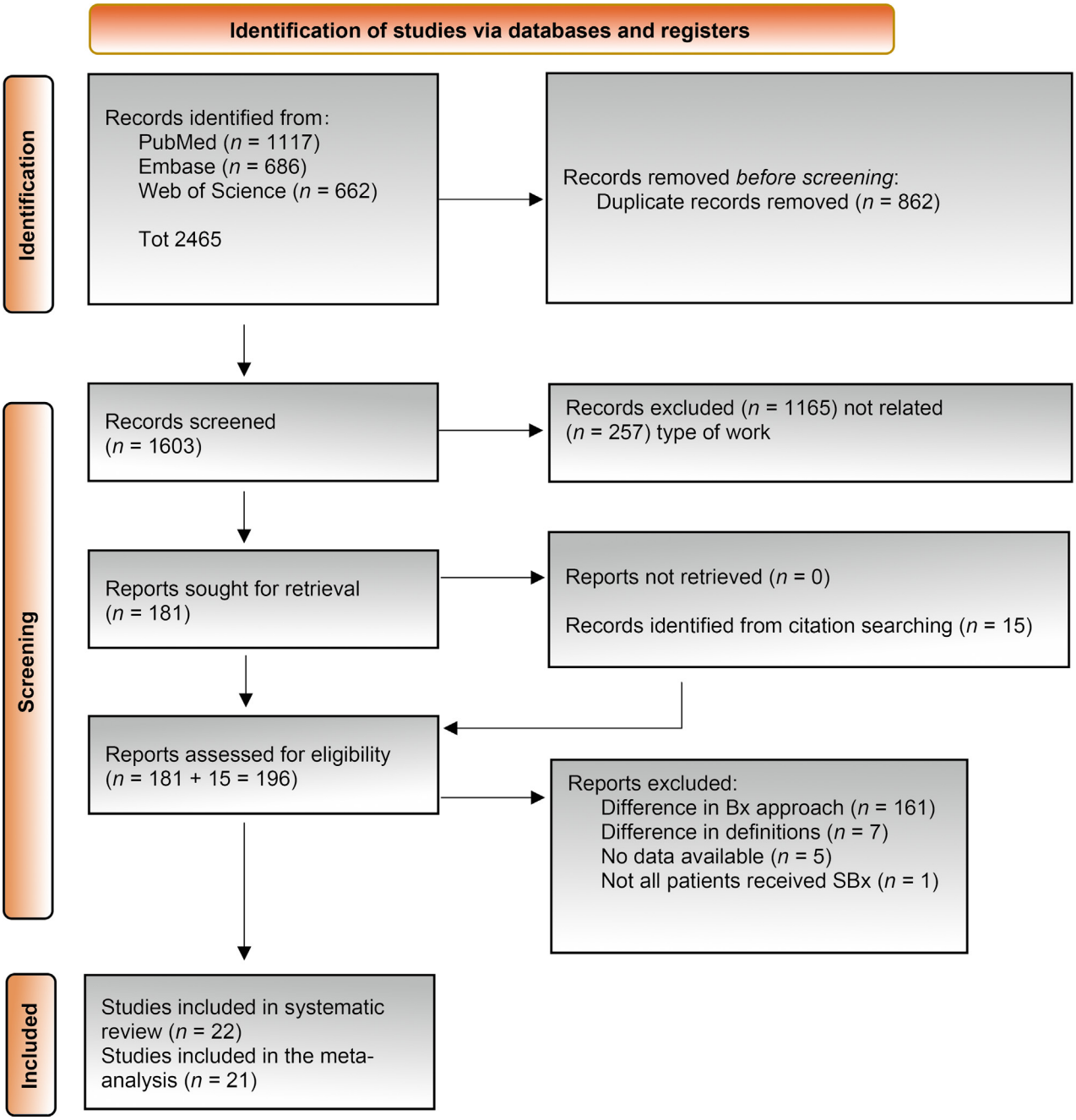

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram showing the search outcome and selection of full studies included in the review and the studies excluded. Bx = biopsy; SBx = systematic biopsy.

3.4. *Secondary outcomes*

3.4.1. *Detection yields of insignPCa*

The TBx + SBx approach was statistically significantly associated with a higher detection yield for insignPCa (OR 1.16, 95% CI 1.04–1.30, $p = 0.008$). As shown in Figure 2B, no significant heterogeneity was found at Cochrane Q test.

3.4.2. *Detection yields of higher-grade PCa*

Pooled data showed a nonsignificant difference in the detection of ISUP GG ≥3, between reference standard and intervention (OR 1.06, 95% CI 0.92–1.22, $p = 0.43$; Fig. 2C). No significant heterogeneity was found at Cochrane Q test.

3.4.3. *Bx complications—side effects*

No substantial data were available from the selected studies regarding the side effects of the different Bx approaches used in their cohorts. Only van der Leest et al [3] specifically reported their Bx complication rate, assessing that they occurred in minimal percentages and among patients who performed 12-core transrectal ultrasound-guided SBx. Mild

Table 1 – Study characteristics

Study	Journal	Design	Radiological score used	Bx approach	Type of comparison	No. of patients	Age (yr)[a,b]	PSA (ng/ml)[a,b]	Prostate volume (cc)[a,b]	Lesion size (mm)[a,b]	No. of TBx cores[a]	No. of SBx cores[a]	No. of RBx cores[a]
Barrett (2016) [35]	*World Journal of Urology*	RS	Likert	TP	TBx + SBx vs TBx + PLBx	76	68 (53–76)	8.9 (0.8–53.2)	43.2 (13.9–292.6)	10.35	2 (2–6)	24	2 (1–7)
Bryk (2017) [14]	*Urology*	RS	Likert	NA	TBx + SBx vs TBx + iSBx	211	61 (56–66)	5.3 (3.8–6.9)	NA	NA	4	12	6
Calio (2018) [20]	*Journal of Urology*	RS	NIH definition	TR	TBx + SBx vs TBx + PLBx	208	62	7.1	38 (19)	NA	2	12	4 (2–6)
Calio (2019) [31]	*Therapeutic Advances in Urology*	RS	PI-RADS	TR	TBx + SBx vs TBx + PLBx	99	66.9	9.7	83.1 (45.5)	19.6 (2.9)	2–4	12	4
Diamand (2022) [36]	*Urologic Oncology*	RS	PI-RADS v2 and 2.1	TR	TBx + SBx vs TBx + PLBx	134	67 (61–72)	7.7 (6–11)	36 (30–54)	13 (10–19)	4 (3–4)	12	1 (1–2)
Freifeld (2019) [21]	*Urologic Oncology*	RS	PI-RADS v2 and Likert	TR	TBx + SBx vs TBx + iSBx	116	63.7 ± 8.33	10.36 ± 14.59	54.12 ± 30.39	14.32 ± 9.50	2–3	12	6
Hagens (2022) [32]	*European Urology Open Science*	RS	PI-RADS v2.1	TP	TBx + SBx vs TBx + PLBx	235	69 (63–73)	7.8 (5.6–14)	45 (34–65,8)	NA	5 (4–6)	8 (5–10)	7 (6–9)
Hansen (2020) [33]	*BJU International*	RS	PI-RADS v2 and Likert	TP	TBx + SBx vs TBx + iSBx vs TBx + PLBx	487	66 (60–69)	7.2 (5–10.5)	46 (34–73)	0.50 (0.28–1.00)	2	24	10–20
Jager (2022) [22]	*Therapeutic Advances in Urology*	RS	PI-RADS v2	TR and TP	TBx + SBx vs TBx + iSBx	228	65.6 ± 7.76	7.6	46 (27)	12.55 (9)	3 (2–3)	12	6
Lee (2023) [34]	*World Journal of Urology*	RS	PI-RADS v2	TP	TBx + SBx vs TBx + iSBx vs TBx + PLBx	398	65.7 ± 7.8	10.1 ± 8.4	39.2 ± 17.9	NA	9 (6–12)	23 (19–29)	5 (3–6)
Noujeim (2023) [15]	*Prostate Cancer and Prostatic Diseases*	RS	PI-RADS v2 and 2.1	TR	TBx + SBx vs TBx + PLBx	505	66 (61–72)	7.4 (5–10)	48 (37–69)	13 (10–17)	4 (3–5)	8 (7–10)	6
Novara (2023) [37]	*World Journal of Urology*	PS	PI-RADS	TR	TBx + SBx vs TBx + iSBx vs TBx + PLBx	168	65 (60–71)	6 (4–8)	52 (40–66)	11 (8–14)	3 (3–3)	24 (24–24)	4 (4–4)
Park (2020) [18]	*Abdominal Radiology*	RS	PI-RADS v2	TP	TBx + SBx vs TBx + PLBx	212	65 (60–71)	7 (5–10)	36 (28–50)	9 (6–13)	2–3	12	2–4
Phelps (2023) [23]	*Abdominal Radiology*	RS	PI-RADS v2.1	NA	TBx + SBx vs TBx + iSBx	212	67 (61–72)	6.48 (4.30–9.83)	62.5 (44–88.3)	12 (8–15)	2 (2–6)	12	6
Raman (2021) [16]	*The Journal of Urology*	RS	Likert and PI-RADS v2	TP	TBx + SBx vs TBx + PLBx	971	64.5 ± 7.4	8.4 ± 7.9	60.8 ± 29.1	0.9 ± 2.2	5	12	8
Ruan (2023) [38]	*Abdominal Radiology*	PS + RS	PI-RADS v2.1	TP + TR	TBx + SBx vs TBx + iSBx vs TBx + PLBx	464	67.36 ± 8.03	9.05 (6.52–12.46)	45.98 (33.05–64.02)	NA	2 (2–4)	12	6
Saner (2023) [17]	*European Urology Oncology*	PS	PI-RADS v2.1	TP	TBx + SBx vs TBx + PLBx	85	66.5	7.4	50 (38–65)	NA	4	24	9
Shen (2020) [24]	*Ultrasound in Medicine & Biology*	RS	PI-RADS v2	TR	TBx + SBx vs TBx + iSBx	113	70.7 ± 9.14	9.70 (6.65–16.22)	47.73 (32.08–62.95)	16.5 ± 7	2	12	6
Tschirdewahn (2021) [19]	*European Urology Focus*	RS	PI-RADS v2	TP	TBx + SBx vs TBx + PLBx	213	66 (61–71)	7.8 (5.6–10.3)	50 (40–65)	NA	4	24	9–10
van der Leest (2019) [3]	*European Urology*	PS	PI-RADS v2	TR	TBx + SBx vs TBx + PLBx	317	65 (59–68)	6.4 (4.6–8.2)	55 (41–77)	6.3 (5–9)	2–4	12	4
Wang (2021) [25]	*BMC Urology*	PS	PI-RADS v2	TR	TBx + SBx vs TBx + iSBx	279	71 (65–77)	10.04 (6.38–18)	57 (41–82.30)	NA	2	10	5
Yusim (2023) [26]	*The Prostate*	RS	PI-RADS v2.1	TP	TBx + SBx vs TBx + iSBx	364	68 (64–73)	6.55 (5.0–9.2)	51 (36–70.7)	NA	3–4	16–20	8–10

Bx = biopsy; iSBx = ipsilateral SBx; NA = not available; No. = number; PI-RADS = Prostate Imaging Reporting and Data System; PLBx = perilesional Bx; PS = prospective study; PSA = prostate-specific antigen; RS = retrospective study; SBx = systematic Bx; TBx = targeted Bx; TP = transperineal; TR = transrectal; RBx = regional Bx (PLBx or iSBx).

[a] Data for continuous variables are reported as the median (interquartile range).

[b] Data for continuous variables are reported as mean ± standard deviation.

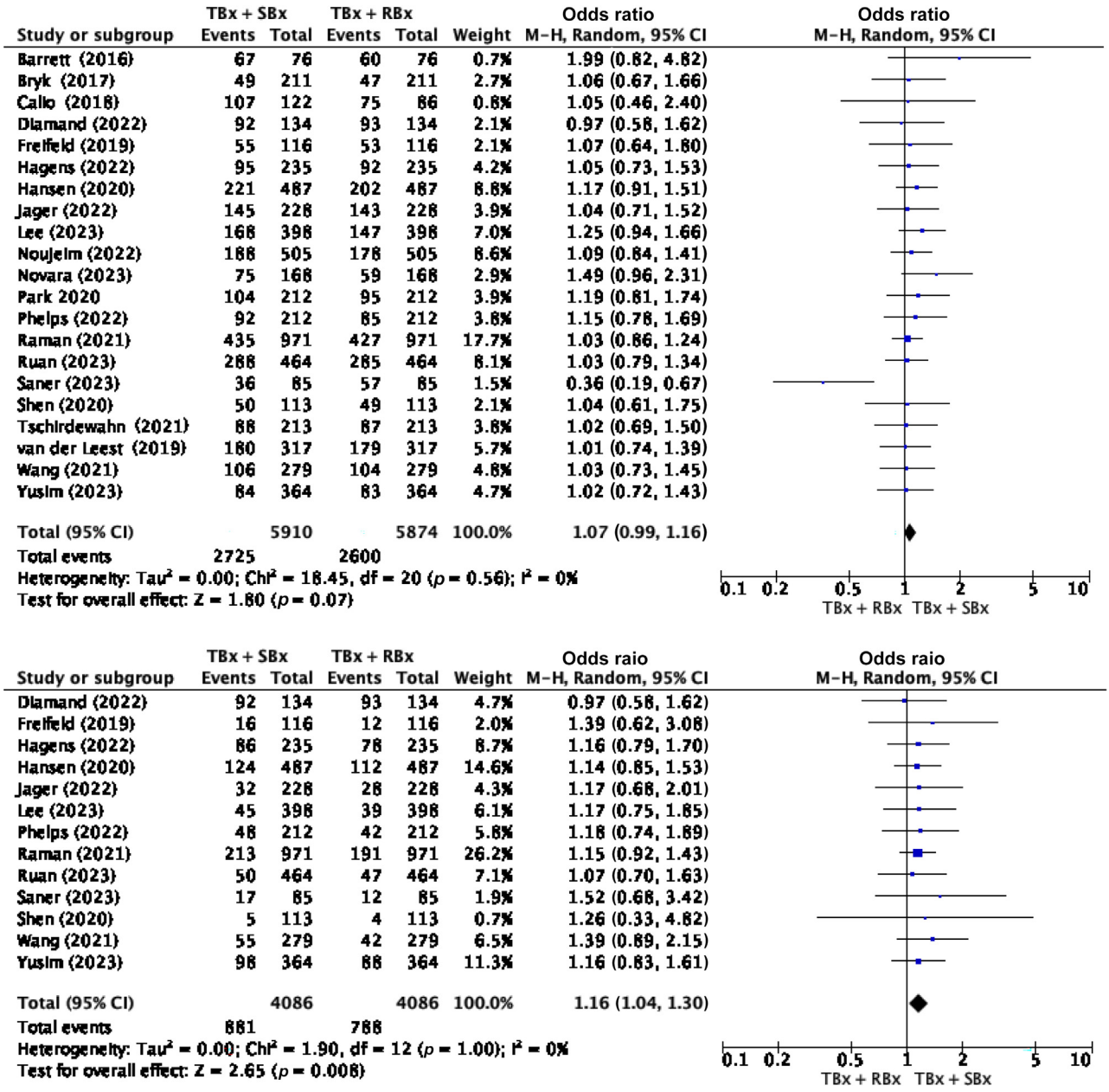

Fig. 2 – (A) CD of csPCa—TBx + RBx versus TBx + SBx. (B) Clinically insignificant PCa detection—TBx + RBx versus TBx + SBx. (C) High-risk PCa (ISUP grade ≥3) detection—TBx + RBx versus TBx + SBx. CD = cancer detection; CI = confidence interval; csPCa = clinically significant prostate cancer; ISUP = International Society of Urological Pathology; M-H = Mantel-Haenszel; PCa = prostate cancer; RBx = regional biopsy; SBx = systematic biopsy; TBx = targeted biopsy.

and self-limiting haematuria, lower urinary tract infections, vasovagal episode, and transient ischaemic attack after discontinuation of anticoagulant medication were among the complications reported.

3.5. Subgroups analysis

3.5.1. Detection yields of csPCa according to RBx strategies

There was high variability in the strategy and core number of RBx, across the selected papers. Therefore, a subgroup analysis was performed according to the template of TBx + RBx applied in the different studies. Eleven studies provided data regarding the ipsiSBx strategy [14,21–26,33,34,37,38], and no significant difference was found in the detection yields of csPCa for TBx + SBx versus ipsiSBx (OR 1.09, 95% CI 0.98–1.21, $p = 0.13$). No significant heterogeneity was found at Cochrane Q test (Supplementary Fig. 2A).

When pooling data from the 14 studies including PLBx cores in the TBx + RBx approach [3,15–20,32–38], no difference was found regarding the detection yield of csPCa between the reference standard and intervention groups (OR 1.09, 95% CI 0.96–1.22, $p = 0.08$). No significant heterogeneity was found at Cochrane Q test. The number of TBx and PLBx cases varied significantly across the relevant studies; for example, while Calio et al [20] undertook two TBx and two PLBx cases, Hansen et al's [33] template included an overall number of up to 20 cores (two per lesion and two per sector adjacent to the lesion; Supplementary Fig. 2B).

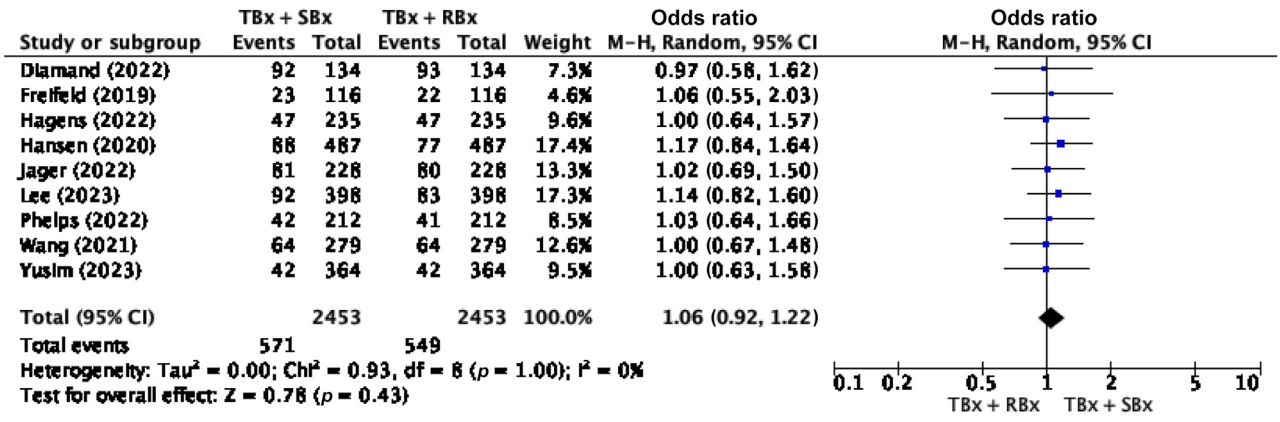

Fig. 2 (*continued*)

3.5.2. Detection yields of csPCa according to PI-RADS or Likert scores

Three studies reported data stratified by PI-RADS or Likert score 3, 4, or 5 [18,19,32]. The csPCa detection yield showed no significant difference for each score when comparing the reference standard with TBx + RBx. Even when pooling data from 14 studies stratifying the lesions only as per PI-RADS or Likert score 4 and 5, no statistical significance was found (OR 1.09, 95% CI 0.96–1.22, p = 0.17) [3,15–20,32–38]. No significant heterogeneity was found at Cochrane Q test (Supplementary Fig. 2C).

3.5.3. Detection yields of csPCa according to transperineal/transrectal routes

When pooling data from the reference standard and intervention groups for studies reporting a transperineal route, no difference was observed regarding the cancer detection of csPCa (OR 1.06. 95% CI 0.90–1.24, p = 0.5) [16–19,26,32–35]; a similar outcome was found when pooling data from studies with a transrectal route (OR 1.03, 95% CI 0.90–1.18, p = 0.68) [3,15,20,21,24,25,36,37]. No significant heterogeneity was found at Cochrane Q test (Supplementary Fig. 2D and 2E).

3.5.4. Detection yields of csPCa according to SBx templates

When pooling data from the seven studies including only patients who underwent SBx according to the Ginsburg template, no statistically significant association was found between TBx + SBx and TBx + RBx for csPCa detection (OR 1.10, 95% CI 0.84–1.44, p = 0.49) [17,19,26,33–35,37]. No significant heterogeneity was found at Cochrane Q test.

Similar findings were observed for the remainder 15 studies where the 12-core SBx template was applied (OR 1.02, 95% CI 0.94–1.12, p = 0.59) [3,14–16,18,20–25,32,36–38]. No significant heterogeneity was found at Cochrane Q test (Supplementary Fig. 2F and 2G).

3.5.5. Detection yields of csPCa according to lesion size

There was high variability of the mean/median lesion size across the selected articles, with smaller lesions (mean size 0.50 mm; IQR 0.28–1.00 mm) reported by Hansen et al [33] and bigger ones (mean 16.5 mm; standard deviation ±7 mm) by Shen et al [24]. Among the studies comparing detection yields for intervention versus reference according to lesion size, the most common cut-off was 10 mm. Accordingly, data from five studies reporting detection yields for lesion size of ≤10 mm [3,18,21,33,37] and from those ones with lesion size of >10 mm [15,18,21,24,37] were pooled out without showing any statistical difference (lesion size ≤10 mm: OR 1.16, 95% CI 0.97–1.39, p = 0.10; lesion size >10 mm: OR 1.13, 95% CI 0.94–1.35, p = 0.21). No significant heterogeneity was found at Cochrane Q test (Supplementary Fig. 2H and 2I).

3.5.6. Detection yields of csPCa for Bx-naïve versus previously biopsied patients

A total of 1057 patients had a previous prostate Bx, but no data were available with respect to either the type/approach performed formerly (SBx vs TBx only vs TBx + SBx) or the proportion of patients who underwent TBx + RBx or the reference standard at the rebiopsy [14–19,22,23,25,33,35,38]. For these latter reasons, a quantitative analysis was not possible to be undertaken. Among these 1957 patients, 355 were on active surveillance, with the majority of them because of a ISUP GG 1 lesion; nevertheless, only Freifeld et al [21] undertook a subgroup analysis of 18 patients with ISUP GG 1 undergoing a reclassification Bx, showing upgrading in 16.7% (3/18) and 5.6% (1/18) when performing TBx only and TBx+ ipsiSBx, respectively. Park et al [18] were the only ones providing a head-to-head analysis of Bx-naïve versus prior negative Bx patients, showing an added value for both the TBx + RBx and the TBx + SBx approaches for the detection of csPCa.

4. Discussion

Our study shows that different sampling strategies saturating the ROI of an MRI-visible lesion has a diagnostic yield for csPCa comparable with the reference standard, while reducing the overdiagnosis of insignPCa, thereby limiting the number of cores. Cancer detection of csPCa in the intervention group (TBx + RBx) was not statistically different from that of the reference standard (TBx + SBx), even though it was slightly inferior to the reference standard; a similar finding was also observed for ISUP GG ≥3 PCa. On the contrary, the detection yield for insignPCa was significantly higher for the reference standard. Furthermore, sub-

group analyses showed that the csPCa detection yields were not statistically different regarding the RBx strategy adopted (ipsiSBx vs PLBx), PI-RADS/Likert scores, Bx route, SBx template (Ginsburg vs 12 cores), and lesion size (≤/>10 mm).

The rationale behind this Bx strategy is that the RBx adjusts for the potential systematic (or missampling) errors produced at any point during the fusion process, from the image acquisition to the lesion segmentation and/or fusion registration [12,13,39,40]. Furthermore, it implies that the main driver for the detection of csPCa is the visibility of a lesion at MRI. The expanding field of radiogenomics provides evidence that the molecular hallmarks of an aggressive disease are expressed more frequently and in higher proportion in MRI-visible lesions than in the invisible ones [41–43]. This knowledge should mitigate the fear of missing csPCa detected by SBx only. Several studies have shown that omitting SBx in Bx-naïve patients would miss no more than 5–6% of csPCa cases [4,44,45]; in our study, the difference was only 1.9% for ISUP GG≥2 PCa and even lower for ISUP GG≥3 (23.2% vs 22.3%, a difference of 0.9%). This discrepancy can be explained by the high proportion (up to 34%) of double sampling of ROI by SBx, suggesting that the added value of 5% is overestimated [46].

A similar systematic review in 2021 included only eight studies [13] and did not perform any subgroup analysis. Nevertheless, these data were deemed sufficient to prompt the EAU guidelines in 2024 to recommend TBx + PLBx, although only with a weak recommendation [27]. To date, no other international guidelines have adopted such a significant change in the prostate Bx strategy [47,48], suggesting the need for more robust data.

However, in the succeeding years, multiple studies have been published on this topic; accordingly, in the current analysis, we were able to include 21 articles and 11 784 patients for the meta-analysis, thus providing more robust estimates of Bx yields and helping to confirm TBx + RBx as a new standard for prostatic Bx.

Our findings also highlight some aspects of the RBx that requires standardisation, especially in terms of the definition and spatial template. First, two main RBx approaches are currently used, that is, PLBx and ipsiSBx, with the latter considered as a surrogate of the former. Nevertheless, the current trend is towards a PLBx strategy, as shown by the higher proportion of studies involving PLBx, so that a PLBx should become synonymous with an RBx [3,15–20,32–35,38]. Second, we found significant heterogeneity regarding the number of cores taken during an RBx, varying from a minimum of one to a maximum of 20 cores. Intuitively, for smaller lesions, a higher number of cores may be necessary to correctly sample the ROI. On the contrary, for larger lesions, fewer cores should be necessary; nevertheless, at the moment no data are available in this regard. Third, the distance range from the edge of the ROI is debated; Raman et al [16] have shown that 94.2% of SBx cores containing csPCa were found within 15 mm from the lesion edge. In a similar study, Brisbane et al [12] reported that 90% of csPCa detected by SBx were found from a range of 1 cm from the ROI edges. From another perspective, Noujeim et al [15] showed that avoiding Bx in regions farther than 10 mm from the MRI lesion prevents the detection of 19% of non-csPCa cases [13]. Overall, current evidence in the literature suggests that perilesional area sampling should be within 10 mm from the edge of the ROI.

Our study has some limitations: (1) as we have noted, the lack of standardisation of the RBx strategy as well as the different templates and routes might limit the generalisability of the outcomes; (2) most of the studies were retrospective in nature, so that inevitably a selection bias was generally present; (3) in almost all studies, the intervention test was performed first, followed by SBx by the same operator, thereby introducing a high risk of conduction and interpretation bias; and (4) for certain subgroups and secondary outcomes, the lack of significant findings might be due to insufficient statistical power, rather than the absence of a true difference. For instance, the comparison of detection rates in small versus large lesions showed no statistical difference; however, the variability in lesion sizes and the relatively small number of studies in each subgroup might limit the ability to detect an effect.

Nevertheless, given the good quality of the studies selected, this systematic review provides the strongest evidence to date to support TBx + RBx as a new standard strategy for prostate Bx. The clinical implications might not be generalisable to all patients. For Bx-averse patients, a region-targeted approach of highly suspicious lesions (PI-RADS 4 and 5) may be appropriate; for patients selected for active treatment, the SBx result may still be necessary. In the former case, considering the shift from the opportunistic early diagnosis to an organised screening programme, the region-targeted approach will reduce the risk of complications, time for histology examination, and overall costs [49,50]. In the latter case, detection of secondary MRI-invisible foci with the systematic approach might affect patient management, for example, in defining whether a patient is suitable for focal therapy or when undertaking nerve sparing during radical prostatectomy. Nevertheless, we do not know whether leaving the MRI-invisible foci untreated would inevitably cause treatment failure (ie, a harm to the patient). Finally, patients with a previous negative SBx with persistently visible MRI lesions might benefit from the intensification of RBx instead of a repeated SBx (Supplementary Fig. 3). Longitudinal studies are warranted to better define which patient groups would benefit most from which of these Bx strategies, and the impact of eventual grade migration.

5. Conclusions

This systematic review provides the strongest evidence supporting TBx + RBx as a valuable strategy for the detection of csPCa in MRI-visible lesions while avoiding overdiagnosis of insignPCa. There are on-going needs to be addressed, including standardisation of the number and spatial placements of TBx and PLBx cores, as well as the area defining

the perilesional zone in relation to the size of the MRI target.

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Appendix A. Supplementary data

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References

[1] Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med 2018;378:1767–77.
[2] Rouviere O, Puech P, Renard-Penna R, et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. Lancet Oncol 2019;20:100–9.
[3] van der Leest M, Cornel E, Israel B, et al. Head-to-head comparison of transrectal ultrasound-guided prostate biopsy versus multiparametric prostate resonance imaging with subsequent magnetic resonance-guided biopsy in biopsy-naive men with elevated prostate-specific antigen: a large prospective multicenter clinical study. Eur Urol 2019;75:570–8.
[4] Drost FH, Osses D, Nieboer D, et al. Prostate magnetic resonance imaging, with or without magnetic resonance imaging-targeted biopsy, and systematic biopsy for detecting prostate cancer: a Cochrane systematic review and meta-analysis. Eur Urol 2020;77:78–94.
[5] Ahdoot M, Wilbur AR, Reese SE, et al. MRI-targeted, systematic, and combined biopsy for prostate cancer diagnosis. N Engl J Med 2020;382:917–28.
[6] Leapman MS, Thiel CL, Gordon IO, et al. Environmental impact of prostate magnetic resonance imaging and transrectal ultrasound guided prostate biopsy. Eur Urol 2023;83:463–71.
[7] Madej A, Wilkosz J, Rozanski W, Lipinski M. Complication rates after prostate biopsy according to the number of sampled cores. Cent European J Urol 2012;65:116–8.
[8] Eggener SE, Berlin A, Vickers AJ, Paner GP, Wolinsky H, Cooperberg MR. Low-grade prostate cancer: time to stop calling it cancer. J Clin Oncol 2022;40:3110–4.
[9] Weinstein IC, Wu X, Hill A, et al. Impact of magnetic resonance imaging targeting on pathologic upgrading and downgrading at prostatectomy: a systematic review and meta-analysis. Eur Urol Oncol 2023;6:355–65.
[10] Ahdoot M, Lebastchi AH, Long L, et al. Using Prostate Imaging-Reporting and Data System (PI-RADS) scores to select an optimal prostate biopsy method: a secondary analysis of the trio study. Eur Urol Oncol 2022;5:176–86.
[11] Padhani AR, Weinreb J, Rosenkrantz AB, Villeirs G, Turkbey B, Barentsz J. Prostate Imaging-Reporting and Data System Steering Committee: PI-RADS v2 status update and future directions. Eur Urol 2019;75:385–96.
[12] Brisbane WG, Priester AM, Ballon J, et al. Targeted prostate biopsy: umbra, penumbra, and value of perilesional sampling. Eur Urol 2022;82:303–10.
[13] Hagens MJ, Fernandez Salamanca M, Padhani AR, van Leeuwen PJ, van der Poel HG, Schoots IG. Diagnostic performance of a magnetic resonance imaging-directed targeted plus regional biopsy approach in prostate cancer diagnosis: a systematic review and meta-analysis. Eur Urol Open Sci 2022;40:95–103.
[14] Bryk DJ, Llukani E, Taneja SS, Rosenkrantz AB, Huang WC, Lepor H. The role of ipsilateral and contralateral transrectal ultrasound-guided systematic prostate biopsy in men with unilateral magnetic resonance imaging lesion undergoing magnetic resonance imaging-ultrasound fusion-targeted prostate biopsy. Urology 2017;102:178–82.
[15] Noujeim JP, Belahsen Y, Lefebvre Y, et al. Optimizing multiparametric magnetic resonance imaging-targeted biopsy and detection of clinically significant prostate cancer: the role of perilesional sampling. Prostate Cancer Prostatic Dis 2023;26:575–80.
[16] Raman AG, Sarma KV, Raman SS, et al. Optimizing spatial biopsy sampling for the detection of prostate cancer. J Urol 2021;206:595–603.
[17] Saner YM, Wiesenfarth M, Weru V, et al. Detection of clinically significant prostate cancer using targeted biopsy with four cores versus target saturation biopsy with nine cores in transperineal prostate fusion biopsy: a prospective randomized trial. Eur Urol Oncol 2023;6:49–55.
[18] Park MY, Park KJ, Lim B, Kim MH, Jeong IG, Kim JK. Comparison of biopsy strategies for prostate biopsy according to lesion size and PSA density in MRI-directed biopsy pathway. Abdom Radiol (NY) 2020;45:4166–77.
[19] Tschirdewahn S, Wiesenfarth M, Bonekamp D, et al. Detection of significant prostate cancer using target saturation in transperineal magnetic resonance imaging/transrectal ultrasonography-fusion biopsy. Eur Urol Focus 2021;7:1300–7.
[20] Calio BP, Sidana A, Sugano D, et al. Risk of upgrading from prostate biopsy to radical prostatectomy pathology-does saturation biopsy of index lesion during multiparametric magnetic resonance imaging-transrectal ultrasound fusion biopsy help? J Urol 2018;199:976–82.
[21] Freifeld Y, Xi Y, Passoni N, et al. Optimal sampling scheme in men with abnormal multiparametric MRI undergoing MRI-TRUS fusion prostate biopsy. Urol Oncol 2019;37:57–62.
[22] Jager A, van Riel L, Postema AW, de Reijke TM, van der Sluis TM, Oddens JR. An optimized prostate biopsy strategy in patients with a unilateral lesion on prostate magnetic resonance imaging avoids unnecessary biopsies. Ther Adv Urol 2022;14:17562872221111410.
[23] Phelps TE, Yilmaz EC, Harmon SA, et al. Ipsilateral hemigland prostate biopsy may underestimate cancer burden in patients with unilateral mpMRI-visible lesions. Abdom Radiol (NY) 2023;48:1079–89.
[24] Shen WW, Cui LG, Ran WQ, et al. Targeted biopsy with reduced number of cores: optimal sampling scheme in patients undergoing magnetic resonance imaging/transrectal ultrasound fusion prostate biopsy. Ultrasound Med Biol 2020;46:1197–207.
[25] Wang F, Chen T, Wang M, et al. Clinically significant prostate cancer (csPCa) detection with various prostate sampling schemes based on different csPCa definitions. BMC Urol 2021;21:183.
[26] Yusim I, Mazor E, Frumkin E, et al. Evaluation of the optimal strategy in men with a single unilateral suspicious lesion on MRI undergoing transperineal MRI/ultrasound fusion prostate biopsy. Prostate 2023;83:1255–62.
[27] Cornford P, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on prostate cancer—2024 update. Part

I: screening, diagnosis, and local treatment with curative intent. Eur Urol 2024;86:148–63.
[28] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
[29] Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529–36.
[30] Assel M, Sjoberg D, Elders A, et al. Guidelines for reporting of statistics for clinical research in urology. Eur Urol 2019;75:358–67.
[31] Calio BP, Deshmukh S, Mitchell D, et al. Spatial distribution of biopsy cores and the detection of intra-lesion pathologic heterogeneity. Ther Adv Urol 2019;11:1756287219842485.
[32] Hagens MJ, Noordzij MA, Mazel JW, et al. An magnetic resonance imaging-directed targeted-plus-perilesional biopsy approach for prostate cancer diagnosis: "less is more". Eur Urol Open Sci 2022;43:68–73.
[33] Hansen NL, Barrett T, Lloyd T, et al. Optimising the number of cores for magnetic resonance imaging-guided targeted and systematic transperineal prostate biopsy. BJU Int 2020;125:260–9.
[34] Lee AYM, Chen K, Cheng CWS, et al. Intensive sampling of the umbra and penumbra improves clinically significant prostate cancer detection and reduces risk of grade group upgrading at radical prostatectomy. World J Urol 2023;41:2265–71.
[35] Barrett T, Patterson AJ, Koo BC, et al. Targeted transperineal biopsy of the prostate has limited additional benefit over background cores for larger MRI-identified tumors. World J Urol 2016;34:501–8.
[36] Diamand R, Hollans M, Lefebvre Y, et al. The role of perilesional and multiparametric resonance imaging-targeted biopsies to reduce the risk of upgrading at radical prostatectomy pathology: a retrospective monocentric study. Urol Oncol 2022;40:192.e11–e17.
[37] Novara G, Zattoni F, Zecchini G, et al. Role of targeted biopsy, perilesional biopsy, and random biopsy in prostate cancer diagnosis by mpMRI/transrectal ultrasonography fusion biopsy. World J Urol 2023;41:3239–47.
[38] Ruan M, Wang H, Li X, Song G. Novel sampling scheme with reduced cores in men with multiparametric MRI-visible lesions undergoing prostate biopsy. Abdom Radiol (NY) 2023;48:2139–47.
[39] Klingebiel M, Arsov C, Ullrich T, et al. Reasons for missing clinically significant prostate cancer by targeted magnetic resonance imaging/ultrasound fusion-guided biopsy. Eur J Radiol 2021;137:109587.
[40] Williams C, Ahdoot M, Daneshvar MA, et al. Why does magnetic resonance imaging-targeted biopsy miss clinically significant cancer? J Urol 2022;207:95–107.
[41] Lehto TK, Pylvalainen J, Sandeman K, et al. Histomic and transcriptomic features of MRI-visible and invisible clinically significant prostate cancers are associated with prognosis. Int J Cancer 2024;154:926–39.
[42] Houlahan KE, Salmasi A, Sadun TY, et al. Molecular hallmarks of multiparametric magnetic resonance imaging visibility in prostate cancer. Eur Urol 2019;76:18–23.
[43] Li P, You S, Nguyen C, et al. Genes involved in prostate cancer progression determine MRI visibility. Theranostics 2018;8:1752–65.
[44] Morote J, Picola N, Munoz-Rodriguez J, et al. A diagnostic accuracy study of targeted and systematic biopsies to detect clinically significant prostate cancer, including a model for the partial omission of systematic biopsies. Cancers (Basel) 2023;15:4543.
[45] Muthigi A, George AK, Sidana A, et al. Missing the mark: prostate cancer upgrading by systematic biopsy over magnetic resonance imaging/transrectal ultrasound fusion biopsy. J Urol 2017;197:327–34.
[46] Connor MJ, Eldred-Evans D, van Son M, et al. A multicenter study of the clinical utility of nontargeted systematic transperineal prostate biopsies in patients undergoing pre-biopsy multiparametric magnetic resonance imaging. J Urol 2020;204:1195–201.
[47] Wei JT, Barocas D, Carlsson S, et al. Early detection of prostate cancer: AUA/SUO guideline part II: considerations for a prostate biopsy. J Urol 2023;210:54–63.
[48] National Institute for Health and Care Excellence. Prostate cancer: diagnosis and management (NG131). 2024. https://www.nice.org.uk/guidance/ng131/resources/prostate-cancer-diagnosis-and-management-pdf-66141714312133.
[49] Hugosson J, Mansson M, Wallstrom J, et al. Prostate cancer screening with PSA and MRI followed by targeted biopsy only. N Engl J Med 2022;387:2126–37.
[50] Bratt O, Godtman RA, Jiborn T, et al. Population-based organised prostate cancer testing: results from the first invitation of 50-year-old men. Eur Urol 2024;85:207–14.