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TOPIC PAPER

Micro-ultrasound-guided biopsies versus systematic biopsies in the detection of prostate cancer: a systematic review and meta-analysis

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Abstract

Purpose The diagnosis of prostate cancer (PCa) still relies on the performance of both targeted (TB) and systematic biopsies (SB). Micro-ultrasound (mUS)-guided biopsies demonstrated a high sensitivity in detecting clinically significant prostate cancer (csPCa), which could be comparable to that of magnetic resonance imaging (MRI)-TB, but their added value has not been compared to SB yet.

Methods We conducted a systematic review and meta-analysis, based on Medline, EMBASE, Scopus, and Web of Science, in accordance with PRISMA guidelines, to compare mUS-guided biopsies to SB.

Results Based on the literature search of 2957 articles, 15 met the inclusion criteria (2967 patients). Most patients underwent mUS-guided biopsies, followed by MRI-TB and SB. Respectively 5 ($n=670$) and 4 ($n=467$) studies, providing raw data on SB, were included in a random-effect meta-analysis of the detection rate of csPCa, i.e. Gleason Grade Group (GGG) ≥ 2 or non-csPCa (GGG = 1). Overall, PCa was detected in 56–71% of men, with 31.3–49% having csPCa and 17–25.4% having non-csPCa. Regarding csPCa, mUS-guided biopsies identified 196 and SB 169 cases (Detection Ratio (DR): 1.18, 95% CI 0.83–1.68, $I^2=69\%$), favoring mUS-guided biopsies; regarding non-csPCa, mUS-guided biopsies identified 62 and SB 115 cases (DR: 0.55, 95% CI 0.41–0.73, $I^2=0\%$), also favoring mUS-guided biopsies by decreasing unnecessary diagnosis.

Conclusion Micro-ultrasound-guided biopsies compared favorably with SB for the detection of csPCa and detected fewer non-csPCa than SB. Prospective trials are awaited to confirm the interest of adding mUS-guided biopsies to MRI-TB to optimize csPCa detection without increasing overdiagnosis of non-csPCa.

Keywords Prostate cancer · Meta-analysis · Micro-ultrasound · Targeted biopsies · Systematic biopsies

Introduction

The prostate cancer (PCa) imaging pathway is nowadays based on multiparametric magnetic resonance imaging (mpMRI) before prostate biopsies, assessing disease extension and local staging [1]. The MRI pathway also relies on the ability of pre-biopsy mpMRI to identify suspicious lesions within the prostate and allows for the performance of targeted biopsies (TB) in addition to random systematic biopsies (SB). While MRI-TB has been shown to be superior to SB [2], the combination of both techniques is still recommended for the detection of clinically significant PCa (csPCa) [3], although some authors suggested that SB contralateral to the suspicious MRI lesion detected mainly non-clinically significant PCa (non-csPCa) [4].

Hence, while transitioning from SB to TB enhanced our ability to detect clinically significant disease, novel strategies are needed to decrease overdiagnosis of non-csPCa [5]. Micro-ultrasound (mUS) is a new imaging technique relying on a high-frequency transducer which confers a 300% improvement in spatial resolution over conventional ultrasound (US) [6]. A grading system has been proposed to stratify mUS images according to the probability of

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detecting csPCa (Prostate Risk Identification using Micro-ultrasound—PRI-MUS score) [6]. Micro-ultrasound-guided biopsies have been described as a promising alternative to MRI-TB with comparable detection rates for csPCa [7]. Moreover, recent studies showed additional benefit of adding mUS to mpMRI and systematic mapping, owing to the ability to detect csPCa that may be missed by mpMRI [8]. However, whether mUS-guided biopsies may favorably replace SB with a similar detection of csPCa without increasing the detection of non-csPCa is still an unanswered question.

The aim of our study was to assess the detection rates of csPCa and non-csPCa by mUS-guided biopsies compared to SB, through a systematic review and meta-analysis of the existing literature.

Methods and evidence acquisition

Search strategy and registration

We conducted a systematic review in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [9]. The aims and methods of our study were prespecified and registered in a protocol at PROSPERO (ID: CRD42021247932). A systematic literature search was conducted in 4 databases (Medline, Embase, Scopus, and Web of science), without time restriction up to December 2021. A targeted search of the grey literature was conducted comprising conference abstracts, clinical trial registries (ClinicalTrials.gov), and websites (exactimaging.com). We then manually screened the references of included articles for any additional reference.

The systematic search strategy was created for Medline and revised accordingly for the other databases. The Embase search was conducted using the "exclude Medline journals" limit. Duplicates were removed automatically on Zotero, as well as articles without an abstract or a DOI. We pooled the terms (("biopsies" OR "pathology" OR "aspiration") AND ("prostate cancer" OR "prostatic neoplasms") AND ("micro-ultrasound" OR "microUS" OR "29 MHz" OR "Exactvu" OR "high resolution")) using the Boolean operator OR and AND (Supplementary Appendix 1).

Inclusion and exclusion criteria

The study design was established according to the PICOS (Population, Intervention, Comparator, Outcome, Study design) process. Studies were selected if they included men of any age with clinical suspicion of PCa (PSA value and/or suspicious digital rectal examination) (Population), undergoing high-resolution mUS-guided biopsies (Intervention) compared to SB (Comparator). We analyzed the detection rate of clinically significant PCa (csPCa) (defined as a Gleason Grade Group (GGG) ≥ 2) and non-clinically significant PCa (non-csPCa) (GGG = 1) (Outcome), in prospective and retrospective studies (Study design).

Studies in which each patient received consecutively mUS-guided biopsies and SB were included, regardless of the realization of MRI-TB. Studies including patients without SB, patients on active surveillance, and studies with mUS performed in patients already diagnosed with PCa or studies on contrast-enhanced US or computerized US were excluded. Articles written in English, French, and Spanish only were considered. Case reports, reviews, and editorial comments were also excluded, but abstracts and posters were considered for inclusion. When we identified records with potential overlapping populations, the most recent was selected, or the one available as full-text.

The quantitative synthesis included studies with available raw data on SB results as well as mUS results.

Data extraction and quality assessment

Two review authors (C.D. and G.F.) performed an independent initial study selection and data extraction. All discrepancies regarding study selection and data extraction were resolved by discussion with a third co-author (G.P.). For each included record, we retrieved information about study and participant characteristics, interventions, and PCa classification according to the International Society of Urological Pathology (ISUP) GGG [10], detection rate of csPCa and non-csPCa.

We estimated the risk of bias and applicability concerns of each study using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [11]. Each study was independently assessed by two authors (C.D., G.F.), using the Risk-Of-Bias VISualization (robvis) tool [12], and disagreements solved by consensus. Funnel plots were drawn to assess publication bias across studies [13].

Data synthesis and statistical analysis

The detection rate was estimated as the number of participants diagnosed with the relevant GGG of PCa for each outcome divided by the number of participants who underwent both mUS-guided biopsies and SB.

We performed a random-effect meta-analysis of detection ratios (DRs). DR was estimated as the mUS-guided biopsies detection rate divided by the SB detection rate. DRs with the corresponding 95% confidence intervals (CIs) were obtained for the two following outcomes: (i) mUS vs SB for the detection of csPCa (GGG ≥ 2); (ii) mUS vs SB for the detection of non-csPCa (GGG = 1).

Between-study heterogeneity was estimated by the I^2 and its significance assessed by the p value of the Cochran's Q test [13]. Statistical analyses were performed with the

R statistical program version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org/) using the "metafor" package, with significance set at $p \leq 0.05$.

Results

Literature search and study results

The literature search was first performed on 4th April 2021 and renewed on 14th December 2021. The selection flow diagram adapted from the PRISMA recommendations is illustrated in Fig. 1, and the Pubmed search syntax and search string are detailed in Supplementary Appendix 1.

The initial literature search (databases search and manual search) yielded 2619 potentially relevant records after removal of duplicates. After title and abstract screening, 51 full-text articles and 9 posters or abstracts were assessed for eligibility. At the end of the process, after excluding 45 reports, 15 studies were included in the qualitative synthesis, comprising 11 studies published as full-texts [8, 14–23] and 4 as posters or conference abstracts [24–27].

Quality assessment

Applying the QUADAS-2 tool for the included studies, the overall methodological quality was evaluated as moderate. In particular, regarding risk of bias, 2 studies were estimated of low risk of bias, 8 of moderate risk, and 5 of high risk of bias. Regarding applicability concerns, 10 studies were considered of low risk, 3 of moderate risk, and 2 of high risk of bias. The detailed assessment is available in Supplementary Appendix 2.

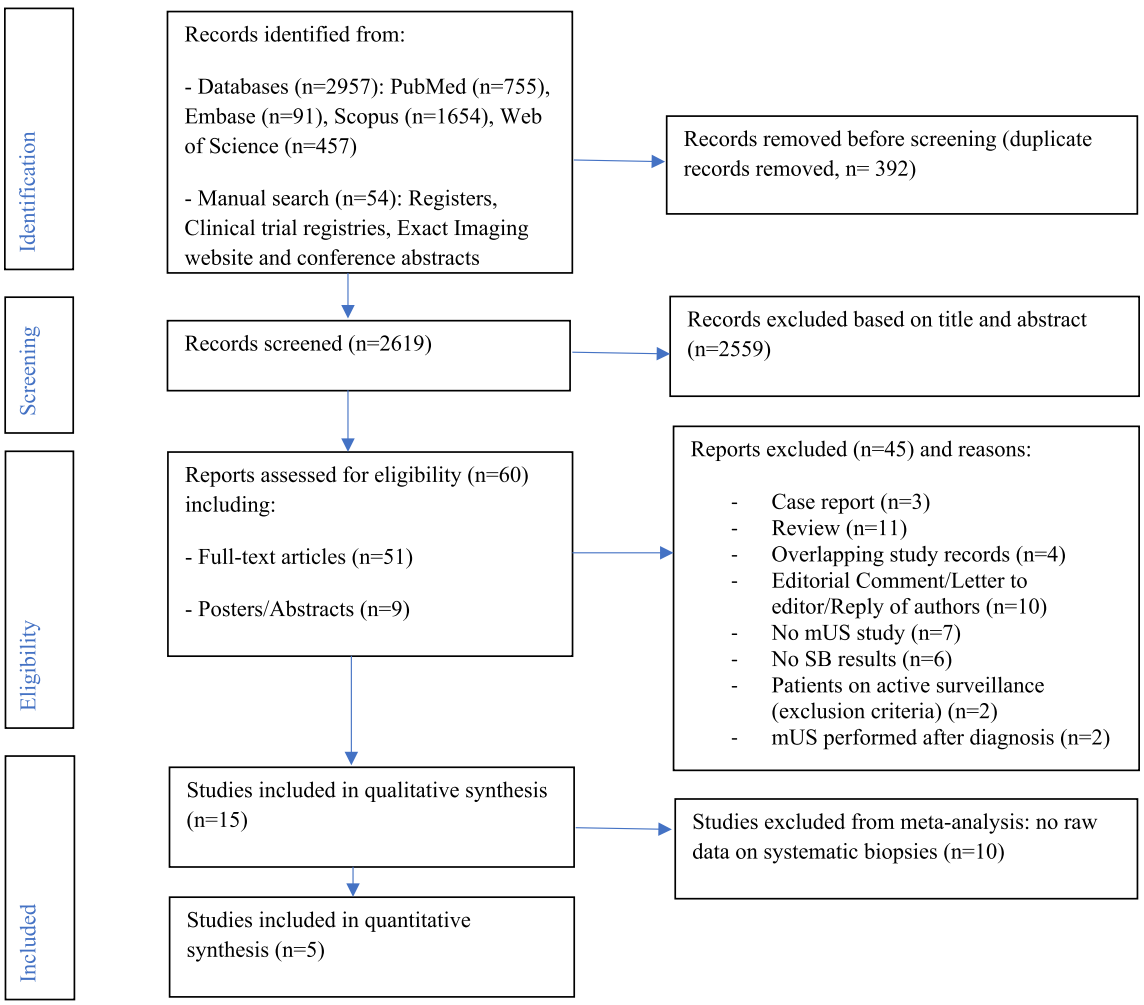

Fig. 1 Preferred reporting items of systematic reviews and meta-analyses (PRISMA) flow-diagram of selected studies

Qualitative synthesis

Population and study design (15 studies)

A total of 2967 participants from 15 published trials were included in the qualitative synthesis (Table 1). Ten studies were prospective and 5 were retrospective, and all patients included underwent biopsies between 2017 and 2020, with the exception of the study of Pavlovich et al. (mUS-guided biopsies performed in 2010–2011 compared to conventional trans-rectal US (TRUS)-guided biopsies) [23].

In all studies, patients underwent first mUS-guided biopsies, followed by MRI-TB (except for two studies [14, 23]) and systematic TRUS-guided biopsies (defined as systematic, completion samples or non-targeted areas cores). When specified, all authors were using the ExactVu™ micro-ultrasound system (Exact Imaging, Makham, Canada), with a 29 MHz high resolution for the performance of mUS-guided biopsies and also for guiding MRI-TB, after a standardized training program from Exact Imaging. Micro-US lesions were documented according to the prostate risk identification for micro-US (PRI-MUS) protocol [6] and targeted independently of the mpMRI lesions. Lesions that scored ≥ 3 in PRI-MUS or PI-RADS were defined as targets.

The median number of patients in each study ranged from 25 to 1040. The median age varied from 59 to 70 years old. The median PSA ranged from 5.32 to 9.2 ng/mL, with 16–74% of patients having had prior prostate biopsies. Prostate biopsies were performed by an exclusive trans-rectal ($n = 6$), trans-perineal approach ($n = 1$), or both depending on the target ($n = 2$), and this information was not reported in 6 studies. For anesthesia, 2 studies described a local nerve block when using a trans-rectal approach [14, 20] and 1 a spinal short-term anesthesia with Lidocaine for a trans-perineal exclusive approach [8]. Operators were blinded to mpMRI results in 8/15 studies (53.3%). Operators performed a median range of 2–9 targeted biopsies and 10–32 systematic biopsies. Biopsy cores were analyzed by specialized uropathologists using the ISUP Gleason grading system [10].

Regarding the diagnostic accuracy of mUS, sensitivity, specificity, positive predictive value, and negative predictive value for the detection of csPCa at the patient level ranged from 65 to 100%, 15 to 72%, 19 to 66%, and 71 to 100%, respectively [8, 14–27].

Five studies provided raw data on the comparator arm (SB) and were included in the meta-analysis [8, 14, 20–22].

Population and study design from the 5 studies included in the quantitative analysis

Five studies compared mUS to SB in the clinical context of a suspicion of PCa (based on elevated PSA values and/or suspicious digital rectal examination), with SB raw data available [8, 14, 20–22].

Biopsies were performed between 2017 and 2019 on a total of 670 patients. Three studies were prospective and 2 were retrospective.

All studies but one focused on demonstrating either the non-inferiority of mUS to detect csPCa, compared to mpMRI, or the added value of mUS to the mpMRI pathway [8, 20–22]. Abouassaly et al. aimed at evaluating the added value of mUS over SB. No major publication bias was suspected from the shape and symmetry of the funnel plots (Supplementary Appendix 3).

Quantitative synthesis

Clinically significant PCa detection rate

In the quantitative analysis of men with GGG ≥ 2 PCa, we included the 5 studies providing raw data on SB comprising 670 participants receiving mUS-guided biopsies, followed by MRI-TB (but for 48 patients) [14], followed by SB [8, 14, 20–22]. Overall, PCa was found in 56–71% of men, with 31.3–49% having csPCa defined as GGG ≥ 2 and 14.9–32.7% when defined as GGG ≥ 3 [14, 21].

By adding the results of the 3 techniques, 278 patients with GGG ≥ 2 PCa were identified. The mUS-guided biopsies identified 196 and the SB 169 cases (DR: 1.18, 95% CI 0.83–1.68, $I^2 = 69\%$), favoring mUS-guided biopsies (Fig. 2).

Non-clinically significant PCa detection rate

In the quantitative analysis of men with non-clinically csPCa (GGG = 1), we included the 4 studies (among the 5 previous studies) providing raw data on SB comprising 467 participants receiving mUS-guided biopsies, followed by SB [8, 14, 20, 21]. Non-significant PCa (GGG1) was detected in 17–25.4% of men. By adding the results of mUS-guided biopsies, MRI-TB, and SB, 138 patients with GGG1 PCa were identified. The mUS-guided biopsies identified 62 and the SB 115 cases (DR: 0.55, 95% CI 0.41–0.73, $I^2 = 0\%$) significantly favoring mUS-guided biopsies (Fig. 3).

Discussion

This systematic review and meta-analysis demonstrated that mUS-guided biopsies compared favorably with SB for the detection of csPCa, and detected fewer non-csPCa, in an unselected population of men undergoing prostate biopsies in a pathway integrating mpMRI assessment.

Previous studies have shown a comparable detection rate of mUS-guided biopsies compared to MRI-TB, suggesting

Table 1 Baseline characteristics of the included studies ($n = 15$), with micro-ultrasound accuracy for the detection of clinically significant prostate cancer (Gleason Grade Group ≥ 2)

Author Year Full-text (FT) or poster (P)	Study duration and design	Compared techniques	Patients ($n = 2967$)	Clinical context	mpMRI blinding	Prior biopsies (n,%)	Age (yr, IQR)	PSA (ng/mL, IQR)	Abnormal DRE (n,%)	Prostate volume on US (mL, IQR)	Number of cores per mUS target/per SB	Sn of mUS vs MRI (%)	Sp of mUS vs MRI (%)	PPV of mUS vs MRI (%)	NPV of mUS vs MRI (%)
Abouassaly et al. 2020 [13] FT	01/2018-08/2018 Prospective	mUS vs mpMRI vs SB	67 (only 19 with MRI data)	Suspicion of PCa	No	19 (28)	66 (59–69)	5.39 (4.13–8.74)	7 (10.4)	38 (24–50)	2 (2–3) /12	75	26	NA	NA
Astobieta et al. 2018 [24] P	NA Retrospective	mUS vs mpMRI	79	Men with available mpMRI results	Yes	NA	NA	NA	NA	NA	NA	82 vs 30	40 vs 91	19 vs 36	93 vs 88
Avolio et al. 2021 [14] FT	10/2017-03/2020 Retrospective	mUS vs mpMRI	111	PI-RADS = 3 (no PI-RADS 4–5 lesion)	Yes	55 (49.5)	63 (58–68)	6 (4.3–8.2)	18 (16.2)	50 (35–68)	NA/14	100 vs NA	33.7 vs NA	27.2 vs NA	100 vs NA
Hofbauer et al. 2021 [21] FT	01/2019-12/2019 Prospective	mUS vs mpMRI vs SB (completion samples)	203	Suspicion of PCa with pre-biopsy mpMRI	Yes	56 (28)	66 (59–70)	6.5 (4.8–9.3)	31 (15)	48 (37–63)	2/10–14	NA	NA	NA	NA
Klotz et al. 2021 [15] FT	NA Prospective	mUS vs mpMRI	1040	Multi-centric study. Variable inclusion criteria	No	352 (34)	67 (61–72)	7 (5.1–10)	208 (128 NA)	38 (28–53)	2–3/12–14	94 vs 90	22 vs 22	44 vs 43	85 vs 77
Lopez et al. 2019 [23] P	NA Prospective	mUS vs mpMRI	51	Elevated PSA or abnormal DRE	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Luger et al. 2019 [16] FT	01/2018-05/2019 Prospective	mUS vs mpMRI (only 35 pts)	372	Clinical suspicion of PCa	No	NA	NA	NA	NA (30)	NA	NA/16	NA	NA	4.4–71.4 vs NA	NA

Table 1 (continued)

Author Year Full-text (FT) or poster (P)	Study duration and design	Compared techniques	Patients ($n=2967$)	Clinical context	mpMRI blinding	Prior biopsies (n,%)	Age (yr, IQR)	PSA (ng/mL, IQR)	Abnormal DRE (n,%)	Prostate volume on US (mL, IQR)	Number of cores per mUS target/per SB	Sn of mUS vs MRI (%)	Sp of mUS vs MRI (%)	PPV of mUS vs MRI (%)	NPV of mUS vs MRI (%)
Lughezzani et al. 2020 [17] FT	10/2017-09/2019 Prospective	mUS vs mpMRI	320	PI-RADS ≥ 3	Yes	NA	65 (59–70)	7.3 (5.2–9.9)	72 (22.5)	45 (30–70)	NA/14	89.7 vs NA	26 vs NA	40.8 vs NA	81.5 vs NA
Martel et al. 2019 [25] P	05/2018-03/2019 Retrospective	mUS vs mpMRI	148	Men with targeted biopsy for suspicion of PCa	No	66 (45)	67 (60–71)	7 (4.6–104)	NA	NA	NA/(12–21)	NA	NA	NA	NA
Pavlovich et al. 2014 [22] FT	2010–2011 Prospective	High-resolution US versus low-resolution conventional TRUS (LoTRUS)	25	Men harboring cT1-2 PCa scheduled for RALP	Yes	Yes	59 (50–70)	5.5 (2.5–9.9)	NA	NA	NA/12	65 vs 38 Low-TRUS	72 vs 65 Low-TRUS	66 vs 48 Low-TRUS	71 vs 55 Low-TRUS
Pereira-Arias et al. 2019 [18] FT	02/2017-02/2018 Prospective	mUS vs mpMRI (92%)	96	Clinical suspicion of PCa	Yes	45 (47)	67 (48–81)	7.49 (1.29–34.9)	NA	48 (15–113)	2/12	82	39	19	93
Perez et al. 2019 [26] P	NA Prospective	mUS vs mpMRI vs SB	55	Suspicion of PCa and available mpMRI	No	9 (16)	67 (62–69)	9.2 (6.7–12)	NA	NA	NA	93.3	27.5	32.6	91.7
Rodriguez-Socarras et al. 2020 [7] FT	02/2018-09/2019 Retrospective	mUS vs mpMRI vs SB	194	Suspicion of PCa	Yes	65 (34)	62 -58–68)	6.5 –(4.7–9.2)	31 (16.5)	47 (32–67)	5 (3–6)/32 (30–37)	99.7	23.1	46	99.2

Table 1 (continued)

Author Year Full-text (FT) or poster (P)	Study duration and design	Compared techniques	Patients ($n = 2967$)	Clinical context	mpMRI blinding	Prior biopsies (n,%)	Age (yr, IQR)	PSA (ng/mL, IQR)	Abnormal DRE (n,%)	Prostate volume on US (mL, IQR)	Number of cores per mUS target/per SB	Sn of mUS vs MRI (%)	Sp of mUS vs MRI (%)	PPV of mUS vs MRI (%)	NPV of mUS vs MRI (%)
Rojas Claros et al. 2020 [19] FT	02/2017–09/2018 Retrospective	mUS vs mpMRI vs SB (random samples)	47	Suspicion of PCa	No	200 (74)	68 (62–72)	7.8 (5.5–102)	NA	48.5 (36–65)	3 (2–4)/10 (8–12)	95	62	NA	NA
Wiemer et al. 2020 [20] FT	02/2018-12/2018 Prospective	mUS vs mpMRI vs SB (non-targeted biopsies)	159	Suspicion of PCa	Yes	42 (26)	70 (64–74)	7.59 (5.78–11.5)	42 (26)	53 (35.5–76.5)	6 (2–9)/6 (5–8)	95	15	52	75

DRE digital rectal examination, *FT* full-text, *IQR* interquartile range, mL milliliter, *MRI* magnetic resonance imaging, *mpMRI* multiparametric magnetic resonance imaging, *mUS* micro-ultrasound, *n* number of men, *NA* non-available, *NPV* negative predictive value, *P* poster, *PCa* prostate cancer, *PI-RADS* prostate imaging reporting and data system, *PPV* positive predictive value, *PSA* prostate specific antigen, *RALP* robotic-assisted laparoscopic prostatectomy, *SB* systematic biopsy, *Sn* sensitivity, *Sp* specificity, *TRUS* trans-rectal ultrasound, *US* ultrasound, *vs* versus

that mUS may replace MRI for the early detection of PCa [7, 28]. Yet, the added value of MRI is not limited to the definition of potential biopsy targets. MRI also provides key information for local staging, risk classification and treatment planning, and, to date, will remain irreplaceable for these reasons [29, 30]. Conversely, the addition of SB to MRI-TB, while offering the highest detection rate for csPCa, also results in the overdetection of non-csPCa. This study is, to our knowledge, the first to suggest the interest of adding mUS-guided biopsies to MRI-TB, offering comparable accuracy to MRI-TB + SB while significantly reducing overdiagnosis of non-csPCa.

Recent advances in US technology have been made with the goal to provide a readily accessible and cost-effective tool for detection of PCa [31, 32], among which high-frequency mUS has emerged as a promising imaging modality for PCa diagnosis [6]. Indeed, mUS uses a 29 MHz frequency (compared to 7–12 MHz for the conventional US) which corresponds to a three-fold improvement in spatial resolution (70 µm), at the expense of the depth of penetration [6, 33]. Initial results have shown high sensitivity of mUS in detecting and ruling out PCa in the peripheral zone [7] and proved a useful tool to improve the accuracy of TB by allowing for real-time visualization of the needle inside the target, rather than relying on cognitive or software MRI-US fusion. Both mUS imaging and biopsy targeting can be done in a single session, and the learning curve for operators experienced in TRUS is reported to be short and limited to simple techniques issues and understanding of PRI-MUS characteristics [6]. Of note, little is known on the use of mUS for the detection and targeting of suspicious lesions of the transition zone and anterior areas, such as the anterior fibro-muscular stroma, where mUS is expected to be limited by the depth of US penetration and the feasibility certainly unpredictable [32].

The results of this meta-analysis are in favor of mUS-guided biopsies over SB for the detection of csPCa while detecting significantly fewer non-csPCa than SB. This is an important finding, since the addition of SB to MRI-TB leads to a significant increase in non-csPCa detection [34]. Although high between-study heterogeneity was noted in the pooled analysis of the detection rate of csPCa, results proved consistency for non-csPCa detection. This result is in line with previous studies demonstrating a higher sensitivity of mUS in detecting csPCa than conventional TRUS, whether cores were taken either systematically or from a target near the systematic position, still with the same total number of biopsy samples [23]. Given the known limitations of SB, leading to non-csPCa overdetection while missing up to 30% of csPCa [3], mUS-guided biopsies could offer a promising option to optimize csPCa rate while avoiding overdiagnosis, although these exploratory results have yet to be confirmed in dedicated, prospective studies.

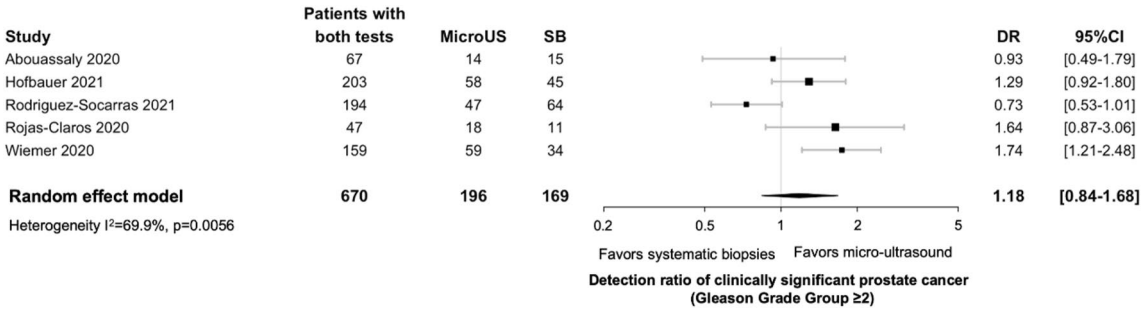

Fig. 2 Forest plot of the detection rate of micro-ultrasound versus systematic biopsies for clinically significant prostate cancer (Gleason Grade Group ≥ 2). *CI* confidence interval, *DR* detection ratio, *Micro-US* micro-ultrasound, *SB* systematic biopsy

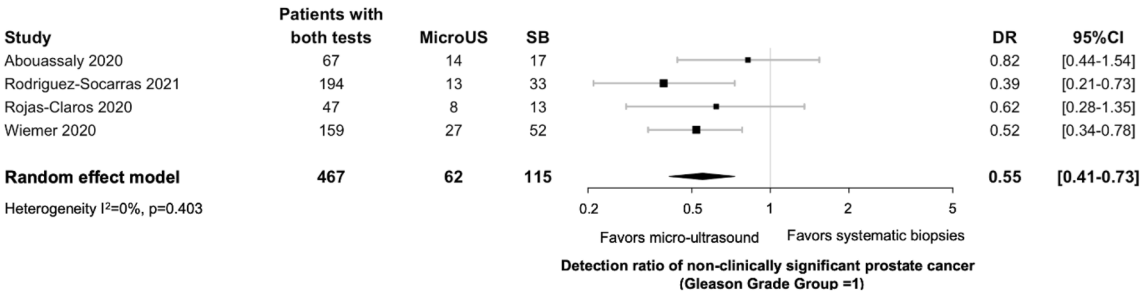

Fig. 3 Forest plot of the detection rate of micro-ultrasound versus systematic biopsies for non-clinically significant prostate cancer (Gleason Grade Group = 1). *CI* confidence interval, *DR* detection ratio, *Micro-US* micro-ultrasound, *SB* systematic biopsy

MRI-TB was rapidly integrated in the PCa diagnostic pathway, with the hope that omitting systematic sampling would be associated with a reduced risk of detecting non-csPCa, shorter procedures, and reduced patient discomfort and biopsy complications, but this strategy was also shown to impair the accurate prediction of pathological features at radical prostatectomy [29]. Given the false-negative rate of MRI and MRI-TB in the initial biopsy and active surveillance settings, SB remains recommended in addition to MRI-TB, while SB can now be omitted in patients with previous negative biopsies [35], representing 26–74% of the patients included in this meta-analysis. Recent publications suggested that the increased sensitivity of SB added to MRI-TB may be explained by the presence of csPCa also in the perilesional biopsies (penumbra), introducing the potential benefit from perilesional saturation biopsy [36]. Some authors recently showed that both 99% of csPCa lesions and men harboring csPCa were identified by target-saturation biopsies (including targeted cores and cores from the adjacent SB sectors), thus suggesting that this approach may allow to omit random SB cores without compromising csPCa detection [37].

We chose to approach this systematic review and meta-analysis with mUS as an add-on test to the mpMRI pathway, used in conjunction to MRI-TB. Indeed, taking into account the added value of MRI beyond the definition of biopsy targets (local staging, monitoring of lesions during active surveillance, treatment planning for focal therapy, surgery or radiation therapy in men undergoing active treatment), and the limitations of mUS (increased attenuation in large adenoma with anterior lesion or with calcifications and cysts) [7], the added value of mUS seems more promising as a complement to MRI rather than a replacement diagnostic test, which is supported by a number of csPCa only diagnosed by one of the two methods in the present review [14, 21]. Rodriguez Socarras et al. showed an additional benefit of adding mUS to mpMRI and systematic mapping, owing to its potential to detect csPCa that may be invisible on mpMRI [8]. Micro-ultrasound detected 11% additional cancers not detected by MRI or SB, while a 2.6% improvement in csPCa detection was observed in another study assessing PI-RADS ≥ 3 patients, by sampling mUS targets in addition to MRI-TB and SB [18]. Conversely, for Hofbauer et al. MRI-TB added 3% additional csPCa lesions (i.e., 7/203). These lesions were located in anterior and transition zone in 3/7 and 2/7 cases, respectively [22].

Dias et al. recently proposed a new algorithm incorporating mUS-guided biopsies as an adjunct to a biparametric MRI (omitting the sequence of perfusion), since the sensitivity of mUS in detecting PCa in the peripheral zone compared favorably with dynamic contrast-enhanced sequences [32]. This combination of biparametric MRI + mUS is even

emphasized by the authors as a possible screening strategy, although limited by both MRI and mUS availability.

Based on these results, the next step would be to evaluate whether mUS-guided biopsies added to MRI-TB (either multiparametric or biparametric) have the potential to finally render random sampling obsolete while reducing overdiagnosis of non-csPCa. There is rationale in this strategy, since mUS-guided biopsies replaces systematic by targeted sampling of hypoechoic and ultrasound-suspicious lesions, irrespective of MRI results. Given the limited added value of SB in patients with previous negative biopsies, we believe this evaluation would be best conducted among biopsy-naïve men in randomized trials.

Some limitations have to be taken into account when reaching these conclusions. The first one lies on the biopsy template used by authors for the performance of SB. Indeed, some studies reported the use of "completion samples," probably voluntarily omitting areas previously sampled by TB [22], which may have underestimated the accuracy of SB. Furthermore, in the registry-based study by Klotz et al. from 11 centers, conventional 12-core SB was not performed in most patients due to the inclusion of mUS targets within the systematic samples and adjustment of systematic positions to reflect tissue variations observed on mUS [16]. Thus, mUS could not be compared to SB in this large prospective cohort of 1040 patients, which was not included in the quantitative analysis. It is also noteworthy that the number of SB and TB cores per patient was not standardized in this registry, as in the other studies evaluated. Therefore, some cases of csPCa may have been missed as a consequence of fewer cores taken from both TB and SB.

Secondly, many studies evaluated were retrospective, some with small number of patients, and with a substantial heterogeneity between cohorts, which may also limit the generalizability of our findings. Although the importance of our results was deemed critical, the overall strength of evidence was considered low or moderate for all outcomes between the reviewers. Bias concerns were linked to the absence of blinding of operators to the mpMRI findings in some studies, which could have biased both mUS-guided biopsies and SB, and to non-adherence to PRI-MUS score in others. Current studies where the US annotation is performed blinded to the MRI are ongoing (ClinicalTrials.gov Identifier: NCT03938376; NCT03762616). Additionally, the observational design of all studies, the unclear or high-risk of bias of some trials, and the fact that about half of the included records were published as conference abstracts or registries downgraded the quality of evidence.

Finally, it is likely that many operators performing mUS-guided biopsies were new to this novel technique and to the PRI-MUS score, and the impact of this learning curve on the diagnostic performance of mUS still has to be determined. Moreover, the PRI-MUS protocol provides a user-dependent, B-mode-based, and subjective scoring system (e.g., cauliflower/smudgy/mottled appearance description for PRI-MUS score 4), compared to the multiparametric standardized PI-RADS score, thus possibly leading to poor reproducibility [38]. Still, it was beyond the scope of the present study to assess the sensitivity, specificity, and predictive values of mUS-guided vs SB.

The results of ongoing prospective trials are awaited (OPTIMUM) [39] and will help assess the role of mUS in the diagnosis pathway of csPCa compared to the usual MRI/US fusion pathway in terms of detection rate, economic impact, and with secondary objective, including the detection rate/negative predictive value of each imaging modality-TB compared to SB.

Conclusions

Micro-ultrasound showed high sensitivity in detecting PCa in men undergoing prostate biopsies for clinical suspicion of PCa. Micro-ultrasound-guided biopsies compared favorably with SB for the detection of csPCa and detected fewer non-csPCa than SB. Prospective trials are awaited to assess if add-on of mUS-guided biopsies to MRI-TB pathway is helpful to optimize csPCa detection while reducing overdiagnosis of non-csPCa.

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Data availability Data can be made available upon reasonable request.

Declarations

Conflict of interest The authors state that they have no conflicts of interest to disclose regarding the current manuscript.

Research involving human participants and/or animals Based on systematic review with meta-analysis on published data, this research did not involve human participants and/or animals.

Informed consent This systematic review with meta-analysis on published data has provided consent retrieved within each study.

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