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Comparing the biopsy strategies of prostate cancer: a systematic review and network meta-analysis

Yiqi Huang[1†], Cailiu Wei[2†], Fenjuan Chen[3], Yanling Zhang[1] and Feifei Pu[4*]

Abstract

The introduction of three kinds of magnetic resonance imaging-guided prostate biopsies (MRI-PB) has changed the paradigm regarding prostate biopsies (PB). We aimed to compare and rank PB strategies to provide the latest evidence of PB option for prostate cancer (PCa) diagnosis. We searched PubMed, the Cochrane Library Central, Scopus, Embase and the reference lists of relevant articles for randomized controlled trials published up to Dec, 2024, of different PB strategies. Finally, 24 randomized trials were included. Eleven PB strategies published were considered. For overall PCa detection rates exclusively previously negative biopsy patients, we found robust improvements of 3.92 (95% CI: 2.17–6.41) for MRI-cognitive- and 1.78 (95% CI: 1.02–3.07) for MRI/TRUS- compared to TRUS(10–12)-PB. For PCa detection when prostate volume ≤ 50 mm^3, only MRI/TRUS- was significantly effective than TRUS(10–12)-PB (OR 1.78, 95% CI: 1.0–2.89). Our study indicated that MRI-cognitive-PB was associated with better overall PCa detection rates compared with TRUS(10–12)-PB, but it had no remarkable advantages in csPCa and ciPCa detection. More head-to-head comparisons of MRI-PB techniques are needed in the future.

Keywords Prostate cancer, Biopsy, Network meta-analysis

Introduction

Prostate cancer (PCa) is the second most general cancer in men worldwide. For 2024, an estimated of 180,890 new cases will be diagnosed in the USA and 26,120 men will die of the disease [1, 2]. Due to the widespread application of prostate-specific antigen (PSA) testing into clinical routine, the frequency of prostate biopsies (PBs) and the diagnosis of PCa has been increasing [3]. Currently, the standard modality for PCa detection is a 10–12 core transrectal ultrasound prostate biopsy [TRUS(10–12)-PB] [4]. For men undergoing initial biopsy, overall PCa detection rates are approximately 40–45%, whereas 40% of cancer diagnosed by TRUS(10–12)-PB is upgraded following corroboration with radical prostatectomy histopathology.4 In the U.S.A. alone, more than 1.3 million men are subjected to PB per year, of whom merely around 240,000 are diagnosed with a tumour [5]. Overdetection and overtreatment expenditure for PCa was estimated at $1.3 billion annually [6].

In addition to low overall PCa detection rates, we are now facing several problems: First, efficient and accurate methods which can exclude dispensable PB are not available; Second, the low accuracy of current standard modality to identify clinically significant PCa (csPCa),

†Yiqi Huang and Cailiu Wei contributed equally to this work.

*Correspondence:
Feifei Pu
13575508962@163.com
[1] Department of Nephrology, Shaoxing Second Hospital, Shaoxing, Zhejiang, China
[2] Affiliated Hospital of Youjiang Medical University for Nationalities, Baise, Guangxi, China
[3] Department of Internal Medicine, Shaoxing Second Hospital, Shaoxing, Zhejiang, China
[4] Department of Ultrasonic, Shaoxing Second Hospital, Shaoxing, Zhejiang, China

which is advanced and fatal. Third, the diagnosis of clinically insignificant PCa (ciPCa) and later follow-up may result in psychological and physical impairment to patients. In particular, the risk of complications subsequent to PB such as infection and bleeding is appreciable, given the large number of cores performed. Considering the extensive frequency and demand of PBs around the world, even a small negligence of csPCa, or increased risk of complications would constitute a great public health problem.

Biopsy strategies have evolved considerably to accurately identify, characterize, and localize lesions while trying to minimize complication risks and reduce overall costs [7]. Some of these strategies include taking biopsies with discrepant anatomic approaches, increasing the number of cores taken and decreasing the number of cores but improving their deployment into the prostate [8]. The currently available strategies include: MRI-cognitive-, MRI/TRUS (magnetic resonance imaging/ ultrasound fusion-guided)-, MRI-in bore-, RTE (real-time sonoelastography)-, CEUS (contrast-enhanced ultrasonography)-, TRUS(10–12)-, and TPUS (transperineal ultrasound guided)-PB. No consensus exists as to which biopsy strategy should be preferred for detection of PCa. Although four systematic reviews and meta-analysis have looked at the comparative effectiveness of discrepant PB strategies, the majority has not been quantitatively analyzed in head-to-head comparisons [9–12]. Thus, we carried out a network meta-analysis (NMA) by integrating all available direct and indirect evidence, to assess the effectiveness and perform a comprehensive ranking of all available PB strategies.

Materials and Methods

Data sources and search strategy

This systematic review is reported in line with the PRISMA [29] (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR [30] (Assessing the methodological quality of systematic reviews) Guidelines, and the PRISMA statement extension for network meta-analysis [21]. To compare different PB strategies, we identified RCTs published up to Dec, 2024 with no language restriction, and compiled from the following databases: Scopus, PubMed, Embase and the Cochrane Library Central Register of Controlled Trials (CENTRAL). The search strategy included the following different keywords: ['randomized controlled trial', 'trial', 'prostate cancer', 'prostate', 'biopsy', 'transrectal ultrasound', 'transperineal ultrasound', 'MRI', 'magnetic resonance', and 'elastography']. The reference lists of retrieved publications as well as relevant meta-analyses in the discipline were manually checked. We searched international trial registries for trials in progress. A modified search algorithm for each database was adapted and attached in the supplemental materials (appendix 1). Three independent investigators initially screened the citation titles and abstracts. This study has been registered in the PROSPERO database (CRD42024568378).

Inclusion and Exclusion Criteria

Titles and abstracts were used to screen for initial study inclusion. Eleven types of biopsy strategy were mainly assessed, including MRI-cognitive-, MRI/TRUS-, MRI-in bore-, RTE-, CEUS-, TRUS(10–12)-, TPUS(10–12)-, TRUS(> 12)-, TRUS(Vienna nomogram)-, TRUS(< 10)-, and TPUS (< 10)-PB. Studies were finally involved based on the inclusion criteria: (1) Participant: reporting patients who need pathologic diagnosis for finally confirming PCa occurrence; (2) Intervention: comparing different biopsy strategies for the detection of PCa; (3) Control: at least 2 kinds of PB were compared to reach a conclusion; The protocol of biopsy was listed clearly in the article; (4) Outcome: exact statistics of target biopsy and systematic biopsy group were identified; (5) Study design: full-length reports of RCTs with high quality. We excluded systematic reviews, meta-analyses, qualitative designs, single-case, single-armed studies and abstracts only. Study selection was done independently by two authors. Any discrepancies in the study inclusion were resolved by consulting a third author.

Data extraction and quality assessment

Data on study-, patient- and biopsy-related characteristics were extracted by the same three reviewers. The validity of the meta-analysis was assessed by qualitative appraisal of study designs and methods before statistical analyses were performed. We executed the tool recommended by the Cochrane Collaboration to evaluate the risk of bias [22], and seven specific bias domains including methods for generating the random sequence, allocation concealment, blinding of participants and investigators, blinding of outcome assessment, incompleteness of outcome data and selective outcome reporting were assessed to assure the scientific quality of all the included RCTs.

Outcome definition

The primary outcome was overall PCa detection rate, which was defined as the number of patients with detected cancer, divided by the total number of patients that underwent biopsy. The secondary outcomes were csPCa, ciPCa and positive core rate (cores with acinar adenocarcinoma, neuroendocrine tumors, mesenchymal tumors or any other malignant findings). csPCa on biopsy was defined as cancers with Gleason's

score ≥ 7(4 + 3/3 + 4). CiPCa detection rate was PCa detection rate minus csPCa.

Data synthesis and statistical analysis

Appendix 2 provides the details of the applied statistical approaches. A pair-wise meta-analysis by using a random-effects model was done initially [23]. We estimated relative diagnostic effects of the competing interventions through the application of OR because all results were extracted as binary outcomes. The statistical heterogeneity among studies was evaluated by the Cochran's Q test and the I^2 statistic. A P value of 0.10 or less for the Q test or an I^2 greater than 50% was suggestive of substantial study heterogeneity. The level of statistical significance was set at $P < 0.05$ and all statistical tests were 2-sided.

For indirect and mixed comparisons, random-effects Bayesian network meta-analyses were conducted using Markov chain Monte Carlo methods in WinBUGS version 1.4.3 (MRC Biostatistics Unit) which use informative prior distributions for all diagnostic effects and the between-study variance parameter simultaneously [24]. We report the resultant effect as posterior median ORs with corresponding 95% CrIs, which are the Bayesian analogue of 95% confidence intervals (CIs). We estimated the relative ranking probability of each strategy and obtained the hierarchy of competing interventions using rankograms, surface under the cumulative ranking curve [25].

To check for the presence of inconsistency, the loop-specific approach was executed in order to assess the difference between direct and indirect estimates for a specific comparison in the loop. We assumed a common heterogeneity estimate within each loop [26]. We employed the node-splitting method, excluding one direct comparison at a time and estimating the indirect treatment effect for the excluded comparison. To check the assumption of consistency in the entire network, the design-by-treatment model was conducted [27]. Finally, subgroup analyses and multiple sensitivity analyses were performed to value the robustness of the findings.

Quality of Evidence

The GRADE approach was carried out to rate the quality of evidence of estimates derived from network meta-analysis. In this approach, direct evidence from RCTs starts at high quality and can be downgraded based on risk of bias, indirectness, imprecision, inconsistency (or heterogeneity) and publication bias to levels of moderate, low and relatively low quality [28].

Results

Search and selection

From a total of 2,369 citations identified using the search strategy, 24 randomized controlled trials (RCTs), including 6,497 participants, were included in this network meta-analysis (appendix 13). The PRISMA flowchart depicting electronic searching processes is presented in Fig. 1. The trials were conducted to compare 11 prostate biopsy strategies (Table 1). The number of patients allocated to each method ranged between 26 and 570 (median, 107 adults [interquartile range, 100–152]). All of the trials were two-armed and data were available for at least one of the outcomes.

The network plot had a polygonal network configuration with mixed connections (Fig. 2 and appendix 5). All biopsy strategies had at least one controlled trial and were directly compared. For the primary outcome, 12 (22%) of 55 pairwise comparisons had direct evidence. TRUS(10–12)-PB was most investigated (18 trials; 2,174 patients), whereas three interventions were investigated by only one trial (MRI-in bore-, TRUS [Vienna nomogram]-, TPUS [< 10]-PB).

Population characteristics

Across trials, the mean age of patients ranged from 61 to 88 years, the mean PSA value ranged from 4.4 to 23.3 ng/mL and the mean prostate volume ranged from 27.8 to 60 mL (Table 2 and appendix 3). The population investigated by 20 (83.3%) trials underwent an initial biopsy, 2 (8.3%) with previous negative biopsy population and 2 (8.3%) with mixed population. The baseline characteristics of image and biopsy protocol are described in appendix 3. MRI was performed in 7 (29%) of the involved studies, four of them employed PI-RADS classification for the evaluation of TB threshold.

Quality assessment

Overall, 11 trials were regarded to be at high risk of bias. The risk of bias was high or unclear for adequate sequence generation in 11 trials; concealment of treatment allocation in 13 trials; masking of participants, masking of investigators, or both in 12 trials; completeness of outcome reporting in 8 trials and selective reporting of outcomes in 6 trials. None of the trials received financial funding from a commercial body and source of funding was unclear for 13 trials. The funnel plots for primary outcomes were not suggestive of any publication bias (appendix 4).

Network consistency

The networks of individual intervention end points are exhibited in appendix 3. The common heterogeneity

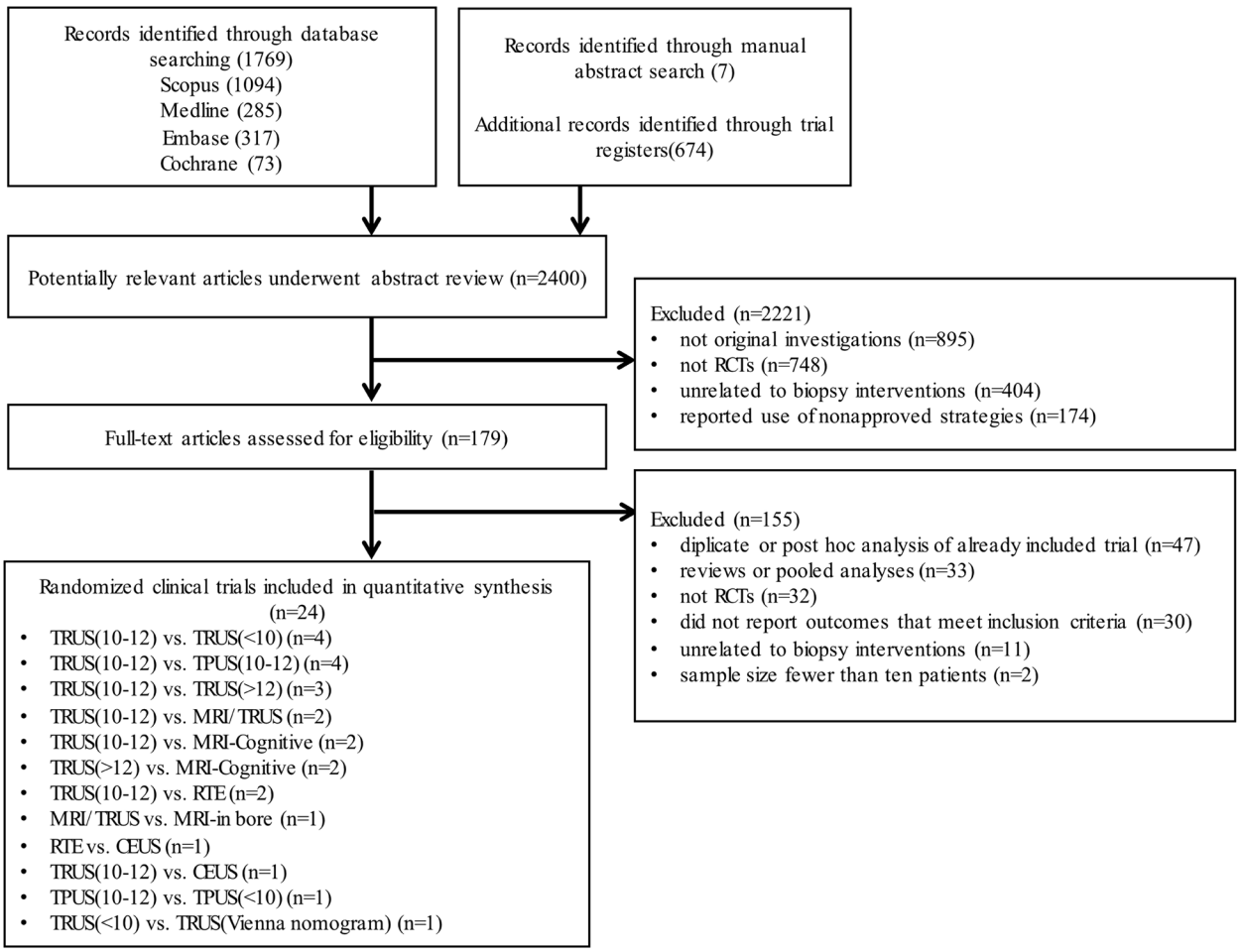

Fig. 1 The flowchart of study selection. RCT = randomized controlled trial. MRI = magnetic resonance imaging. TRUS = transrectal ultrasound. RTE = real-time sonoelastography. CEUS = contrast-enhanced ultrasonography. TPUS = transperineal ultrasound

Table 1 General characteristics of the biopsy strategies included

Abbreviations	General characteristics
MRI-cognitive	Physician first reviewed the lesion seen on MRI and uses the anatomic information aimed visually to select the area during TRUS-guided prostate biopsy
MRI/TRUS	Physician combined a prebiopsy MRI with a live ultrasound image at time of biopsy to guide prostate biopsies, either with or without a tracking device
MRI-in bore	Real-time MRI was used to directly guide prostate biopsy in the MRI suite
RTE	Real-time sonoelastography was used to perform targeted biopsies of suspicious areas
CEUS	Doppler imaging and contrast agents were used to help TRUS-guided prostate biopsy
TRUS(< 10)	TRUS-guided prostate biopsy schemed of at most 10 cores was used
TRUS(10–12)	TRUS-guided prostate biopsy schemed of 10–12 cores was used
TRUS(> 12)	TRUS-guided prostate biopsy schemed of at least 12 cores was used
TRUS(Vienna nomogram)	Vienna nomogram was used to determine the optimal number of TRUS-guided biopsy cores in men with a serum PSA level of 2–10 ng/mL, by taking into account the patient's age and prostate volume
TPUS(10–12)	TPUS-guided prostate biopsy schemed of 10–12 cores was used
TPUS(< 10)	TPUS-guided prostate biopsy schemed of at most 10 cores was used

MRI Magnetic resonance imaging, *TRUS* Transrectal ultrasound, *RTE* Real-time sonoelastography, *CEUS* Contrast-enhanced ultrasonography, *TPUS* Transperineal ultrasound

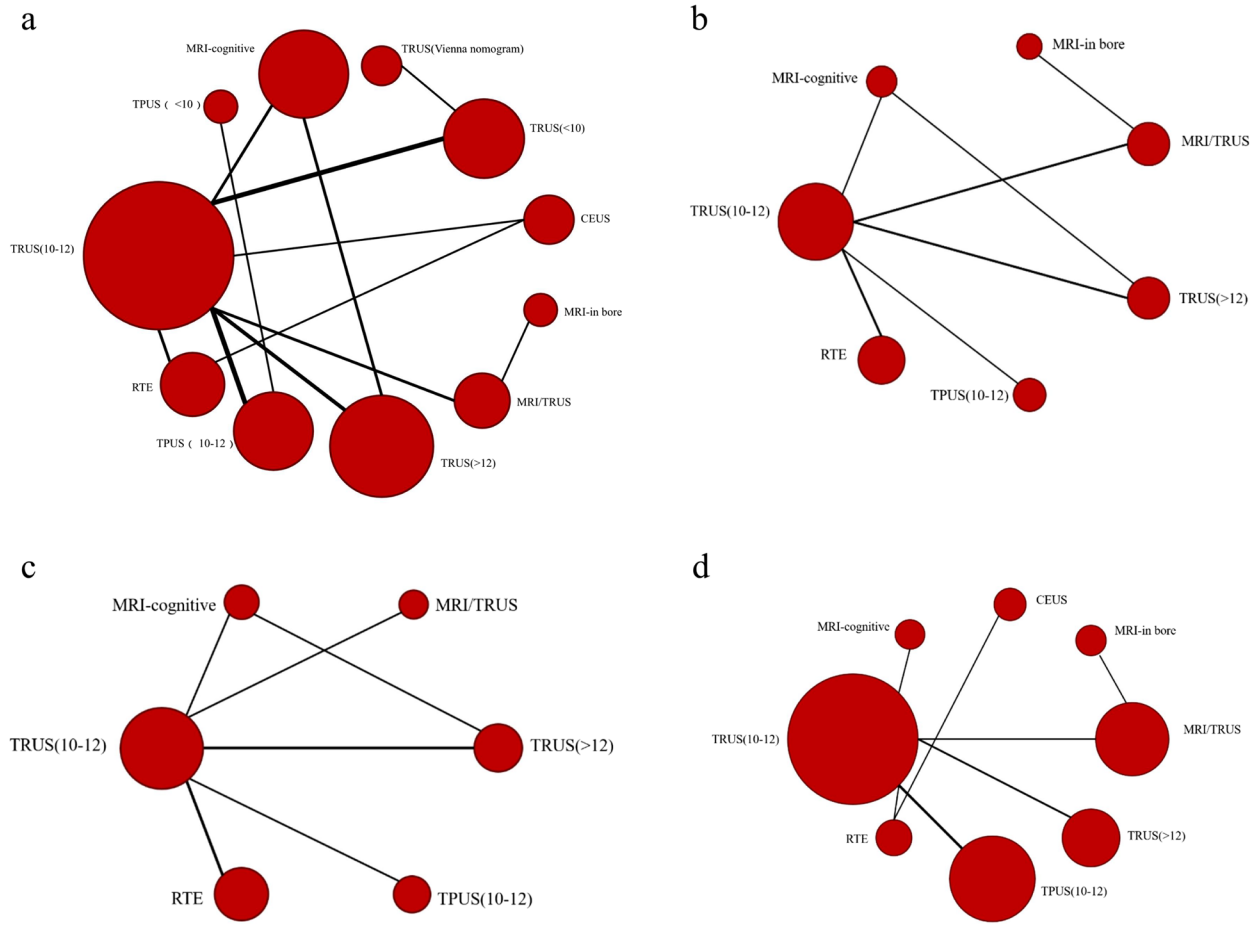

Fig. 2 Network of eligible comparisons. **a** Network of eligible comparisons for overall PCa detection rate; **b** Network of eligible comparisons for clinically significant PCa detection rate. **c** Network of eligible comparisons for clinically insignificant PCa detection rate; **d** Network of eligible comparisons for positive core rate. The width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of every circle is proportional to the number of randomly assigned participants (sample size). MRI = magnetic resonance imaging. TRUS = transrectal ultrasound. RTE = real-time sonoelastography. CEUS = contrast-enhanced ultrasonography. TPUS = transperineal ultrasound

(τ^2) was 0.48 (95% CrI 0.28–0.83) for overall PCa detection rate, 0.72 (95% CrI 0.24–1.76) for csPCa detection rate, 1.02 (95% CrI 0.33–1.95) for ciPCa detection rate and 0.27 (95% CrI 0.07–1.20) for positive core rate. By testing of global inconsistency, the network meta-analysis model gave an adequate fit to the data. Tests of local inconsistency showed no statistically significant inconsistency in the loops within the network for overall PCa detection rate and ciPCa detection rate. Most loops were consistent indicating lack of evidence of inconsistency in the network. Finally, by applying node-splitting model, we did not note any inconsistencies between evidence derived from direct and indirect comparisons in any of the primary or secondary analyses (appendix 6).

Pairwise and network results

Results of direct pairwise meta-analysis are summarized in Table 3 and appendix 7. Only MRI/TRUS- and MRI-cognitive- were significantly better than TRUS(10–12)-PB [odds ratio (OR) 1.58, 95% confidence intervals (CIs) 1.35–1.86; OR 3.88, 95% CI 1.99–7.52] based on 2 studies (5,600 participants) regarding positive core rate. For other outcomes, there were no remarkable differences in the associations between any procedure ($p > 0.05$). Since some direct pairwise comparisons were conducted based on single trial, the p values for the network analysis are not available. P values can be obtained when at least 2 trials were included in the analysis. The unavailable p values in the Tables 3 are unlikely to influenced the results.

Table 2 Randomized controlled trials included in the systematic review and network meta-analysis

Authors	Recruiting area	Population investigated	Methodology recruitment (number of participants)	Target/Random biopsy (number of cores)	Outcome of interested reported
Baco et al	USA	IPB	MRI/TRUS (86) vs. TRUS(10–12) (89)	TB (2) + RB (12) vs TB (2) + RB (12)	overall CDR, csCDR, ciCDR
Arsov et al	Germany	PNB	MRI in-bore (106) vs. MRI/TRUS (104)	TB (5.6 [0.80]) vs TB + RB (17 [1.2])	overall CDR, csCDR, ciCDR, positive core rate
Tonttila et al	Finland	IPB	MRI-Cognitive (53) vs TRUS(10–12) (60)	TB + RB (12) vs RB: 12 (10–12)	overall CDR, csCDR, ciCDR
Panebianco et al	Italy	IPB	MRI-Cognitive (570) vs TRUS(10–12) (570)	TB + RB (12) vs RB (14)	overall CDR, csCDR, ciCDR
Koh et al	Korea	Mixed	CEUS (26) vs. RTE (26)	TB (NA) vs TB (NA)	overall CDR, positive cores rate
Guo et al	China	IPB	TPUS(10–12) (173) vs. TRUS(10–12) (166)	RB (12) vs RB (10–12)	overall CDR, csCDR, ciCDR positive cores rate
Zhang et al	China	IPB	CEUS (213) vs. TRUS(10–12) (218)	TB + RB (12)[a] vs RB (12)	overall CDR, positive cores rate
Irani et al	France	IPB	TRUS(> 12) (166) vs. TRUS(10–12) (169)	RB (10) vs RB (20)	overall CDR, positive cores rate
Brock et al	Germany	IPB	RTE (178) vs. TRUS(10–12) (175)	TB + RB (≥ 10) vs RB (10)	overall CDR, csCDR, ciCDR
Byung et al	Korea	IPB	MRI-Cognitive (44) vs. TRUS(10–12) (41)	TB + RB (10–12) vs TB + RB (10–12)[b]	overall CDR, positive core rate
Chae et al	Korea	IPB	TPUS(10–12) (100) vs. TRUS(10–12) (100)	RB (10–12) vs RB (10–12)	overall CDR
Rochester et al	UK	IPB	TRUS(> 12) (122) vs. TRUS(10–12) (122)	RB (12) vs RB (15)	overall CDR
Takenaka et al	Japan	IPB	TPUS(10–12) (100) vs. TRUS(10–12) (100)	RB (12) vs RB (12)	overall CDR
Hara et al	Japan	IPB	TPUS(10–12) (126) vs. TRUS(10–12) (120)	RB (12) vs RB (12)	overall CDR, positive core rate
Eggert et al	Germany	IPB	RTE (189) vs. TRUS(10–12) (162)	TB + RB (10) vs RB (10)	overall CDR, csCDR, ciCDR
Naughton et al	USA	Mixed	TRUS(< 10) (122) vs. TRUS(10–12) (122)	RB (6) vs RB (12)	overall CDR
Kim et al	Korea	IPB	TRUS(< 10) (118) vs. TRUS(10–12) (122)	RB (6) vs RB (12)	overall CDR
Emiliozzi et al	Italy	IPB	TPUS(< 10) (107) vs. TPUS(10–12) (107)	RB (6) vs RB (12)	overall CDR
Paul et al	Germany	IPB	TRUS(< 10) (100) vs. TRUS(10–12) (100)	RB (6) vs RB (12)	overall CDR
Taverna et al	Italy	PNB	MRI- Cognitive (100) vs. TRUS(> 12) (100)	TB (4) + RB (13) vs RB (13)	overall CDR, csCDR, ciCDR
Rosette et al	Netherlands	IPB	TRUS(< 10) (132) vs. TRUS(10–12) (128)	RB (8) vs RB (12)	overall CDR
Lecuona et al	South Africa	IPB	TRUS(Vienna nomogram) (152) vs. TRUS(< 10) (151)	RB [10.2 (6–18)] vs RB (8)	overall CDR
Covarrubias et al	Mexico	IPB	TRUS(> 12) (75) vs. TRUS(10–12) (75)	RB (18) vs RB (12)	overall CDR, csCDR, ciCDR
Porpiglia et al	Italy	IPB	MRI/TRUS (107) vs. TRUS(10–12) (105)	TB (6) vs RB (12)	overall CDR, csCDR, ciCDR

TB Targeted biopsy, *RB* Randomized biopsy, *IPB* Initial prostate biopsy, *PNB* Previous negative biopsy, *MRI* Magnetic resonance imaging, *TRUS* Transrectal ultrasound, *RTE* Real-time sonoelastography, *CEUS* Contrast-enhanced ultrasonography, *TPUS* Transperineal ultrasound, *CDR* PCa detection rate, *csCDR* Clinically significant PCa detection rate, *ciCDR* clinically insignificant PCa detection rate

[a] Additional two cores were sampled from every suspicious area detected by TRUS or DRE

[b] Before a systemic biopsy, a target biopsy was conducted where a cancer was suspected from the MRI examination in the MRI group and where a hypoechoic lesion was found at transrectal ultrasound examination in the non-MRI group

Table 3 Results of meta-analysis of direct comparisons

Comparisons	Pairwise meta-analysis relative risk (95% CI)	No. of participants	No. of trials	No. of events	*P*-value	Heterogeneity I^2
Overall PCa detection rate						
MRI/TRUS vs. TRUS(10–12)	1.36 (0.88–2.08)	387	1	184	na	na
TPUS(10–12) vs. TRUS(10–12)	1.01 (0.79–1.28)	985	4	376	0.66	0.0%
CEUS vs. TRUS(10–12)	1.09 (0.76–1.57)	431	1	157	na	na
TRUS(> 12) vs. TRUS(10–12)	1.09 (0.77–1.55)	729	3	324	0.19	40.5%
RTE vs. TRUS(10–12)	1.18 (0.90–1.55)	704	2	297	0.48	0.0%
TRUS(< 10) vs. TRUS(10–12)	0.95 (0.76–1.18)	944	4	269	0.89	0.0%
TPUS(< 10) vs. TPUS(10–12)	0.75 (0.46–1.21)	214	1	96	na	na
TRUS(Vienna nomogram) vs. TRUS(< 10)	1.07 (0.69–1.65)	303	1	112	na	na
MRI/TRUS vs. MRI-in bore	1.07 (0.64–1.79)	210	1	80	na	na
RTE vs. CEUS	1.17 (0.51–2.68)	52	1	39	na	na
TRUS(> 12) vs. MRI-cognitive	0.69 (0.32–1.49)	1340	2	705	0.02	82.6%
TRUS(10–12) vs. MRI-cognitive	0.62 (0.25–1.57)	198	2	85	0.15	51.8%
Clinically significant PCa detection rate						
MRI/TRUS vs. TRUS(10–12)	1.36 (0.45–4.17)	387	2	143	0.01	87.0%
MRI/TRUS vs. MRI-in bore	0.92 (0.53–1.61)	210	1	64	na	na
MRI-cognitive vs. TRUS(10–12)	1.22 (0.64–2.31)	113	1	56	na	na
TPUS vs. TRUS(10–12)	1.25 (0.76–2.06)	339	1	76	na	na
RTE vs. TRUS(10–12)	1.06 (0.76–1.47)	704	2	187	0.94	0.0%
TRUS(> 12) vs. MRI-cognitive	0.80 (0.36–1.79)	200	1	27	na	na
TRUS(> 12) vs. TRUS(10–12)	1.06 (0.73–1.55)	394	2	146	0.76	0.0%
Clinically insignificant PCa detection rate						
MRI-cognitive vs. TRUS(10–12)	0.81 (0.24–2.70)	113	1	12	na	na
TPUS vs. TRUS(10–12)	0.96 (0.48–1.91)	339	1	36	na	na
RTE vs. TRUS(10–12)	1.24 (0.86–1.78)	704	2	181	0.27	16.8%
TRUS(> 12) vs. TRUS(10–12)	1.32 (0.35–4.98)	394	2	56	0.07	69.4%
MRI/TRUS vs. TRUS(10–12)	0.57 (0.22–1.50)	212	1	19	na	na
TRUS(> 12) vs. MRI-cognitive	1.56 (0.64–3.76)	200	1	23	na	na
Positive core rate						
MRI/TRUS vs. MRI-in bore	0.51 (0.38–0.69)	1808	1	210	na	na
RTE vs. CEUS	1.44 (0.90–2.30)	795	1	99	na	na
TPUS vs. TRUS(10–12)	0.96 (0.81–1.14)	8687	3	1234	0.13	50.4%
MRI/TRUS vs. TRUS(10–12)	1.58 (1.35–1.86)	4641	1	670	na	na
TRUS(> 12) vs. TRUS(10–12)	0.93 (0.71–1.21)	4375	2	1106	0.05	75.1%
RTE vs. TRUS(10–12)	4.97 (3.26–7.57)	1406	1	140	na	na
MRI-cognitive vs. TRUS(10–12)	3.88 (1.99–7.52)	959	1	63	na	na

OR Odds ratio, *CI* Confidence interval, *na* not available, *MRI* Magnetic resonance imaging, *TRUS* Transrectal ultrasound, *RTE* Real-time sonoelastography, *CEUS* Contrast-enhanced ultrasonography, *TPUS* Transperineal ultrasound

(See figure on next page.)

Fig. 3 **a** Summary odds ratio (OR) and credible intervals from network meta-analysis of overall PCa detection rate. **b** Summary odds ratio (OR) and credible intervals from network meta-analysis of clinically significant PCa detection rate. **c** Summary odds ratio (OR) and credible intervals from network meta-analysis of clinically insignificant PCa detection rate. **d** Summary odds ratio (OR) and credible intervals from network meta-analysis of positive core rate. Biopsy strategies are reported in order of efficacy ranking according to SUCRAs. Comparisons should be read from left to right. The efficacy estimate is located at the intersection of the column-defining treatment and the row-defining treatment. For efficacy (overall PCa detection rate), an OR over 1 favours the column-defining intervention. To obtain ORs for comparisons in the opposing direction, reciprocals should be taken. Numbers in parentheses indicate 95% credible intervals (95%CrIs). Significant results are in bold and underlined. MRI = magnetic resonance imaging. TRUS = transrectal ultrasound. RTE = real-time sonoelastography. CEUS = contrast-enhanced ultrasonography. TPUS = transperineal ultrasound. SUCRA = surface under the cumulative ranking curve

A **Overall PCa detection rate**

MRI-cognitive										
1.50 (0.60 – 3.63)	MRI/TRUS									
1.68 (0.45 – 6.06)	1.12 (0.44 – 2.86)	MRI-in bore								
1.88 (0.80 – 4.20)	1.26 (0.51 – 3.04)	1.12 (0.30 – 4.07)	RTE							
2.50 (1.41 – 4.15)	1.67 (0.71 – 3.77)	1.49 (0.42 – 5.17)	1.33 (0.63 – 2.79)	TRUS(>12)						
2.57 (0.97 – 6.56)	1.70 (0.63 – 4.75)	1.53 (0.39 – 6.13)	1.36 (0.59 – 3.24)	1.02 (0.43 – 2.55)	CEUS					
2.67 (1.23 – 5.54)	1.78 (0.78 – 4.04)	1.59 (0.45 – 5.54)	1.42 (0.68 – 2.99)	1.07 (0.56 – 2.10)	1.04 (0.42 – 2.49)	TPUS(10-12)				
2.66 (1.44 – 4.72)	1.77 (0.90 – 3.49)	1.58 (0.50 – 5.04)	1.41 (0.80 – 2.53)	1.06 (0.67 – 1.73)	1.04 (0.48 – 2.18)	1.00 (0.63 – 1.58)	TRUS(10-12)			
2.90 (0.88 – 9.19)	1.93 (0.57 – 6.55)	1.73 (0.37 – 8.02)	1.54 (0.49 – 5.00)	1.16 (0.39 – 3.59)	1.13 (0.32 – 3.97)	1.09 (0.36 – 3.31)	1.09 (0.40 – 3.00)	TRUS(Vienna nonogram)		
3.23 (1.48 – 6.79)	2.15 (0.94 – 4.94)	1.92 (0.55 – 6.74)	1.72 (0.81 – 3.65)	1.29 (0.67 – 2.57)	1.26 (0.51 – 3.05)	1.21 (0.63 – 2.36)	1.21 (0.75 – 1.96)	1.11 (0.46 – 2.72)	TRUS(<10)	
4.59 (1.33 – 14.79)	3.05 (0.88 – 10.52)	2.74 (0.57 – 12.93)	2.43 (0.74 – 8.08)	1.83 (0.59 – 5.80)	1.79 (0.49 – 6.37)	1.72 (0.68 – 4.37)	1.72 (0.60 – 4.88)	1.58 (0.37 – 6.74)	1.42 (0.45 – 4.41)	TPUS(<10)

B **Clinically significant PCa detection rate**

MRI/TRUS						
1.01 (0.37 – 2.72)	MRI-cognitive					
1.12 (0.40 – 3.16)	1.11 (0.36 – 3.45)	TPUS(10-12)				
1.12 (0.47 – 2.68)	1.11 (0.30 – 4.17)	1.00 (0.26 – 3.95)	MRI-in bore			
1.33 (0.55 – 3.17)	1.31 (0.50 – 3.50)	1.18 (0.42 – 3.33)	1.18 (0.34 – 4.06)	RTE		
1.33 (0.56 – 3.06)	1.31 (0.60 – 2.84)	1.18 (0.43 – 3.23)	1.18 (0.35 – 3.97)	1.00 (0.43 – 2.30)	TRUS(>12)	
1.50 (0.80 – 2.80)	1.48 (0.69 – 3.22)	1.34 (0.58 – 3.09)	1.34 (0.45 – 3.91)	1.13 (0.61 – 2.09)	1.13 (0.64 – 2.03)	TRUS(10-12)

C **Clinically insignificant PCa detection rate**

MRI-cognitive						
0.79 (0.11 – 6.07)	TRUS(10-12)					
0.82 (0.04 – 20.82)	1.05 (0.09 – 12.56)	TPUS(10-12)				
0.59 (0.04 – 8.48)	0.75 (0.13 – 4.13)	0.71 (0.03 – 14.14)	RTE			
0.58 (0.08 – 4.12)	0.74 (0.14 – 3.52)	0.71 (0.03 – 12.48)	1.00 (0.09 – 9.73)	TRUS(>12)		
0.47 (0.01 – 19.62)	0.60 (0.03 – 13.63)	0.57 (0.01 – 29.77)	0.80 (0.02 – 28.46)	0.81 (0.02 – 28.15)	MRI-in bore	
0.46 (0.03 – 6.95)	0.58 (0.09 – 3.54)	0.56 (0.03 – 11.57)	0.78 (0.06 – 9.37)	0.79 (0.07 – 9.28)	0.97 (0.07 – 12.58)	MRI/TRUS

D **Positive core rate**

RTE							
1.37 (0.31 – 6.05)	MRI-cognitive						
1.51 (0.54 – 4.19)	1.11 (0.18 – 6.65)	CEUS					
1.61 (0.30 – 8.64)	1.18 (0.20 – 6.66)	1.07 (0.15 – 7.57)	MRI-in bore				
3.46 (0.90 – 13.55)	2.52 (0.59 – 10.70)	2.29 (0.42 – 12.66)	2.15 (0.82 – 5.62)	MRI/TRUS			
5.92 (2.20 – 16.20)	**4.32 (1.45 – 13.30)**	3.92 (0.95 – 16.59)	3.68 (0.96 – 14.17)	1.71 (0.68 – 4.39)	TRUS(10-12)		
6.23 (2.04 – 19.73)	**4.55 (1.34 – 15.98)**	4.12 (0.92 – 19.33)	3.88 (0.91 – 16.88)	1.81 (0.62 – 5.38)	1.05 (0.62 – 1.83)	TPUS(10-12)	
6.57 (2.01 – 21.61)	**4.80 (1.34 – 17.58)**	4.35 (0.90 – 21.24)	4.08 (0.91 – 18.17)	1.91 (0.61 – 6.00)	1.11 (0.57 – 2.16)	1.05 (0.44 – 2.49)	TRUS(>12)

Fig. 3 (See legend on previous page.)

The results of the network meta-analyses for the primary outcomes are presented as a league table in Fig. 3. Pooled estimated effects confirmed that six strategies (MRI-cognitive-, MRI/TRUS-, MRI-in bore-, RTE-, TRUS[>12] CEUS-PB) improved overall PCa detection rate when compared with previously recommended standard method (TRUS [10–12]-PB). Of note, only for MRI-cognitive- (OR 2.66, 95% credibility intervals (CrIs) 1.44–4.72] enough evidence exists ($p<0.05$) to support superiority when compared with TRUS(10–12)-PB. MRI-cognitive- was also associated with a significantly increased overall cancer detection rate than TPUS(10–12)- (OR 2.67, 95% CrI 1.23–5.54), TRUS(<10)- (OR 3.23, 95% CrI 1.48–6.79), and TPUS(<10)-PB (OR 4.59, 95% CrI 1.33–14.79) (Fig. 3a).

Results for secondary outcomes of csPCa detection rate and ciPCa detection suggested no significant difference between any group of biopsy techniques (Fig. 3b, Fig. 3c). In terms of positive core rate, RTE- was significantly effective than TRUS(10–12)- (OR 5.92, 95% CrI 2.20–16.20), TPUS- (OR 6.23, 95% CrI 2.04–19.73), and TRUS(>12)-PB (OR 6.57, 95% CrI 2.01–21.61). MRI-cognitive was significantly effective than TRUS(10–12)- (OR 4.32, 95% CrI 1.45–13.30), TPUS(10–12)- (OR 4.55, 95% CrI 1.34–15.98) and TRUS(>12)-PB (OR 4.80, 95% CrI 1.34–17.58) considering positive core rate (Fig. 3d).

Rank

The ranking of interventions based on cumulative probability plots and surface under the cumulative ranking curve (SUCRA) is presented in the appendix 7. Regarding overall PCa detection rate, the most effective treatment was MRI-cognitive-PB (99.8%), followed by MRI/TRUS- (84%), MRI-in bore- (73.6%), RTE- (71%), CEUS- (50.1%), TRUS(10–12)- (39.9%), TPUS(10–12)- (38.7%), TRUS(>12)- (37.3%), TRUS(Vienna nomogram)- (32.4%), TRUS(<10)- (18.1%), and the least effective was TPUS(<10)-PB (4.7%). Considering csPCa detection rate, MRI/TRUS PB (69.1%) was ranking the best, followed by MRI-cognitive- (66.2%), TPUS(10–12)- (56.4%), MRI-in bore- (54.4%), RTE- (40.7%), TRUS(>12)- (39.9%), and TRUS(10–12)-PB (23.2%).

Subgroup and sensitivity analysis

We repeated all the Bayesian network meta-analysis using overall PCa detection rate as an end-point. With respect to the subgroup of patients ≥65 years, we found a significant superiority favoring MRI/TRUS PB compared with TRUS(10–12) PB (OR 2.47, 95% CrI 1.30–4.75). A similar preference was observed in the subgroup of PSA<10 ng/ml (OR 2.45, 95% CrI 1.20–5.09) (appendix 8).

Results from multiple sensitivity analyses were reported in the appendix 9. In terms of overall PCa detection rates exclusively previously negative biopsy patients, we found robust improvements of 3.92 (95% CrI 2.17–6.41) for MRI-cognitive- and 1.78 (95% CrI 1.02–3.07) for MRI/TRUS- compared to TRUS(10–12)-PB. In terms of PCa detection when prostate volume ≤50 mm^3, only MRI/TRUS- was significantly effective than TRUS(10–12)-PB (OR 1.78, 95% CrI 1.0–2.89). In the remaining sensitivity analyses with alternative statistical models and priors distribution, OR was similar in magnitude and direction of effect estimates without changing the rankings considerably (appendix 9).

Quality of Evidence

According to GRADE, there was moderate quality evidence for MRI-cognitive PB being associated with higher overall PCa detection rate compared with TRUS(10–12)-, TPUS(10–12)-, TRUS(<10)-,and TPUS(<10)-PB. The quality of evidence was mainly downgraded due to study imprecision and indirectness (appendix 10).

Discussion

Since the introduction of digital-guided biopsy in 1930, millions of negative and insignificant biopsy cores have been conducted representing a tremendous burden for health care systems [11]. It is clear that improving PB diagnostic performance is urgently in need. The ideal biopsy strategy would identify men suspicious of PCa while maximizing detection of only csPCa and limiting ciPCa detection [9]. To work it out, this network meta-analysis has several key results for the diagnostic performance and patient morbidity associated with currently available biopsy approaches. First, MRI-cognitive PB significantly improved the overall PCa detection rate as well as positive core rate compared to the routinely performed TRUS(10–12)- and TPUS(10–12)-PB. Second, all PB methods were comparable with all the procedures in terms of csPCa and ciPCa detection rate.

The paradigm regarding PCa biopsy strategies is being shifted from ultrasound-guided biopsy to MRI-guided biopsy. Our work suggests that MRI-cognitive PB is a promising strategy that offers better overall PCa detection rate compared to standard systematic TRUS-PB. According to the evaluation of positive TBs, MRI-cognitive has high reliability in normal clinical practice even in hands with limited experience, as shown in the studies before [13, 14]. Contemporary guidelines also recommend MRI in spite of negative biopsies previous to repeated biopsy [15].

MRI/TRUS PB represents the most accurate and practical TB strategy [7, 10]. The use may reduce the learning curve necessary for visual targeting and improve community adoption of MRI-TB [11]. Of note, no pronounced differences were detected between the MRI/TRUS- and

TRUS(10–12)-PB in overall PCa detection rate or the csPCa detection rate in our study. These resultant effects are similar to findings of a previous meta-analysis [9]. In contrast, some nonrandomised studies have concluded that MRI/TRUS-PB limited overdetection of ciPCa and provided greater detection of csPCa than SB alone [16]. These conflicting upshots may account for several essential diagnostic components. First, the applied threshold for MRI-TB seemed variable. This will directly impact tumour detection yields, as studies that incorporate patients with benign findings on MRI will demonstrate lower tumour yields than studies that only incorporate patients with particularly suspicious findings on MRI [15, 16]. Additionally, the inconsistent usage of definitions for csPCa encompassing PSA density, clinical stage and histologic result. As some studies were based on variables such as cancer core length and number of positive cores, and therefore might significantly overestimate csPCa detection rate during TB [9, 17]. The largest concern with MRI/TRUS-PB is obtaining accurate registration between the MRI images and the real-time TRUS images [18]. Patient motion and deformation of the prostate gland by the TRUS probe are the two largest impediments to accurate registration [16].

The potential reasons for the insignificant detection rates between csPCa and ciPCa need careful exploration. First, sample quantity included for current analysis may result in the insignificant detection rate between csPCa and ciPCa. Emerging data from more prospective clinical trials with large sample are needed to further calculate or quantify the detailed distinguishment capacity of MRI-guided PB. Second, due to the accurate detection ability of multiparameter MRI (mpMRI) on the potential tumor lesions, even microlesions or oligolesions at very early stage can be identified. Thus, for either csPCa or ciPCa, the overall detection rate of MRI-guided biopsies was obviously higher than TRUS-guided prostate biopsies. Despite no significant differences presented between the two subgroups, MRI shows promising profile in precise diagnosis.

Initially, prostate MRI was based solely on morphologic assessment using T1-weighted (T1W) and T2-weighted (T2W) pulse sequences, and its role was primarily for locoregional staging in patients with biopsy proven cancer. It provided limited capability to distinguish benign pathological tissue and ciPCa from csPCa. However, advances in technology (both in software and hardware), combined with a growing interpreter experience with mpMRI, have substantially improved diagnostic capabilities for addressing the central challenges in prostate cancer care: 1) Improving detection of csPCa, which is critical for reducing mortality; and 2) Increasing confidence in benign diseases and dormant malignancies (ciPCa), which are not likely to cause morbidity in a man's lifetime, in order to reduce unnecessary biopsies and treatment. Thus, mpMRI-guided prostate biopsies can greatly aid in distinguish between csPCa and ciPCa, which brings novel insights to benefit PCa population.

MRI-guided prostate biopsy was first described as a potential diagnosis strategy for prostate cancer in 1983 [31]. The specific advantages propel the advances of MRI-guided biopsy in the field of PCa diagnosis. Compared with computed tomography (CT), positron emission computed tomography (PET) and ultrasound methods, the main advantages of using MRI guidance are its superior soft tissue contrast and multi-plane imaging capability, which enables more precise localization of suspected lesions within the prostate, improving biopsy accuracy and diagnostic efficacy [32]. Thus, MRI guidance can display the injection depth and location of the puncture needle in real time, visualize the location of the lesion, provide accurate positioning, and then significantly reduce the number of puncture needles. Patients will also experience lower possibility of puncture-induced complications. However, MRI-guided prostate puncture needs long operating time, tedious steps, high-standard equipment and expensive costs [33]. Additionally, to maximize the fusion effect of the MRI-guidance, experienced imaging experts are required to cooperate as well. All these mentioned issues make it difficult to be widely used in clinical practice, and the current standard PB strategy is still ultrasound-guided systematic puncture.

Given that the MRI-in bore-PB was not widely available, more studies are needed to determine the qualified patients for whom this strategy should be reserved [18]. Limitations of MRI-in bore-PB primarily include increased procedure duration and increased expense, relative to TRUS biopsy [7, 12, 19].

The initial upfront cost in performing MRI has to be offset against the possible savings that might result from a reduced number of biopsies, unnecessary treatments and post-operative complications [15]. From a clinical perspective, the decision maker should always take the overall clinical picture into consideration, and patient management plans need to balance the risks and benefits [20]. TRUS(10–12)-PB has the merits of speed, ease, cost-effectiveness, availability and portability [3, 4, 9]. Wegelin et al. [12] noted that omitting TRUS PB would result in missing 19% of all PCa cases, and 10% of csPCa cases in their meta-analysis. Thus, in the area where MRI machines or fusion technology were not widely available, TRUS(10–12)-PB remained the optimal choice to date [6].

Different to the previous meta-analysis, our study integrated all available high-quality randomized evidence on the efficiency of PB strategies in one comprehensive

investigation. However, some limitations must be noted. First, the current number of RCTs that applied a comparative strategy in conjunction with TB is limited. Although the standards of reporting for MRI-TB studies consensus group has published recommendations for the reporting of the histological results using Gleason's score and maximum cancer core length to facilitate comparisons for the detection of csPCa, the number of individual trials assessing histological results and lesion characteristics was still scarce [5, 6]. We excluded abstracts which placed the results at risk for publication bias. Second, there is clinical and methodological heterogeneity in the recruited trials in terms of discrepant study characteristics, various interventions and broad group populations. Findings should be interpreted with caution since a majority of comparisons did not reach statistical significance. Specifically, credible intervals were not narrow in network meta-analysis comparisons and confidence intervals were wide in pairwise meta-analysis comparisons. Third, no real attention was given to the issue of cost-effectiveness according to the available studies. This aspect may influence the decision-making process for doctors and patients. Finally, it is necessary for meta-analyses of more reliable multi-center RTCs. However, there's still a long way to encounter adequate multi-center prospective trials for selecting optimal prostate biopsy modalities in the setting of suspicious tumor lesions. Thus, there is an urgent need for our preliminary evidence under current clinical practice until larger prospective trials of head-to-head comparisons are carried out.

Conclusions

Using randomized trial data and a novel evidence synthesis approach, our study indicated that MRI-cognitive-PB was associated with better overall PCa detection rates compared with TRUS(10–12)-PB. However, comparable diagnostic performance considering csPCa and ciPCa were manifested between any pairs of PB strategies. Specifically, MRI/TRUS- had a superior overall PCa detection compared with TRUS(10–12)-PB in patients ≥ 65 years old and prostate volume ≤ 50 mm^3. Doctors need to consider our results with all known safety and economic information synergistically as well as patients' desire when selecting the strategy. Head-to-head comparisons of MRI-PB techniques are limited and are needed to confirm our findings.

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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FFP: conceptualization and methodology; YQH and CLW: data acquisition and analysis; FJC and YLZ: data interpretation; YQH and CLW: writing-original draft. FFP: writing-review and editing, supervision and funding acquisition.

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