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The value of magnetic resonance imaging and ultrasonography (MRI/US)-fusion biopsy platforms in prostate cancer detection: a systematic review

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Despite limitations considering the presence, staging and aggressiveness of prostate cancer, ultrasonography (US)-guided systematic biopsies (SBs) are still the 'gold standard' for the diagnosis of prostate cancer. Recently, promising results have been published for targeted prostate biopsies (TBs) using magnetic resonance imaging (MRI) and ultrasonography (MRI/US)-fusion platforms. Different platforms are USA Food and Drug Administration registered and have, mostly subjective, strengths and weaknesses. To our knowledge, no systematic review exists that objectively compares prostate cancer detection rates between the different platforms available. To assess the value of the different MRI/US-fusion platforms in prostate cancer detection, we compared platform-guided TB with SB, and other ways of MRI TB (cognitive fusion or in-bore MR fusion). We performed a systematic review of well-designed prospective randomised and non-randomised trials in the English language published between 1 January 2004 and 17 February 2015, using PubMed, Embase and Cochrane Library databases. Search terms included: 'prostate cancer', 'MR/ultrasound(US) fusion' and 'targeted biopsies'. Extraction of articles was performed by two authors (M.G. and A.A.) and were evaluated by the other authors. Randomised and non-randomised prospective clinical trials comparing TB using MRI/US-fusion platforms and SB, or other ways of TB (cognitive fusion or MR in-bore fusion) were included. In all,

11 of 1865 studies met the inclusion criteria, involving seven different fusion platforms and 2626 patients: 1119 biopsy naïve, 1433 with prior negative biopsy, 50 not mentioned (either biopsy naïve or with prior negative biopsy) and 24 on active surveillance (who were disregarded). The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was used to assess the quality of included articles. No clear advantage of MRI/US fusion-guided TBs was seen for cancer detection rates (CDRs) of all prostate cancers. However, MRI/US fusion-guided TBs tended to give higher CDRs for clinically significant prostate cancers in our analysis. Important limitations of the present systematic review include: the limited number of included studies, lack of a general definition of 'clinically significant' prostate cancer, the heterogeneous study population, and a reference test with low sensitivity and specificity. Today, a limited number of prospective studies have reported the CDRs of fusion platforms. Although MRI/US-fusion TB has proved its value in men with prior negative biopsies, general use of this technique in diagnosing prostate cancer should only be performed after critical consideration. Before bringing MRI/US fusion-guided TB in to general practice, there is a need for more prospective studies on prostate cancer diagnosis.

Keywords

prostate, cancer, fusion, biopsy, MRI, ultrasound

Introduction

Diagnostic tools for prostate cancer consist of DRE, serum PSA measurements, and definite diagnosis is always based on pathological evaluation of TRUS-guided systematic biopsies (SBs). However, TRUS-guided biopsy has several limitations. As 25–39% of the prostate carcinomas are iso-echoic on grey scale TRUS, biopsies cannot be limited to lesion-directed biopsies and therefore SBs have to be taken [1,2]. Limitations

of SB include the low negative predictive value (NPV) and poor correlation with pathology results after radical prostatectomy (RP) [3].

To overcome these problems, in the last decade, the focus has been on developing more accurate imaging methods for taking targeted biopsies (TBs). Research has been focused on multiparametric MRI (mpMRI), elastography, dynamic contrast-enhanced ultrasonography (DCEUS), histoscanning,

and artificial neuronal network analysis (ANNA)/computerised TRUS (C-TRUS). In general, mpMRI includes two or three MRI modalities: T2-weighted imaging, diffusion-weighted imaging (DWI), and in most cases dynamic contrast-enhancement MRI (DCE-MRI), and sometimes four, adding MR-spectroscopy. mpMRI has been reported to have a high accuracy for the detection of prostate cancer [4], and has already been recommended for patients with a persistent clinical suspicion of prostate cancer after prior negative biopsies in the European Society of Urogenital Radiology (ESUR) prostate MR guidelines 2012 [5] and in the European Association of Urology guidelines on Prostate Cancer 2014 [6].

TRUS is a non-invasive procedure used to guide the needle for taking prostate biopsies. Image fusion can combine advantages of both TRUS and mpMRI. Approaches of taking MRI-guided TBs of the prostate include 'in-bore' MRI-guided biopsies, cognitive fusion, and MRI/ultrasonography (MRI/US) software-based image-fusion techniques. In in-bore MRI-guided techniques, TBs are taken during real-time MRI. With fusion techniques, MRI is performed before taking US-guided TBs, using cognitive or software-based MRI-US image fusion. A higher detection rate of clinically significant disease was assessed using any of the three techniques [7]. Recently, a comparison has been made between MRI TBs and randomised TRUS-guided SBs by Van Hove et al. [8]. They concluded that no clear advantage of TBs over the current standard of SBs could be seen in biopsy naïve men, but in cases of prior negative biopsies, TBs tended to have improved prostate cancer detection rates (CDRs).

Eight fusion platforms were USA Food and Drug Administration (FDA) registered at the time this review was performed. They all require a pre-biopsy MRI for real-time TRUS fusion; however, great differences between the platforms exist. Of most importance is the difference between 'rigid' and 'elastic' registration. Often, the shape of the prostate differs significantly between MRI and TRUS imaging. Elastic methods stretch or warp one of the image datasets, so that the shapes correlate with each other. Other differences include mechanical vs manually controlled arm, patient movement compensation, and accuracy of three-dimensional modelling. To the best of our knowledge, no systematic review has been performed to compare different MRI/US-fusion platforms for taking prostate TBs.

The aim of the present review was to assess the CDRs of different MRI/US-fusion platforms for prostate cancer detection by comparing MRI/US-fusion TB to random SB and to the other MRI/US-fusion techniques, in-bore and cognitive fusion-guided TB. Only well-designed and prospective randomised and non-randomised trials were included in the review.

Patients and Methods

Eligibility Criteria

Randomised and non-randomised prospective clinical trials comparing prostate CDRs between MRI/US fusion-guided TB or another way of MRI TB, such as cognitive or in-bore MR/US-fusion, and SB were selected. Participants of any age with a clinical suspicion on prostate cancer because of high PSA level and/or abnormal DRE were considered. The primary outcome measure was (clinically significant) prostate CDRs per patient.

Study Selection

Studies were identified by searching on-line databases. A systematic literature review of PubMed, Embase and Cochrane Library was performed. The last search was conducted on 17 February 2015. The following search terms were used: prostate cancer AND ((MR/US fusion) OR (MRI/US fusion) OR (MR/ultrasound fusion) OR (MRI/ultrasound fusion) OR (ultrasound fusion) OR (targeted biopsy) OR (targeted biopsies)) with the limitations: English, humans, 01 January 2004 till 17 February 2015, full text.

Eligibility assessment was performed by two reviewers (M.G. and A.A.). Disagreements were resolved by consensus. All abstracts published before January 2004 were excluded, as in this year the first MRI/US-fusion platform was FDA registered. Articles only including patients on active surveillance were also excluded, because the objective was to assess CDRs for prostate cancer diagnosis.

Data Extraction

One review author (M.G.) extracted the following data: type of fusion platform, number and type of patients, method, comparison, outcome measures, and results, and entered the information in a data extraction sheet. All other authors checked these data and disagreements were resolved by discussion and consensus. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [9] was used to assess the quality of included the articles.

The primary outcome measure was the prostate CDR in MRI/US fusion platform-guided TB compared with SB or another way of MRI-guided TB, such as cognitive or in-bore.

Results

Characteristics of Included Studies

In all, 2098 records were identified during the systematic literature search. After adjusting for duplicates 1865 records remained, of which 130 titles seemed relevant. Of these, 107 records were excluded because after analysing abstracts the

papers did not meet the inclusion criteria. Next, the content of 23 papers were screened on relevance, and finally 11 studies met all our inclusion criteria. A flowchart of study selection is provided in Figure 1. All 11 studies finally selected were prospective non-randomised controlled trials or in-patient control studies published in English between January 2004 and February 2015. Of the 11 included studies, there were eight studies comparing transrectal MRI/US-fusion TBs with SBs and three studies comparing transperineal MRI/US-fusion TBs with SBs. Unfortunately, no study comparing MRI/US-fusion TB with in-bore TB, was detected.

Participants

The included studies involved 2626 patients: 1119 biopsy naïve men, 1433 after prior negative biopsy, 50 not mentioned (either biopsy naïve or after prior negative biopsy) and 24 on active surveillance. Despite active surveillance being an exclusion criterion, one study including 125 patients of whom 24 patients were on active surveillance was included in the present review, because the authors presented a separate analysis for the active surveillance group, so that these men could be disregarded.

Intervention

Table 1 shows the characteristics of the 11 included studies. For the intervention, a pre-biopsy 1.5 T or 3.0 T mpMRI including at least T2-weighted imaging, DWI and DCE modalities, with or without endorectal coil, was used. MRI/US-fusion TBs were performed first in eight studies, SBs were performed first in the other three studies. The physician taking SBs was 'blinded' to the MRI images in five studies. In two studies, the physician taking the SBs was not blinded to the MRI images, and in the other four studies, blinding was not mentioned.

The mpMRI lesions were scored using the Prostate Imaging-Reporting And Data System (PI-RADS), Likert score or National Institutes of Health (NIH) score. MRI/US-fusion TBs were taken transrectally in eight studies and transperineally in three studies, with the mean number of cores taken ranging from 1.5 to 8.9 per patient.

Outcomes

In all studies, the primary or secondary outcome assessed was the CDR of all prostate cancer and/or the CDR of clinically significant prostate cancer. When clinically significant

Fig. 1 Study selection flowchart.

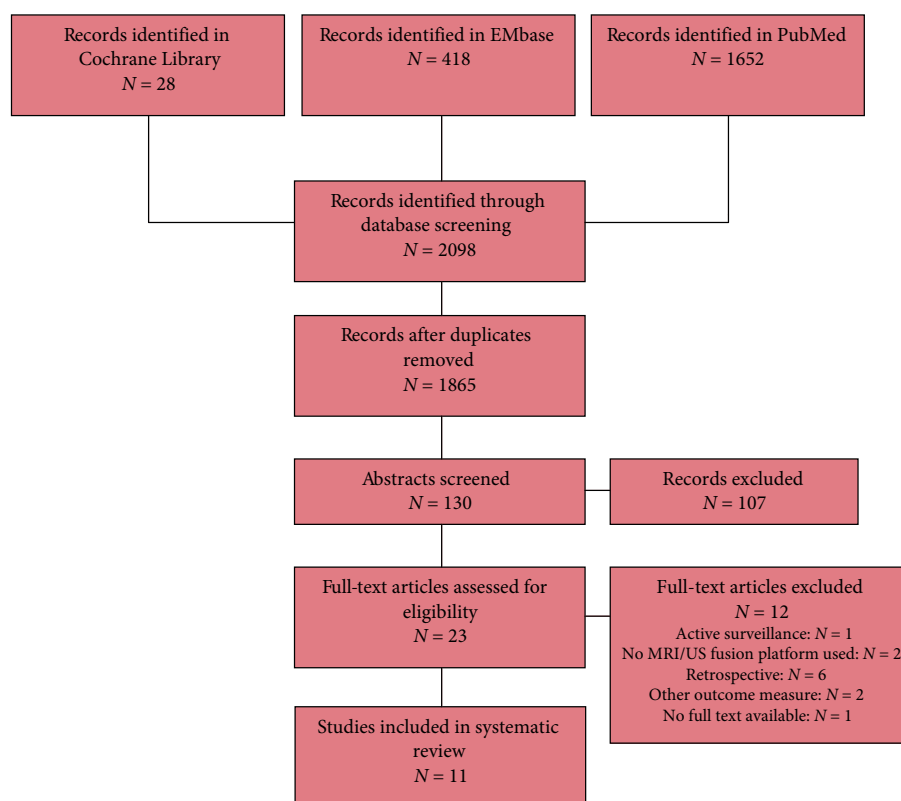


Table 1 Characteristics of the 11 included studies.

Study	Fusion platform	Sample size, <i>n</i>	Patients	MRI			MRI/US fusion-guided TB			Comparison				
				Strength, T	Sequences	Endorectal coil	Score	Patients with positive MRI, %	Route	Mean no. of cores	TB first	Standard test	No. of cores	Blinded to MRI
Borkowetz et al. [10]	BioJet	263	Biopsy naive (68), prior negative biopsy (195)	3.0	T1, T2, DWI, DCE	No	PI-RADS	100.0	TP	8.9	Yes	TR SB	12	No
Delongchamps et al. [14]	Virtual Navigator and Urostation	391	Biopsy naive	1.5	T2, DWI, DCE	Yes	NIH	40.7	TR	3.6	No	TR SB	10–12	NM
Fiard et al. [17]	Urostation	30	Biopsy naive (13), prior negative biopsy (17)	3.0	T2, DWI, DCE	No	PI-RADS	66.7	TR	1.5	No	TR SB	12	NM
Junker et al. [21]	Logiq 9	50	Biopsy naive (# NM), prior negative biopsy	3.0	T2, DWI, DCE	No	PI-RADS	100.0	TR	4.5	Yes	TR SB	10	Yes
Kuru et al. [19]	BiopSee	347	Biopsy naive (177), prior negative biopsy	3.0	T1, T2, DWI, DCE, spectroscopy	No	NIH	72.9	TP	4.0	Yes	TP SB	12–36	NM
Mozer et al. [15]	Urostation	152	Biopsy naive	1.5	T2, DWI, DCE	No	Likert	100.0	TR	2.0	No	TR SB	12	Yes
Rastinehad et al. [11]	UroNav	105	Biopsy naive (35), prior negative biopsy (70)	3.0	T2, DWI, DCE	No	NIH	100.0	TR	3.9	Yes	TR SB	12	Yes
Salami et al. [12]	UroNav	140	Prior negative biopsy	3.0	T2, DWI, DCE	Yes	Likert	100.0	TR	NM	Yes	TR SB	12	NM
Shoji et al. [16]	BioJet	20	Biopsy naive	1.5	T1, T2, DWI, DCE	No	PI-RADS	100.0	TP	NM	Yes	TP SB	12	No
Siddiqui et al. [18]	UroNav	1003	Biopsy naive (196), prior negative biopsy (807)	3.0	T2, DWI, DCE	Yes	NIH	100.0	TR	5.4	Yes	TRSB	12	Yes
Wysock et al. [13]	Artemis	125	Biopsy naive (67), prior negative biopsy (34), AS (24)	3.0	T2, DWI, DCE	No	Likert	100.0	TR	2.8	Yes	TR VE-TB and SB	12	Yes

AS, active surveillance; NM, not mentioned; TR, tranrectal; TP, transperineal; T1, T1-weighted imaging; T2, T2-weighted imaging.

AS, active surveillance; NM, not mentioned; TR, transrectal; TP, transperineal; T1, T1-weighted imaging; T2, T2-weighted imaging.

prostate cancer based on prostate biopsies was mentioned, it was defined as:

- 1 Epstein criteria: any Gleason score ≥ 7 or Gleason score 6 with a lesion volume of >0.2 mL (Borkowetz et al. [10], Rastinehad et al. [11], Salami et al. [12], Wysock et al. [13]);
- 2 All cancers excluding microfocal cancer, defined as a single core with <5 mm of Gleason score 6 cancer (Delongchamps et al. [14]);
- 3 At least one core with a Gleason score 3 + 4 or 6 with a maximum cancer core length of ≥ 4 mm (Mozer et al. [15], Shoji et al. [16]);
- 4 Total serum PSA level of >10 ng/mL or clinical stage $\geq T2b$ /or Gleason score ≥ 4 or total cancer length on biopsy of ≥ 10 mm (Fiard et al. [17]).

Siddiqui et al. [18] did not mention clinically significant prostate cancer, but made a separate analysis of high-grade prostate cancer, defined as Gleason score $\geq 4 + 3$.

Kuru et al. [19] did not mention clinically significant prostate cancer either, but made separate analyses for low vs high/intermediate prostate cancers, defined according to the National Comprehensive Cancer Network (NCCN) guidelines [20].

Risk of Bias Within Studies

For a transparent rating of bias and applicability of diagnostic accuracy studies, the QUADAS-2 tool was used to assess the quality of included articles (Table 2). In all studies, patient selection and index test were defined as low risk of bias. Risk of bias concerning the reference test was assessed high in all included studies because of the low accuracy of prostate SBs. Applicability of the index test was scored as a high risk of bias in all studies, because of the different fusion platforms and strategies for MRI/US fusion-guided prostate TBs. The item 'flow and timing' was assessed as high risk of bias in a few studies, because time from mpMRI until prostate TB was not mentioned.

Results of Individual Studies

The CDR of all prostate cancers and when mentioned, clinically significant prostate cancers, per patient of individual studies are presented in Table 3. A sub-analysis with the CDRs for low- vs moderate- to high-risk lesions, graded on mpMRI is presented in Table 4.

Syntheses of Results

In all, 11 studies were included in this systematic review, using Virtual Navigator (one study, [14]), Urostation (three studies [14,15,17]), Logiq 9 (one study [21]), UroNav (three studies [11,12,18]), Artemis (one study [13]), BiopSee (one study [19]) and BioJet (two studies, [10,16]).

The CDRs per patient were available for all 11 trials, including 2626 patients. Excluding the 24 patients on active surveillance results for 2602 patients were available for analysis.

Borkowetz et al. [10] compared transperineal MRI/US-fusion TB, using the BioJet platform, to transrectal SB in 263 patients. The overall CDR was 52%. For both the CDRs of all prostate cancers and clinically significant prostate cancer, MRI/US-fusion TB detected significantly more cancer than SB (44.1% vs 34.6% and 35.7% vs 28.5% respectively).

Delongchamps et al. [14] made a comparison of the accuracy of visually estimated TB (VE-TB) vs MRI/US-guided TB using a rigid (Virtual Navigator) or elastic (Urostation) approach, all compared to standard 12-core SB. In all, 391 biopsy naïve men were included and divided into three groups (VE-TB, rigid fusion, elastic fusion). In conclusion, MRI/US-guided TB performed significantly better (CDRs of 79.5% and 75.6% for Virtual Navigator and Urostation, respectively) than SB (ranging from 33.1% to 45.8% in all three groups), whereas VE-TB did not (74.1%).

Fiard et al. [17] included 30 patients with a clinical suspicion of prostate cancer, 17 men with prior negative biopsy and 13

Table 2 QUADAS-2 results.

Study	Judgments on bias				Judgments on applicability		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Borkowetz et al. [10]	Low risk	Low risk	High risk	High risk	Low risk	High risk	Low risk
Delongchamps et al. [14]	Low risk	Low risk	High risk	High risk	Low risk	High risk	Low risk
Fiard et al. [17]	Low risk	Low risk	High risk	High risk	Low risk	High risk	Low risk
Junker et al. [21]	Low risk	Low risk	High risk	High risk	Low risk	High risk	Low risk
Kuru et al. [19]	Low risk	Low risk	High risk	High risk	Low risk	High risk	High risk
Mozer et al. [15]	Low risk	Low risk	High risk	Low risk	Low risk	High risk	Low risk
Rastinehad et al. [11]	Low risk	Low risk	High risk	High risk	Low risk	High risk	Low risk
Salami et al. [12]	Low risk	Low risk	High risk	High risk	Low risk	High risk	Low risk
Shoji et al. [16]	Low risk	Low risk	High risk	High risk	Low risk	High risk	Low risk
Siddiqui et al. [18]	Low risk	Low risk	High risk	Low risk	Low risk	High risk	Low risk
Wysock et al. [13]	Low risk	Low risk	High risk	High risk	Low risk	High risk	Low risk

Table 3 Prostate CDR in trials comparing MRI/US fusion-guided prostate TB with other ways of TB or SB.

Study	Platform	MRI/US-fusion TB Total CDR, n/N (%) CDR of clinically significant prostate cancer, n/N (%)	VE-TB Total CDR, n/N (%) CDR of clinically significant prostate cancer, n/N (%)	SB Total CDR, n/N (%) CDR of clinically significant prostate cancer, n/N (%)
Borkowetz et al. [10]	BioJet	116/263 (44.1) 94/263 (35.7)	— —	91/263 (34.6) 75/263 (28.5)
Delongchamps et al. [14]	Virtual Navigator and Urostation	— — 62/78 (79.5) 56/78 (71.8) 62/82 (75.6) 58/82 (70.7)	40/54 (74.1) 40/54 (74.1) — — — —	55/127 (43.3) 43/127 (33.9) 60/131 (45.8) 45/131 (34.4) 44/133 (33.1) 35/133 (26.3)
Fiard et al. [17]	Urostation	82/152 (53.9) 66/152 (43.4)	— —	86/152 (56.6) 56/152 (36.8)
Junker et al. [21]	Logiq 9	23/50 (46.0) —	— —	18/50 (36.0) —
Kuru et al. [19]	BiopSee	103/253 (40.7) —	— —	175/347 (50.4) —
Mozer et al. [15]	Urostation	82/152 (53.9) 66/152 (43.4)	— —	86/152 (56.6) 56/152 (36.8)
Rastinehad et al. [11]	UroNav	53/105 (50.5) 47/105 (44.8)	— —	51/105 (48.8) 34/105 (32.4)
Salami et al. [12]	UroNav	73/140 (52.1) 67/140 (47.9)	— —	68/140 (48.6) 43/140 (30.7)
Shoji et al. [16]	BioJet	14/20 (70.0) —	— —	8/20 (40.0) —
Siddiqui et al. [18]	UroNav	461/1003 (46.0) —	— —	469/1003 (46.8) —
Wysock et al. [13]	Artemis	34/101 (33.7) —	31/101 (30.7) —	— —

biopsy naïve men. Suspicious area(s) were found on MRI in 20 cases. MRI/US-fusion TBs were performed using the Urostation. The CDRs of MRI/US-guided TB and SB were 55.0% and 43.3%, no further statistical analysis was made. The NPVs of SB and TB were 94% and 85%.

Junker et al. [21] analysed 50 patients using the Logiq 9 fusion system. The CDRs of TB and SB were 46% and 36%, resulting in a sensitivity of 69.2% for SB (18/26) and 88.5% for TB (23/26), respectively.

Kuru et al. [19] made a comparison between transrectal US-guided transperineal-fusion TB, using the BiopSee platform, and transperineal SB. The CDRs of all prostate cancers were equal in both SB and TB (50.4% and 50.6% respectively). However, there was a difference in the CDR in favour of TB for clinically significant prostate cancers according to the NCCN guidelines (41.1% for TB vs 38.0% for SB).

Mozer et al. [15] included 152 biopsy naïve men. The CDRs of all prostate cancers for TB and SB were 53.9% and 56.6%, respectively, but there was a statistical significant difference in the CDRs of clinically significant prostate cancer between the two protocols in favour of TB (43.3% vs 36.8%).

The value of the UroNav platform was examined by Rastinehad et al. [11]. In all, 105 patients were included in their trial. The CDRs of all prostate cancers by TB vs SB were 50.5% and 48.8%, respectively. For clinically significant

disease, the CDRs were 44.8% and 32.4%, respectively, which was a statistically significant difference.

The UroNav platform was also used by Salami et al. [12] in 140 patients with prior negative biopsy. The CDRs of MRI/US fusion-guided TB was 52.1% and 47.9% for all prostate cancers and clinically significant prostate cancers, respectively. The CDR of standard 12-core SB was 48.6% and 30.7% for all prostate cancers and clinically significant prostate cancers, respectively. The CDRs of MRI/US-guided TB and SB were not statistically significantly different, but MRI/US fusion-guided TBs detected more clinically significant prostate cancer when compared with SBs.

Shoji et al. [16] made a comparison between transperineal TB and SB, using the BioJet platform; 20 patients were included in their analysis, with CDRs for TB and SB of 70.0% vs 40.0%.

Siddiqui et al. [18] included 1003 patients in their prospective cohort study. SBs and TBs, using the UroNav platform, were taken. The CDRs of all prostate cancers by TB vs SB were not different (46.0% and 46.8%, respectively). However, TB diagnosed 30% more high-risk cancers than SB (17.2% vs 12.2%, respectively).

Wysock *et al.* [13] included 125 patients, of whom 67 were biopsy naïve, 34 had prior negative biopsy and 24 were on active surveillance. Overall, the CDR per patient was 23.2% and 19.2% for MRI/US-guided TB and VE-TB, respectively,

Table 4 Sub-analysis of CDRs per patient in low- vs moderate- to high-risk prostate cancers, graded on mpMRI.

Study	CDR total, n/N (%)		CDR TB, n/N (%)		CDR SB, n/N (%)	
	Low-risk lesions on mpMRI	High-risk lesions on mpMRI	Low-risk lesions on mpMRI	High-risk lesions on mpMRI	Low-risk lesions on mpMRI	High-risk lesions on mpMRI
Borkowetz et al. [10]	65/269 (24.2)	77/185 (41.6)	NM	NM	NM	NM
Delongchamps et al. [14]	NM	NM	NM	NM	NM	NM
Fiard et al. [17]	NM	NM	NM	NM	NM	NM
Junker et al. [21]	NM	NM	2/7 (28.6)*	29/50 (58.0)*	NM	NM
Kuru et al. [19]	114/243 (46.9)	100/149 (67.0)	NM	NM	NM	NM
Mozer et al. [15]	NM	NM	9/54 (16.7)	73/98 (74.5)	NM	NM
Rastinehad et al. [11]	19/40 (47.5)	47/65 (72.3)	13/40 (32.5)	40/65 (61.5)	14/40 (35.0)	37/65 (56.9)
Salami et al. [12]	31/68 (45.6)	60/72 (83.3)	18/68 (26.5)	55/72 (76.4)	25/68 (36.8)	43/72 (59.7)
Shoji et al. [16]	NM	NM	NM	NM	NM	NM
Siddiqui et al. [18]	NM	NM	NM	NM	NM	NM
Wysock et al. [13]	NM	NM	MR-TB: 15/74 (20.3) VE-TB: 9/74 (12.2)	MR-TB: 30/51 (58.8) VE-TB: 30/51 (58.8)	NM	NM

MR-TB, MRI/US fusion platform-guided TB; NM, not mentioned; *per lesion, not per patient.

with the difference being statistically insignificant. For the 101 biopsy naïve patients or with prior negative biopsy only, the total CDR was 33.7% vs 30.7% for the MRI/US-guided TBs vs VE-TBs. Pooled TBs (MRI/US-guided TB and VE-TB together) compared with SB in 67 biopsy naïve men showed a lower overall CDR (40.3% vs 55.2%) and less Gleason score 6 disease (7.5% vs 22.4%), but detected an equivalent number of Gleason score ≥ 7 disease (32.8% vs 32.8%).

A sub-analysis was made of low- vs moderate- to high-risk lesions, graded on mpMRI.

Moderate- to high-risk lesions include 4–5 lesions on a 5-point scale and 2–3 lesions on a 3-point scale. Four studies gave an overall sub-analysis, with CDRs for low-risk lesions ranging from 24.2% to 47.5% and for moderate- to high-risk lesions from 41.6% to 83.3%.

Five studies made a sub-analysis for TB of low- vs moderate- to high-risk lesions, but only two of these studies also gave a sub-analysis of SB. Within these two studies, including 245 patients, the CDRs in low-risk lesions were almost equal in TB and SB (CDRs of 26.5–32.5% in TB and 35.0–36.8% in SB) with a difference in CDRs in moderate- to high-risk lesions in favour of TB (CDRs 61.5–76.4% in TB and 56.9–59.7% in SB).

Discussion

In the present review, the value of different MRI/US platforms in prostate cancer detection was assessed by comparing the CDRs of MRI/US-fusion TBs with SB, and to other MRI/US-fusion techniques, such as in-bore and VE-TB. Most importantly, seven of eight FDA registered MRI/US-fusion platforms have been validated using prospective studies comparing CDRs of MRI/US-guided TBs with VE-TBs or SBs in the diagnosis of prostate cancer.

To date, the diagnosis of prostate cancer has had substantial limitations. First of all, biopsy Gleason score upgrading after pathological assessment of RP specimens shows a discrepancy between grading in TRUS-guided SBs and RP specimens [22]. Because of this discrepancy and due to the lack of large cohort studies, a good prediction of clinically significant disease is hampered.

Secondly, there is an ongoing debate about the definition of ‘clinically significant’ disease and in addition, with the introduction of TB, the question arises as to whether the same definition for clinically significant prostate cancer should be maintained for cores obtained with SB and TB. To overcome over-diagnosis and overtreatment, it is important to limit the diagnosis of clinically insignificant prostate cancer. There is some evidence that the criteria for clinically significant prostate cancer suggested by Epstein et al. [23] have a high likelihood for identifying organ-confined disease but not clinically insignificant disease [24,25].

Therefore, the most ideal development in prostate cancer diagnosis would be a test with high positive predictive values (PPVs) and NPVs for clinically significant disease. A recently published systematic review by Fütterer et al. [26] showed NPVs and PPVs for clinically significant prostate cancer with mpMRI ranging from 63% to 98% and 34% to 68%, respectively. The overall sensitivity and specificity of mpMRI reported are promising, but the additional value of DCE-MRI is still questioned [27]. Also, of great importance is the evidence that there are statistically significant histological differences between detected and missed prostate cancers on mpMRI [28], with detected prostate cancers on mpMRI showing more clinically significant features. The CDR in patients with prior negative biopsy with in-bore MR-guided TB varies from 52% to 59% [29,30]. TB especially may play a role in improving anterior prostate cancer detection [31].

In our present analysis, no clear advantage of MRI/US fusion-guided TBs could be seen for the CDRs of all prostate cancers, but MRI/US fusion-guided TBs tended to give a higher CDR for clinically significant prostate cancers. This is consistent with the results of the systematic reviews of Valerio et al. [32] and Van Hove et al. [8]. It would be interesting to see whether there is a difference between CDRs in low- vs high-risk lesions on mpMRI when comparing TB with SB. Unfortunately, only two studies made this sub-analysis, showing contradictory results. While the study of Rastinehad et al. [11] showed no clear difference between TB and SB, the study of Salami et al. [12] tended to give a higher CDR in high-risk lesions with TB.

There are some general limitations in assessing the value of MRI/US-fusion TBs. First of all, the range in CDRs at SB suggests that there is a difference in the quality of taking biopsies. Furthermore, it seems plausible that the strength of the MRI magnet and the use of an endorectal or pelvic coils determine the quality of MR images and the experience of the radiologist and physician performing the biopsy determines the quality of the biopsy cores, which determines the CDR. However, this has not been properly studied. In most of the included studies, men with negative mpMRI were disregarded, which creates selection bias and makes the results less applicable to clinical practice. And although direct visualisation of the biopsy needle inside the suspicious area is technically possible [33], in common practice, it is almost never used.

The present systematic review has several limitations. First of all, 11 studies met our inclusion criteria, including 2626 patients. Because of this limited number of included studies, no statement can be made about the difference in the CDRs between the different fusion platforms. Another important limitation is the lack of a general definition of clinically significant prostate cancer. As shown in our present results, in the 11 included articles, four different definitions are being used. The aim of our present systematic review was to assess the CDRs in MRI/US-fusion TB vs SB in the diagnosis of prostate cancer. Patients included in the original studies are heterogeneous, containing biopsy naïve men and men with one, two or sometimes more prior negative biopsies. Because previous studies show that the CDR is dependent on biopsy session number [34,35], the included studies are difficult to compare. On the other hand, these results are applicable to clinical practice. A general limitation of studies using SB as a reference test is that it lacks accuracy, i.e. has low sensitivity and specificity [3]. It is used because a good gold standard, such as RP, is unethical to use.

Conclusion

Although MRI/US-fusion TB has proved its value in men with prior negative biopsies, general use of this technique in the diagnosis of prostate cancer should only be performed

after critical consideration because in our present analysis, no clear advantage of MRI/US fusion-guided TB could be found for CDRs of all prostate cancers; however, MRI/US fusion-guided TBs tended to give a higher CDR for clinically significant prostate cancers. Before bringing MRI/US fusion-guided TB in to general practice, there is a need for more prospective studies on its effectiveness for prostate cancer diagnosis.

Parallel to our research question about CDRs, is the important question of whether SB can be omitted, because this will have an impact on clinical practice. There is also a need for more research into how many prostate cancers are missed by TB, and their clinical relevance. Moreover, individual quality of taking prostate biopsies is an under-reported problem that causes bias.

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Conflicts of Interest

None disclosed.

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Abbreviations: CDR, cancer detection rate; DCE, dynamic contrast enhanced; FDA, USA Food and Drug Administration; mpMRI, multiparametric MRI; NCCN, National Comprehensive Cancer Network; NIH, National Institutes of Health; PI-RADS, Prostate Imaging-Reporting And Data System; (N)(P)PV, (negative) (positive) predictive value; QUADAS, Quality Assessment of Diagnostic Accuracy Studies; RP, radical prostatectomy; SB, systematic biopsy; (VE-)TB, (visually estimated) targeted biopsy.