

Magnetic resonance imaging - ultrasound fusion targeted biopsy outperforms standard approaches in detecting prostate cancer: A meta-analysis

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Abstract. The aim of the present study was to determine whether magnetic resonance imaging - ultrasound (MRI-US) fusion prostate biopsy is superior to systematic biopsy for making a definitive diagnosis of prostate cancer. The two strategies were also compared regarding their ability to detect clinically significant and insignificant prostate cancer. A literature search was conducted through the PubMed, EMBASE and China National Knowledge Infrastructure databases using appropriate search terms. A total of 3,415 cases from 21 studies were included in the present meta-analysis. Data were expressed as relative risk (RR) and 95% confidence interval. The results revealed that MRI-US fusion biopsy achieved a higher rate of overall prostate cancer detection compared with systematic biopsy (RR=1.09; P=0.047). Moreover, MRI-US fusion biopsy detected more clinically significant cancers compared with systematic biopsy (RR=1.22; P<0.01). It is therefore recommended that multi-parametric MRI-US is performed in men suspected of having prostate cancer to optimize the detection of clinically significant disease, while reducing the burden of biopsies.

Introduction

Prostate cancer is currently one of the most common malignant tumors in men aged >50 years. The global age-standardized incidence rate of prostate cancer in 2008

was ~30/100,000 individuals, which is second only to that of lung cancer (1). Screening for prostate cancer mostly relies on digital rectal examination, measurement of prostate-specific antigen (PSA) level, magnetic resonance imaging (MRI) and ultrasound (US). The current standard for diagnosing prostate cancer in men at risk relies on a transrectal US (TRUS)-guided biopsy test, which is blind to cancer location. This method has the advantages of speed, ease, cost-effectiveness, availability and portability, and it is more suitable for wide-area sampling of the prostate, including the far-lateral peripheral zones (2). However, despite an increasing number of biopsy cores being included in TRUS-guided biopsy protocols, the current standard of including 10-14 randomized cores lacks sensitivity and frequently detects clinically insignificant disease (3-5).

It was recently suggested that targeted biopsies of suspicious lesions detected by multi-parametric (mp)-MRI may increase the diagnostic accuracy of TRUS-guided biopsy (6). mp-MRI combines T2-weighted images with diffusion-weighted images and dynamic contrast enhancement (7,8). This method exhibits increased sensitivity and specificity and has become the standard imaging technique for biopsy guidance (9,10). As mp-MRI and biopsy are performed on different days, with the latter commonly performed using a TRUS probe, a number of devices that use image-fusion software have been developed to overlay the suspicious area on mp-MRI onto the US images at the time of biopsy (11).

In the present study, a meta-analysis of data extracted from published studies using MRI-US image fusion targeted prostate biopsy was performed to assess the accuracy of prostate cancer detection compared with that of systematic biopsy.

Materials and methods

Literature search strategy. A literature search was conducted through the PubMed, EMBASE and China National Knowledge Infrastructure databases for studies published prior to July 21st, 2015, using the key words ('prostate cancer', 'prostate neoplasm' or 'prostate') in combination with ('magnetic resonance imaging', 'MRI' or 'MR') and ('transrectal ultrasound' or 'TRUS') and ('fusion', 'registration',

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Table I. Main characteristics of the studies included in the meta-analysis.

Author, year (Refs.)	Study design	Country	Sample size (n)	Population characteristics				MRI-TRUS fusion targeted biopsy						
				Age (years)	PSA (ng/ml)	Prostate volume (ml)	Prior biopsy	Anaesthesia	System biopsy	Magnetic field (T)	Software used	Sampling method	Targeted biopsy first	No. of cores per lesion
Baco <i>et al</i> 2015 (29)	RCT	USA	175	Mean (range), 65 (59-69)	Mean (range), 7.3 (5.5-9.9)	Mean (range), 42 (30-59)	Biopsy naive	Local	TRUS 12 cores	1.5	UroStation	Transrectal	Yes	Med (range), 2 (1-4)
Siddiqui <i>et al</i> 2015 (30)	Cohort	USA	1003	Mean \pm SD, 62.1 \pm 7.5	Med (IQR), 6.7 (4.4-10.7)	Med (IQR), 49 (36-71)	Mixed	NR	TRUS 12 cores	3	UroNav	Transrectal	Yes	2
Borkowetz <i>et al</i> 2015 (31)	Cohort	Germany	263	Med (range), 66 (47-83)	Med (range), 8.3 (0.39-86.57)	Med (range), 50 (12-220)	Mixed	General or spinal	TRUS 12 cores	3	Biojet	Transperineal	Yes	\geq 2
Sankineni <i>et al</i> 2015 (12)	Cohort	USA	33	Mean (range), 63 (52-76)	Mean (range), 8.4 (1.22-65.20)	Mean (range), 53 (12-125)	Mixed	NR	TRUS 12 cores	3	UroNav	Transrectal	NR	NR
Zhang <i>et al</i> 2015 (13)	Cohort	China	62	Mean \pm SD, 68.38 \pm 6.57	Mean \pm SD, 10.21 \pm 5.57	Mean \pm SD, 34.05 \pm 9.86	Biopsy naive	General	TRUS 12 cores	3	RVS	Transrectal	Yes	\geq 2
de Gorski <i>et al</i> 2015 (14)	Cohort	France	232	Mean \pm SD, 64 \pm 6.4	Mean \pm SD, 6.65 \pm 1.8	Mean \pm SD, 40 \pm 24.3	Biopsy naive	NR	TRUS 12 cores	1.5	UroStation	Transrectal	No	NR
Ukimura <i>et al</i> 2015 (15)	Cohort	USA	127	Med, 69	Med, 5.8	NR	Mixed	Local	TRUS 10-12 cores	3	UroStation	Transrectal	No	\geq 1
Junker <i>et al</i> 2015 (16)	Cohort	Australia	50	Mean \pm SD, 63.7 \pm 7.9	Mean \pm SD, 7.6 \pm 4.2	Mean \pm SD, 49.2 \pm 21.9	Mixed	NR	TRUS 10 cores	3	Logiq	Transrectal	Yes	Mean, 3.9
Shoji <i>et al</i> 2015 (17)	Cohort	Japan	20	Med (range), 70 (52-83)	Med (range), 7.4 (3.54-19.9)	Med (range), 38 (24-68)	Biopsy naive	Spinal	Transperineal 12 cores	1.5	Biojet	Transrectal	Yes	NR
Salami <i>et al</i> 2015 (18)	Cohort	USA	140	NR	NR	NR	Negative	NR	TRUS 12 cores	3	UroNav	Transrectal	Yes	2
Mozier <i>et al</i> 2015 (19)	Cohort	France	152	Med (IQR), 63.7 (59.3-67.5)	Med (IQR), 6 (5-7.9)	Med (IQR), 38.5 (30-55)	Biopsy naive	NR	TRUS 12 cores	1.5	UroStation	Transrectal	No	2 or 3
Volkin <i>et al</i> 2015 (25)	Cohort	USA	162	Med (range), 63 (44-80)	Med (range), 8.4 (0.3-95.8)	Med (range), 48 (19-187)	Mixed	Local	TRUS 12 cores	3	NR	Transrectal	No	\geq 2
Rastinehad <i>et al</i> 2014 (20)	Cohort	USA	105	Mean (range), 65.8 (42-87)	Mean (range), 9.2 (0.6-62)	NR	Mixed	NR	TRUS 12 cores	3	UroNav	Transrectal	Yes	NR
Sonn <i>et al</i> 2014 (26)	Cohort	USA	105	Med (IQR), 65 (59-70)	Med (IQR), 7.5 (5-11.2)	Med (IQR), 58 (39-82)	Negative	Local	TRUS 12 cores	3	Artemis	Transrectal	Yes	Mean (range), 4.2 (1-9)
Wysock <i>et al</i> 2014 (27)	Cohort	USA	125	Med (range), 65 (56.3-71)	Med (range), 5.1 (3.5-7.3)	Med (range), 46 (31-62.5)	Mixed	Local	TRUS 12 cores	3	Artemis	Transrectal	Yes	2
Fiard <i>et al</i> 2013 (21)	Cohort	France	20	Med (range), 65 (62-68)	Med (range), 6.3 (5.3-10)	Med (range), 39 (29-49)	Mixed	Local or general	TRUS 12 cores	3	UroStation	Transrectal	No	2
Delongchamps <i>et al</i> 2013 (23)	Cohort	France	133	Mean \pm SD, 64.5 \pm 7.9	Mean \pm SD, 9 \pm 3.9	Mean \pm SD, 58.3 \pm 28.6	Biopsy naive	NR	TRUS 10-12 cores	1.5	Koelis	Transrectal	No	\geq 2
Puech <i>et al</i> 2013 (24)	Cohort	France	95	Med (range), 65 (49-76)	Mean \pm SD, 10.05 \pm 8.8	Mean \pm SD, 52 \pm 24	Mixed	Local	TRUS 12 cores	1.5	Virtual Navigator	Transrectal	No	2

Table I. Continued.

Author, year (Refs.)	Study design	Country	Sample size (n)	Population characteristics				MRI-TRUS fusion targeted biopsy						
				Age (years)	PSA (ng/ml)	Prostate volume (ml)	Prior biopsy	Anaesthesia	System biopsy	Magnetic field (T)	Software	Sampling method	Targeted biopsy first	No. of cores per lesion
Kuru <i>et al</i> 2013 (28)	Cohort	Germany	347	Med (range), 65.3 (42-82)	Mean (range), 9.85 (0.5-104)	Mean (range), 48.7 (9-108)	Mixed	General	Transperineal	3	BiopSee	Transperineal	Yes	Med (range), 4 (2-6)
Vourganti <i>et al</i> 2012 (22)	Cohort	USA	195	Med (range), 62 (37-80)	Med (range), 9.13 (0.3-103)	Med (range), 56 (16-187)	Negative	Local	TRUS	3	NR	Transrectal	No	Med (range), 5 (2-14)
Miyagawa <i>et al</i> 2010 (2)	Cohort	Japan	85	Med (range), 69 (56-84)	Med (range), 9.9 (4.0-34.2)	Med (range), 37.2 (18-141)	Negative	Spinal	TRUS/transperineal	1.5	RVS	Transperineal	Yes	Mean, 1.9

PSA, prostate-specific antigen; MRI, magnetic resonance imaging; TRUS, transrectal ultrasound; RCT, randomized controlled trial; med, median; SD, standard deviation; IQR, interquartile range; NR, not reported.

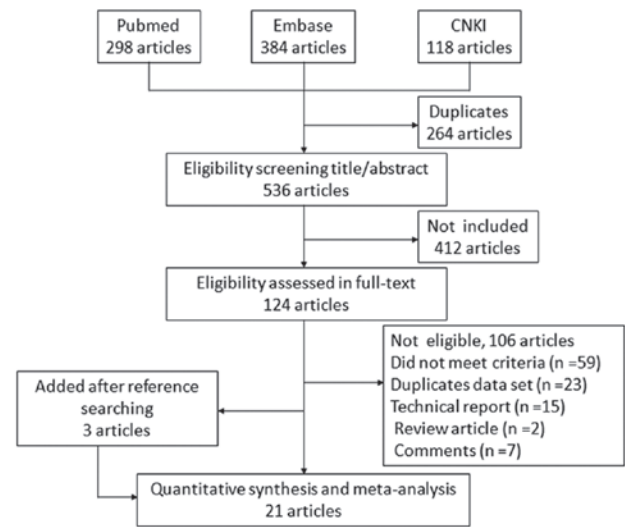


Figure 1. Flow chart of the study selection process. CNKI, China National Knowledge Infrastructure.

‘targeted’, ‘target’, ‘computer’ or ‘software’). Only articles written in English or Chinese and studies on human subjects were included. In addition, references of relevant articles were manually searched to identify potentially eligible studies.

Eligibility criteria. Two authors assessed each identified study independently. The inclusion of individual studies required that software-based MRI-US fusion targeted prostate biopsies and systematic biopsies had been performed within the same study. In addition, each study was required to contain overall or significant cancer detection results for the two modalities. To allow for a valid comparison, only studies directly comparing the two techniques were included. When multiple studies contained overlapping data, only the most informative study was included. Meeting abstracts, editorials, case reports, letters and reviews were excluded.

Data extraction. Two investigators blinded to each others' results independently reviewed the full manuscripts of the eligible studies. The information extracted from each study included first author, year of publication, study design, population (sample size, age, PSA, prostate volume and prior biopsy), type of anaesthesia, systematic biopsy (number of cores and sampling route), MRI-US image fusion targeted biopsy procedure (software used, sampling route, time flow and number of cores per lesion) and separate histological outcomes for systematic vs. targeted biopsy (overall detection rate of cancer and detection rate of clinically significant and insignificant cancer). Disagreements between the two reviewers were resolved through discussion.

Statistical analysis. All the analyses were performed using the statistical Stata software, version SE/12 (StataCorp LP, College Station, TX, USA). The main outcome was the detection rate of overall prostate cancer and the secondary outcomes were the detection rates of clinically significant and insignificant disease by MRI-TRUS image fusion targeted biopsy compared with the systematic biopsy technique. The definition used to determine clinical significance was that

Table II. Quality assessment of the studies included in the meta-analysis.

Author, year (Refs.)	Main race	Definition of clinically significant disease	Overall cancer detection (n/total)		Clinically significant cancer detection (n/total)	
			Fusion biopsy	System biopsy	Fusion biopsy	System biopsy
Baco <i>et al</i> , 2015 (29)	Caucasian	Gleason ≥ 7 or maximum cancer core length ≥ 5 mm	51/86	48/89	33/86	44/89
Siddiqui <i>et al</i> , 2015 (30)	Caucasian	NR	461/1,003	469/1,003	-	-
Borkowetz <i>et al</i> , 2015 (31)	Caucasian	Gleason >6 , or >2 cores, or $>50\%$ of any core	116/263	91/263	94/263	75/263
Sankineni <i>et al</i> , 2015 (12)	Caucasian	Gleason $>3+4$ with 25% biopsy core involvement	24/33	19/33	16/33	13/33
Zhang <i>et al</i> , 2015 (13)	Asian	Gleason $\geq 3+4$ or cancer core length ≥ 4 mm	27/62	21/62	14/62	5/62
de Gorski <i>et al</i> , 2015 (14)	Caucasian	Gleason $\geq 3+4$ or cancer core length ≥ 4 mm	126/232	129/232	102/232	91/232
Ukimura <i>et al</i> , 2015 (15)	Caucasian	Gleason $\geq 3+4$ or cancer core length ≥ 5 mm	78/127	52/127	54/127	29/127
Junker <i>et al</i> , 2015 (16)	Caucasian	NR	23/50	18/50	-	-
Shoji <i>et al</i> , 2015 (17)	Asian	NR	14/20	8/20	-	-
Salami <i>et al</i> , 2015 (18)	Caucasian	Gleason >6 , or >2 cores, or $>50\%$ of any core	68/140	73/140	67/140	43/140
Mozer <i>et al</i> , 2015 (19)	Caucasian	Gleason $\geq 3+4$ or cancer core length ≥ 4 mm	82/152	86/152	66/152	56/152
Volkin <i>et al</i> , 2014 (25)	Caucasian	NR	19/42	18/42	-	-
Rastinehad <i>et al</i> , 2014 (20)	Caucasian	Gleason >6 , or >2 cores, or $>50\%$ of any core	53/105	51/105	47/105	34/105
Sonn <i>et al</i> , 2014 (26)	Caucasian	Gleason $\geq 3+4$ or cancer core length ≥ 4 mm	24/102	27/97	21/102	15/97
Wysock <i>et al</i> , 2014 (27)	Caucasian	Gleason $\geq 3+4$	45/125	40/125	29/125	24/125
Fiard <i>et al</i> , 2013 (21)	Caucasian	Gleason $\geq 3+4$ or total cancer length ≥ 10 mm	11/20	10/20	10/20	9/20
Delongchamps <i>et al</i> , 2013 (23)	Caucasian	NR	45/125	40/125	-	-
Puech <i>et al</i> , 2013 (24)	Caucasian	Gleason $\geq 3+4$ or cancer core length ≥ 3 mm	66/95	56/95	64/95	49/95
Kuru <i>et al</i> , 2013 (28)	Caucasian	NCCN criteria	128/253	161/253	104/253	121/253
Vourganti <i>et al</i> , 2012 (22)	Caucasian	NR	56/195	45/195	-	-
Miyagawa <i>et al</i> , 2010 (2)	Asian	NR	45/85	34/85	-	-
Total ^a			1,562/3,315	1,496/3,313	721/1,795	608/1,793

^aNot all studies were designed as paired cohort studies (e.g., Baco *et al*), resulting in the inequality of case numbers in fusion group and systematic biopsy groups. NR, not reported; NCCN, National Comprehensive Cancer Network; system, systematic.

used by each individual study. Fixed-effects or random-effects meta-analysis was performed to pool the original studies on the basis of their relative risk (RR), depending on the result of the heterogeneity analysis. Forest plots were created to summarize all studies, the pooled estimate and corresponding 95% confidence intervals (95% CIs) in a single overview.

Heterogeneity was assessed using the I^2 statistical method, with $I^2 > 50\%$ indicating significant heterogeneity. When heterogeneity was confirmed, a sensitivity analysis was performed by successively excluding each individual study. Subgroup analysis was performed according to several characteristics. Publication bias was assessed using Begg's funnel plot and Egger's test. All the P-values were two-tailed

and $P < 0.05$ was considered to indicate statistically significant differences.

Results

Study selection and characteristics. Of the 800 articles retrieved during the initial search, 21 (2,12-31) met the inclusion criteria. A flow chart of the study selection process is presented in Fig. 1.

A total of 3,415 patients were included, with a sample size ranging from 20 to 1,003 patients. The majority of studies originated from 6 countries, with studies from the USA comprising the largest proportion (n=10). A total of 6 studies

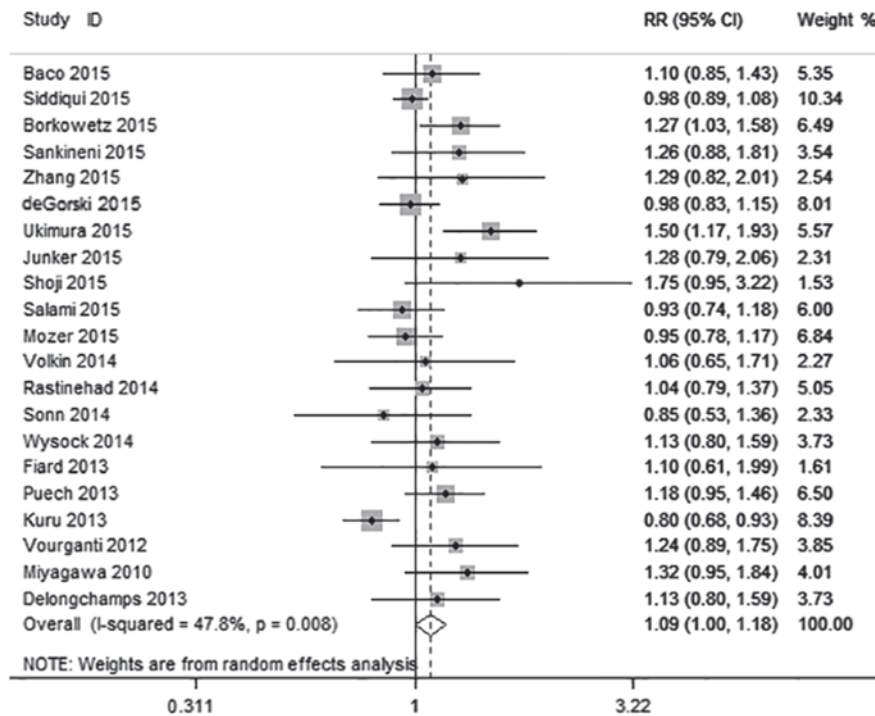


Figure 2. Forest plots of the RR with 95% CI for the heterogeneity of overall prostate cancer detection (MRI-US fusion biopsy vs. systematic biopsy) determined by the random-effects model. $\chi^2=38.34$, $P=0.008$, $I^2=47.8\%$, $Z=1.99$ and $P=0.047$. The grey square indicates the value of RR and its size is inversely proportional to its variance. The horizontal line represents the 95% CI of the RR. The white diamond represents the pooled results. The studies are ordered by the publication year. RR, relative risk; CI, confidence interval; MRI, magnetic resonance imaging; US, ultrasound.

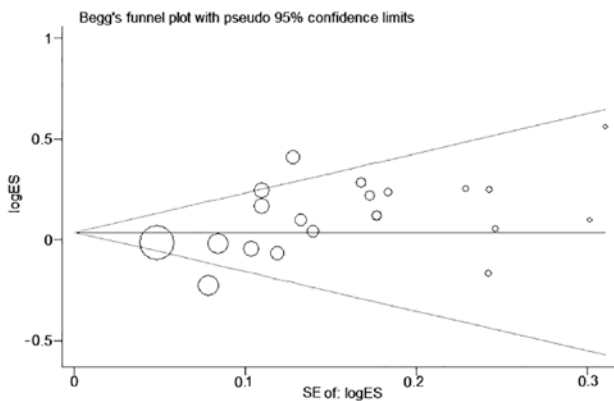


Figure 3. Begg's funnel plot for the assessment of publication bias for overall prostate cancer detection. Begg's test, $P=0.205$; Egger's test, $P=0.017$. The horizontal line represents the summary estimate, while the sloping lines represent the expected 95% confidence interval. The case numbers in Wysock's and Delongchamps's studies were identical, leading to the superposition of the respective circles in the funnel plot. logES, natural logarithm of effect size; SE, standard error.

had been conducted on biopsy-naïve patients, 4 on patients with a previous negative prostate biopsy, and 11 studies reported on a mixed cohort (either biopsy-naïve patients, or those having undergone previous prostate biopsy). All mp-MRI scans had been performed on either a 1.5- or a 3-T scanner and 9 different image fusion platforms currently used in the clinical setting to perform MRI-TRUS targeted biopsies were identified in this meta-analysis. The standard comparator was a 8- to 12-core TRUS biopsy in 18 studies, whereas 3 other studies used transperineal template biopsies, or a combination of the two.

The characteristics of the included studies are summarized in Table I.

Overall prostate cancer detection. Details regarding diagnostic criteria and detection ratios in the individual studies are presented in Table II. Across the 21 studies, the prevalence of prostate cancer was 63.0% (2,153/3,415). MRI-US fusion biopsy detected overall prostate cancer in 1,562 of 3,315 patients and systematic biopsy in 1,496 of 3,313 patients, resulting in an RR of 1.09 (95% CI: 1.00-1.18; $P=0.047$) (Fig. 2). The heterogeneity among these studies was moderate ($I^2=47.8\%$; $\chi^2=38.34$; $P=0.047$). Publication bias in this overall analysis was revealed by the Begg's funnel plot ($P=0.205$, Begg's test; $P=0.017$, Egger's test) (Fig. 3).

Clinically significant prostate cancer detection. A total of 14 studies including 1,884 patients were eligible for inclusion in the analysis. The prevalence of clinically significant and insignificant prostate cancer was 47.2% (890/1,884) and 16.6% (313/1,884), respectively. Clinically significant prostate cancer was diagnosed in 721 of the 1,795 patients with MRI-US fusion biopsy compared with 608 of 1,793 patients with systematic biopsy, with an RR of 1.22 (95% CI: 1.06-1.40; $P=0.005$) (Fig. 4). However, heterogeneity was observed among these studies ($I^2=56.7\%$; $\chi^2=30.04$; $P=0.005$). Begg's funnel plots revealed little publication bias in this analysis (Fig. 5), whereas the Egger's and Begg's tests indicated there was no publication bias.

The results of the subgroup analysis for clinically significant prostate cancer detection are presented in Table III. MRI-US

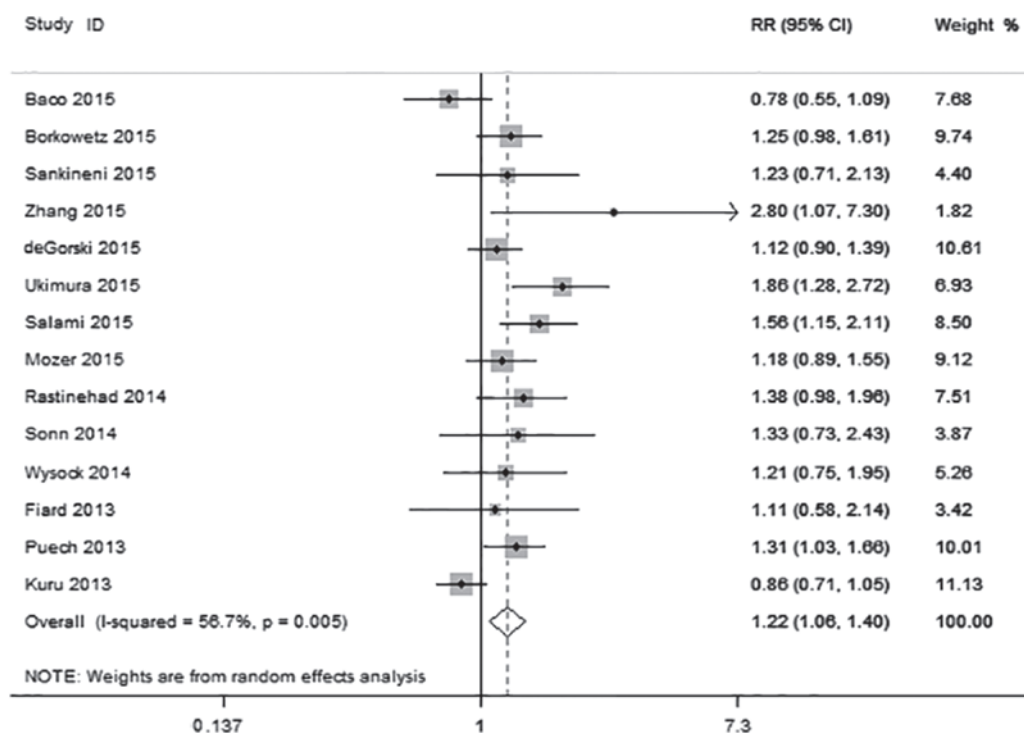


Figure 4. Forest plots of the RR with 95% CI for the heterogeneity of clinically significant prostate cancer detection (MRI-US fusion biopsy vs. systematic biopsy) determined by the random-effects model. $\chi^2=30.04$, $P=0.005$, $I^2=56.7\%$, $Z=2.79$ and $P=0.005$. The grey square indicates the value of RR and the size of the square is inversely proportional to its variance. The horizontal line represents the 95% CI of the RR. The white diamond indicates the pooled results. The studies are ordered by publication year. RR, relative risk; CI, confidence interval; MRI, magnetic resonance imaging; US, ultrasound.

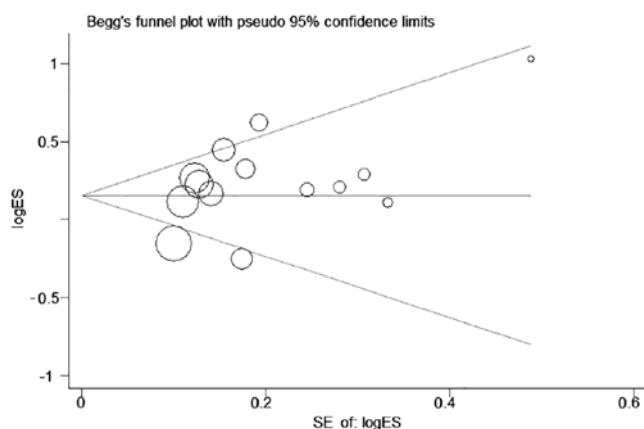


Figure 5. Begg's funnel plot for the assessment of publication bias for clinically significant prostate cancer detection. Begg's test, $P=0.274$; Egger's test, $P=0.124$. The horizontal line represents the summary estimate, while the sloping lines represent the expected 95% confidence interval. logES, natural logarithm of effect size; SE, standard error.

fusion biopsy exhibited a significantly higher detection rate of clinically significant prostate cancer compared with systematic biopsy in 7 subgroups, but there was heterogeneity in all subgroups apart from that of patients with a previous negative biopsy.

Sensitivity analysis of the 14 studies demonstrated that the results of Kuru *et al* (28) diverged from those of most other trials (Fig. 6). Following exclusion of the Kuru *et al* trial, there was no significant variation in the RR value, but the heterogeneity decreased (Table IV).

Clinically insignificant prostate cancer was diagnosed in 178 of 1,795 patients by MRI-US fusion biopsy and in 256 of 1,793 patients by systematic biopsy, resulting in a RR of 0.73 (95% CI: 0.51-1.05; $P=0.089$); there was high heterogeneity among these studies ($I^2=67.5\%$; $\chi^2=39.97$; $P<0.01$).

Discussion

The current gold standard technique for diagnosing prostate cancer in men at risk is systematic prostate biopsy using TRUS. However, there are discrepancies between the results of systematic prostate biopsy and radical prostatectomy specimens (32), as only 24-40% of TRUS-guided biopsy results are consistent with the pathological findings following prostatectomy (33). Furthermore, systematic biopsy may not be able to detect all cases of clinically significant prostate cancer, which may delay the treatment of a tumor with a high Gleason score (3-5). The optimal biopsy strategy should selectively detect clinically significant prostate cancer and minimize clinically insignificant prostate cancer detection to avoid consequent overtreatment. The present meta-analysis demonstrated that MRI-US fusion targeted biopsy may be a promising strategy with certain advantages over systematic biopsy.

The results of the present study demonstrated that the overall prostate cancer detection rate of MRI-US fusion biopsy is higher compared with that of systematic biopsy, with an RR of 1.09. The difference between the results of the present study and those of a prior systematic review (34) may be due to the larger sample size and updated data included herein.

Table III. Results of subgroup analysis of significant prostate cancer detection.

Subgroups	No. of studies	Heterogeneity		Effects model	Meta-analysis	
		I ² (%)	P-value		RR (95% CI)	P-value
Study design						
Paired cohort	13	50.3	0.02	Random	1.258 (1.100-1.438)	0.001
Comparative series	1	-	-	-	0.776 (0.552-1.091)	0.145
Main race						
Caucasian	13	55.2	0.008	Random	1.198 (1.047-1.370)	0.009
Asian	1	-	-	-	2.800 (1.074-7.302)	0.035
Prior biopsy						
Mixed	8	59.8	0.015	Random	1.235 (1.023-1.491)	0.028
Biopsy naive	4	62.4	0.047	Random	1.101 (0.833-1.457)	0.498
Previous negative	2	0.0	0.645	Fixed	1.498 (1.141-1.967)	0.004
Strength of magnetic field						
3T	10	61.5	0.005	Random	1.311 (1.073-1.601)	0.008
1.5T	4	51.6	0.102	Random	1.104 (0.914-1.333)	0.307
Sampling method						
Transrectal	12	40.3	0.072	Random	1.269 (1.104-1.459)	0.001
Transperineal	2	81.7	0.019	Random	1.029 (0.710-1.492)	0.879

RR, relative risk; CI, confidence interval.

Table IV. Results of sensitivity analysis of significant prostate cancer detection.

Sensitivity analysis	Heterogeneity test		Pooled estimate	
	I ² (%)	tau ²	RR (95% CI)	P-value
Kuru <i>et al</i> (28) incorporated	56.7	0.0350	1.218 (1.060,1.399)	0.005
Kuru <i>et al</i> (28) excluded	34.8	0.0162	1.265 (1.119,1.429)	<0.001

RR, relative risk; CI, confidence interval.

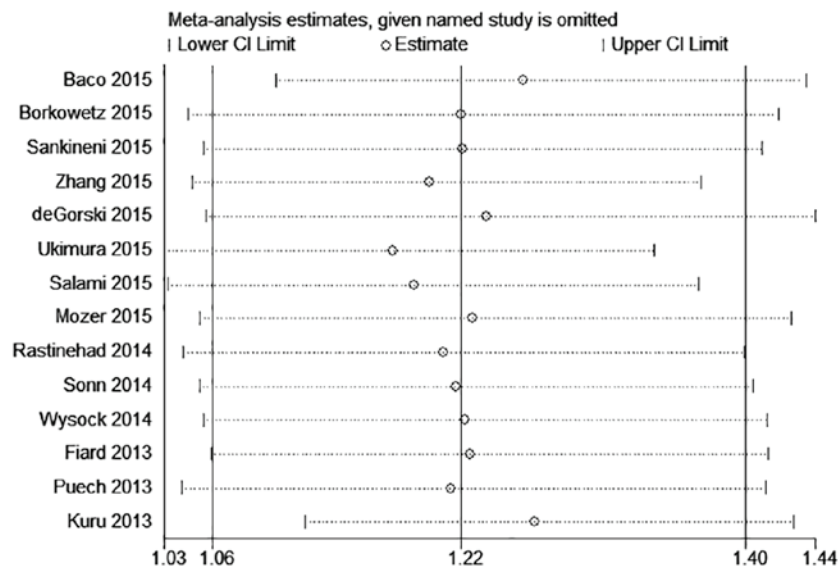


Figure 6. Sensitivity analysis of the RR with 95% CI of clinically significant prostate cancer detection (MRI-US fusion biopsy vs. systematic biopsy). The circles represent the RR estimate and the horizontal lines represent the 95% CI. The studies are ordered by publication year. MRI, magnetic resonance imaging; US, ultrasound; CI, confidence interval; RR, relative risk.

It was reported that mp-MRI exhibits a high diagnosis rate of clinically significant prostate cancer when compared to the histological findings following radical prostatectomy (35), which is in line with the results of the present study. In our study, MRI-US fusion biopsy had an RR of 1.22 for detecting significant prostate cancer, which means that MRI-US fusion biopsy has a 22% increased detection rate for clinically significant prostate cancer compared with systematic biopsy.

MRI-US fusion biopsy and systematic biopsy did not significantly differ in the detection of clinically insignificant prostate cancer; however, an RR of 0.73 indicated that MRI-US had a better performance in terms of avoiding detection of insignificant prostate cancer compared with systematic biopsy in most studies. Thus, the application of MRI-US fusion biopsy may help reduce oversampling of potentially insignificant prostate cancers.

Several studies also compared MRI-US fusion with the systematic approach on a per-core basis (13,21,30). The results demonstrated that MRI-US-guided biopsy required fewer cores for successful tumor detection, thereby reducing patient discomfort compared with systematic biopsy.

The present meta-analysis had several limitations that may reduce the strength of the conclusions. Studies with negative results are less likely to be published, which may result in the overstatement of beneficial effects in meta-analyses. In the analysis of the overall prostate cancer detection rate, Begg's test yielded a P-value of 0.205, while Egger's test yielded a P-value of 0.017, indicating the presence of publication bias, as Egger's test has a higher sensitivity.

In the analysis of the detection of clinically significant prostate cancer, Begg's test and Egger's test indicated no publication bias. However, significant heterogeneity was found in this analysis ($I^2=56.7%$). Subgroup analysis revealed the presence of heterogeneity in all subgroups apart from that including patients with a previous negative biopsy, indicating that the heterogeneity originated in the category of prior biopsy, but not study design, main race, strength of magnetic field or sampling method. The sensitivity analysis revealed that, after excluding the trial by Kuru *et al* (28), heterogeneity was markedly decreased, while the RR value was not significantly affected. Kuru *et al* (28) obtained a higher RR compared with that of the other studies, possibly due to the BiopSee system used in their study, in which US, TRUS/MRI fusion, biopsy planning, perineal targeting, 3D mapping and automated documentation are integrated into a single system. The definition of significant prostate cancer, which included intermediate or high-risk tumors according to the National Comprehensive Cancer Network criteria (36), may also explain their higher RR. In addition, significant heterogeneity may be attributed to the variability across the studies in terms of criteria for defining clinically significant tumors, the methodology of targeted biopsy and the number of cores per target.

On the basis of biopsy data alone, it may be methodologically incorrect to conclude that MRI-US fusion biopsy detects more significant prostate cancers compared with systematic biopsy. This conclusion may be a statistical or methodological effect rather than a true clinical fact. All patients would have to undergo radical prostatectomy and assessment of the final

pathology to draw clinically relevant conclusions. Such studies are warranted in the future.

In summary, a meta-analysis of the currently available high-level clinical studies was performed to evaluate the efficacy of MRI-US fusion prostate biopsy. It was revealed that MRI-US fusion prostate biopsy has a higher detection rate of prostate cancer compared with systematic biopsy. MRI-US fusion biopsy also detects more clinically significant and fewer insignificant prostate cancers compared with systematic protocols. It is therefore recommended that mp-MRI is performed in patients suspected of having prostate cancer in order to optimize the detection of clinically significant prostate cancer, while reducing the burden of biopsies.

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