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Platinum Priority – Review – Prostate Cancer

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Comparing Three Different Techniques for Magnetic Resonance Imaging-targeted Prostate Biopsies: A Systematic Review of In-bore versus Magnetic Resonance Imaging-transrectal Ultrasound fusion versus Cognitive Registration. Is There a Preferred Technique?

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Abstract

Context: The introduction of magnetic resonance imaging-guided biopsies (MRI-GB) has changed the paradigm concerning prostate biopsies. Three techniques of MRI-GB are available: (1) in-bore MRI target biopsy (MRI-TB), (2) MRI-transrectal ultrasound fusion (FUS-TB), and (3) cognitive registration (COG-TB).
Objective: To evaluate whether MRI-GB has increased detection rates of (clinically significant) prostate cancer (PCa) compared with transrectal ultrasound-guided biopsy (TRUS-GB) in patients at risk for PCa, and which technique of MRI-GB has the highest detection rate of (clinically significant) PCa.
Evidence acquisition: We performed a literature search in PubMed, Embase, and CENTRAL databases. Studies were evaluated using the Quality Assessment of Diagnostic Accuracy Studies-2 checklist and START recommendations. The initial search identified 2562 studies and 43 were included in the meta-analysis.
Evidence synthesis: Among the included studies 11 used MRI-TB, 17 used FUS-TB, 11 used COG-TB, and four used a combination of techniques. In 34 studies concurrent TRUS-GB was performed. There was no significant difference between MRI-GB (all techniques combined) and TRUS-GB for overall PCa detection (relative risk [RR] 0.97 [0.90–1.07]). MRI-GB had higher detection rates of clinically significant PCa (csPCa) compared with TRUS-GB (RR 1.16 [1.02–1.32]), and a lower yield of insignificant PCa (RR 0.47 [0.35–0.63]). There was a significant advantage ($p = 0.02$) of MRI-TB compared with COG-TB for overall PCa detection. For overall PCa detection there was no significant advantage of MRI-TB compared with FUS-TB ($p = 0.13$), and neither for FUS-TB compared with COG-TB ($p = 0.11$). For csPCa detection there was no significant advantage of any one technique of MRI-GB. The impact of lesion characteristics such as size and localisation could not be assessed.

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Conclusions: MRI-GB had similar overall PCa detection rates compared with TRUS-GB, increased rates of csPCa, and decreased rates of insignificant PCa. MRI-TB has a superior overall PCa detection compared with COG-TB. FUS-TB and MRI-TB appear to have similar detection rates. Head-to-head comparisons of MRI-GB techniques are limited and are needed to confirm our findings.
Patient summary: Our review shows that magnetic resonance imaging-guided biopsy detects more clinically significant prostate cancer (PCa) and less insignificant PCa compared with systematic biopsy in men at risk for PCa.
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1. Introduction

Prostate cancer (PCa) is the most common malignancy among European men [1]. PCa incidence is expected to increase due to prostate-specific antigen (PSA) testing and aging of the general population [1]. The introduction of PSA testing led to an increased PCa incidence, while mortality from PCa has decreased [2,3]. Disadvantages of PSA screening are the risks of overdiagnosis and overtreatment of clinically insignificant PCa [3].

The current standard technique for PCa detection is transrectal ultrasound-guided biopsy (TRUS-GB). Using TRUS-GB the prostate is randomly sampled for the presence of PCa, and has its limitations due to the inability of grey-scale ultrasonography to distinguish PCa from benign tissue [4,5]. Consequently, TRUS-GB is renowned for its low sensitivity and specificity for PCa. This is underlined by the fact that repeat TRUS-GB due to persisting clinical suspicion on PCa, leads to the diagnosis of PCa in 10–25% of cases following a prior negative biopsy [6,7]. Furthermore, Gleason grading in radical prostatectomy specimens demonstrates upgrading in 36% when compared with preoperative grading using TRUS-GB [8]. Developments of multiparametric MRI (mpMRI) techniques have increased the sensitivity of imaging for PCa [9–12]. According the European Society of Urogenital Radiology (ESUR) guidelines an mpMRI consists of T2-weighted images, dynamic contrast enhanced imaging, and diffusion weighted imaging [13]. Usage of a 3 Tesla (3-T) magnet has further enhanced resolution and quality of imaging compared with 1.5-T [13]. Clinical guidelines advise performing an mpMRI when initial TRUS biopsy results are negative but the suspicion of PCa persists [4].

A standardised method for mpMRI evaluation was developed in order to increase inter-reader reliability and meaningful communication towards clinicians [13]. The Prostate Imaging-Reporting and Data System (PI-RADS) classification was introduced in 2012 by the ESUR, and has recently been updated to version 2.0. [13–15]. It evaluates lesions within the prostate on each of the three imaging modalities (T2-weighted, diffusion weighted imaging, and dynamic contrast enhanced) using a 1–5 scale, and additionally each lesion is given an overall score between 1 and 5 predicting its chance of being a clinically significant cancer [13–15].

Classically the definition of clinically significant PCa (csPCa) was based on the Epstein criteria [16,17] and d'Amico classification [18,19]. These classifications are based on random TRUS-GB outcomes. Due to the introduction of target biopsy procedures the preoperative definition of csPCa has changed. For that reason a number of new definitions of csPCa have been proposed, though as yet none have been widely adopted [20–23].

Various strategies for targeted biopsy of lesions on MRI have been developed, and demonstrate increased detection rates of csPCa compared with TRUS-GB [24–28]. Currently no consensus exists on which strategy of targeted biopsy should be preferred. Existing strategies of MRI guided biopsy (MRI-GB) include: (1) in-bore MRI target biopsy (MRI-TB) which is performed in the MRI suite using real-time MRI guidance [26,28], (2) MRI-TRUS fusion target biopsy (FUS-TB) where software is used to perform a MRI and TRUS image fusion, which allows direct target biopsies of MRI identified lesions using MRI-TRUS fusion image guidance [29–32], (3) cognitive registration TRUS targeted biopsy (COG-TB) where the MRI is viewed preceding the biopsy, and is used to *cognitively* target the MRI identified lesion using TRUS guidance [33,34].

The aim of this systematic review is to answer the following questions. In men at risk for PCa (based on an elevated PSA [>4.0 ng/ml] and/or abnormal digital rectal examination):

- Does MRI-GB lead to increased detection rates of csPCa compared with TRUS-GB?
- Is there a difference in detection rates of csPCa between the three available strategies of MRI-GB?

2. Evidence acquisition

2.1. Search strategy

A search strategy was designed using the STARLITE methodology [35]. A comprehensive search of literature was performed. A range of the last 10 yr was used since mpMRI has evolved rapidly in the last decade, and literature dating further back is not considered useful for current practise. No other search limits were applied. The search terms used were "Prostate OR Prostatic Neoplasm" AND "Biopsy" AND "Magnetic Resonance Imaging OR Image-Guided Biopsy" (see Appendix 1 for the complete search query). The search was assisted by an information specialist on October 27, 2014 using the PubMed, Embase, and CENTRAL databases.

Published primary diagnostic studies reporting on PCa detection rates among patients at risk of PCa using MRI-TB, or FUS-TB, or COG-TB were included. A direct comparison of MRI-GB techniques was not obligatory. Studies were excluded if they reported detection rates of PCa among patients with prior diagnosed PCa (including active surveillance populations, and mixed populations if data for patients with no or negative prior biopsies was not separately reported upon); if the MRI acquisition was not in accordance to the 2012 ESUR guidelines [13]; if the language was other than English, and if studies used alterative target biopsy strategies (such as contrast-enhanced TRUS).

Since the interval between data presentation and initial search was significant, a cursory repeat search was performed on December 15, 2015. This search identified an additional four studies which were not included in the meta-analysis, but are incorporated in the discussion section of this paper.

2.2. Selection procedure

Following initial identification of studies, duplicates were removed by a single reviewer (OW). Titles and abstract of all studies were screened for relevance by two reviewers (OW, RS). Full text review of eligible studies was performed by three reviewers (OW, RS, and HM). Any disagreement was handled by consensus, refereed by a fourth reviewer (RB).

The selection procedure followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) principles and is presented using a PRISMA flow chart [36].

2.3. Quality assessment

The methodological quality of studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 checklist by two reviewers in consensus (OW, LH) [37]. Using the Quality Assessment of Diagnostic Accuracy Studies-2 checklist the risk of bias and concerns of applicability to the review questions was assessed. A sensitivity analysis was performed excluding the studies assessed to have high risk of bias or high concerns regarding applicability to the review questions.

2.4. Data extraction

The data for quantitative assessment was extracted by a single reviewer (OW) in accordance to the START recommendations [38]. Data was collected on the method of recruitment; population investigated; methods of MRI acquisition and evaluation; MRI findings and/or PI-RADS score; threshold applied for MRI positivity; methods of biopsy procedure; number of (systematic and target) cores taken; detection rates of csPCa (per patient and per core); and the applied definition of csPCa.

2.5. Data analysis

For the first review question on the difference in accuracy between TRUS-GB and MRI-GB, we combined the data of the three MRI-GB techniques. For this analysis, we focused on paired studies reporting results of both TRUS-GB and MRI-GB separately. The main accuracy measure was the sensitivity of each technique, which was defined as the number of patients with detected cancer by TRUS-GB (or MRI-GB), divided by the total number of patients with detected cancer by the combination of TRUS-GB and MRI-GB. In other words, 1 minus the sensitivity of a technique is the percentage of patients with a cancer missed by this technique. We calculated the relative sensitivity for each study by dividing the sensitivity of MRI-GB by the sensitivity of TRUS-GB. We used the formula for the standard error of a relative risk without taking the paired nature into account because not all studies reported their data in a paired format [39]. A random effects pooled estimate of this relative sensitivity was calculated using the generic inverse variance method [40]. All sensitivity analyses were done twice: once for all PCa detected as the condition of interest and once focussing on csPCa only. For the per core analysis and detection of insignificant PCa we performed a yield analysis as accuracy measure, which was defined as the number of patient with detected cancer, divided by the total number of patient that underwent biopsy. We calculated the relative yield for each study by dividing the yield of MRI-GB by the yield of TRUS-GB.

For the second review question on the difference in accuracy between the various techniques of MRI-GB, we used studies reporting on at least one of the MRI-GB techniques (MRI-TB or FUS-TB or COG-TB). The applied accuracy measurement was the sensitivity of each MRI-GB technique as defined earlier. These proportions were meta-analysed using a random effects model, incorporating heterogeneity beyond chance due to clinical and methodological differences between studies. The within-study variances (ie, the precision by which yield has been measured in each study) was modelled using the exact binomial distribution. Differences in sensitivity between MRI-GB techniques were assessed by adding the type of MRI-GB technique as covariate to the random effects meta-regression model. These analyses were performed for all PCa and csPCa. Extracted data was analysed using SPSS version 22.0 (SPSS Inc., IBM, Chicago, IL, USA), and the random effects models were analysed in SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

3. Evidence synthesis

3.1. Search and selection

Using the three databases 2562 studies were identified. Following removal of duplicates, abstract and title screening, and full text assessment a total of 43 articles were deemed relevant for the current review question. For an overview of the selection procedure and reason for exclusion see the PRISMA flow chart (Fig. 1).

3.2. Quality assessment

Of the 43 studies subjected to quality assessment 54% ($n = 23$) were estimated to have a low risk of bias, 40%

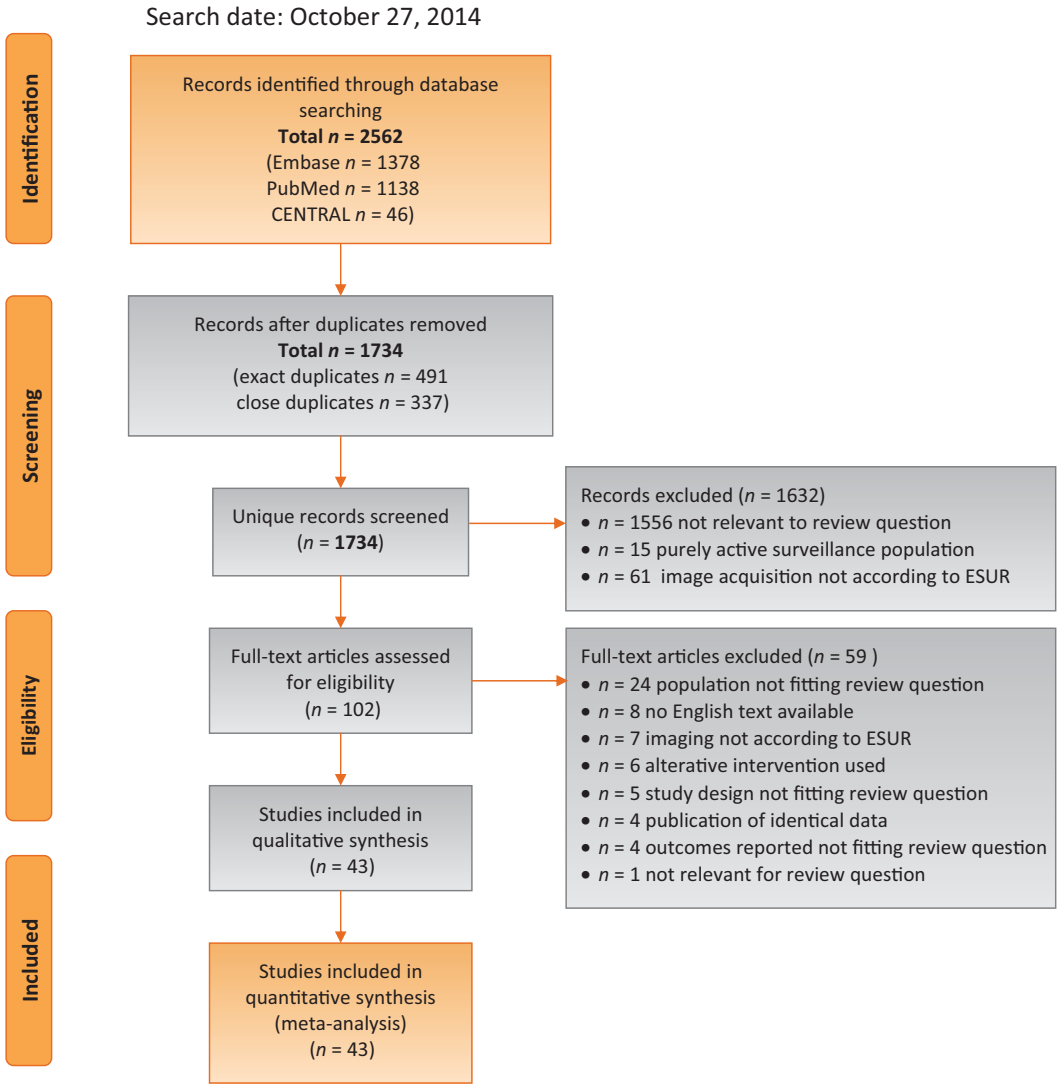

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow chart.
ESUR = European Society of Urogenital Radiology.

(*n* = 17) had a high risk of bias, and 7% (*n* = 3) had an intermediate risk of bias.

Regarding the applicability to the current review 65% (*n* = 28) had low concerns on applicability, and 35% (*n* = 15) had high concerns. Causes for concerns regarding applicability and bias included whether TRUS-GB was performed in conjunction to MRI-GB, whether the operator of TRUS-GB was blinded for MRI results, the number of TRUS-GB cores taken, what radiological threshold was applied to perform MRI-GB, and the population investigated. Of the 43 included studies 35% (*n* = 15) had both a low risk of bias and low concerns regarding the applicability.

3.3. *Population*

The 43 included studies demonstrate significant variation in cohort size, ranging from 16 to 1003 (median, 106) patients. The mean PSA value ranged from 5.1 ng/ml to 15.3 ng/ml and the mean age ranged from 61.8 yr to 70.0 yr. The populations varied with respect to biopsy history. For all subsequent analysis, we used clinical homogenous data on detection rates among patients with no or negative prior biopsies.

A 3-T scanner was used in 72% (*n* = 31) of the included studies. Of the included studies 58% (*n* = 25) applied PI-RADS classification for the evaluation of the mpMRI. The above-mentioned heterogeneity in the evaluation and reporting of imaging is reflected by the variation of thresholds applied for performing a targeted biopsy.

Of the included studies 21% (*n* = 9) performed MRI-GB exclusively, whilst 79% (*n* = 34) combined it with TRUS-GB. Most studies applied a single technique of targeting, although four studies used both COG-TB and FUS-TB within the same population.

Finally, considerable heterogeneity was found with respect to the applied definition of csPCa. Therefore we

performed the analysis on csPCa detection using the definitions as applied in each original paper. Furthermore several studies did not present a definition of csPCa, and consequently did not report data on the detection of csPCa. See Table 1 for an overview of all included studies, baseline characteristics, methodology applied for MRI imaging, and biopsy procedures.

3.4. MRI outcome

An overall estimate of all studies ($n = 20$) reporting on the number of patients with tumour suspicious findings on MRI in patients with a clinical suspicion on PCa yielded 73% (2225/3053) with MRI abnormalities. An overall estimate of studies reporting on the number of patients with tumour suspicious MRI abnormalities exclusively among patients with no prior biopsies ($n = 6$) resulted in a yield of 68% (734/1080), and a yield of 79% (567/716) exclusively among patients with prior negative biopsies ($n = 7$).

3.5. MRI-GB versus TRUS-GB

3.5.1. Does MRI-GB result in a higher overall PCa detection rate compared with TRUS-GB?

For this analysis we evaluated 25 studies that reported on both MRI-GB (any technique) and TRUS-GB results separately within the same population. The pooled estimates of detection rates on a per patient basis demonstrates that MRI-GB and TRUS-GB did not significantly differ in overall PCa detection with a relative sensitivity of 0.98 (95% confidence interval [CI]: 0.90–1.07, sensitivity for MRI-GB of 0.81 [95% CI: 0.76–0.85], and sensitivity for TRUS-GB of 0.83 [95% CI: 0.77–0.88]). In other words MRI-GB missed 19% of all cancers, while TRUS-GB missed 17% (Fig. 2A).

In addition to detection on a per patient basis, 14 included studies presented detection rates on a per core basis for both MRI-GB and TRUS-GB. A pooled analysis on detection rates of PCa per core demonstrates that MRI-GB cores have a significant higher yield of PCa detection compared with TRUS-GB biopsy cores (relative yield 3.91 [95% CI: 3.17–4.83], yield of MRI-GB 0.41 [95% CI 0.33–0.49], yield of TRUS-GB 0.10 [95% CI: 0.08–0.13]).

3.5.2. Does MRI-GB result in a higher detection rate of csPCa and a lower detection rate of insignificant PCa compared with TRUS-GB?

For this analysis we evaluated 14 studies that reported on the detection of csPCa for both MRI-GB and TRUS-GB separately within the same population. A pooled analysis of the detection rates of csPCa on a per patient basis, demonstrates that MRI-GB detected significantly more csPCa than TRUS-GB with a relative sensitivity of 1.16 (95% CI: 1.02–1.32, sensitivity for MRI-GB of 0.90 [95% CI: 0.85–0.94], sensitivity for TRUS-GB of 0.79 [95% CI: 0.68–0.87)]. In other words MRI-GB missed 10% significant cancers whilst TRUS-GB missed 21% (Fig. 2B).

A pooled analysis of the detection rates of insignificant PCa demonstrates that MRI-GB detected significantly less insignificant PCa than TRUS-GB with a relative yield of 0.47 (95% CI: 0.35–0.63, yield for MRI-GB 0.07 [95% CI: 0.04–0.10], yield for TRUS-GB of 0.14 [95% CI: 0.11–0.18]). In other words TRUS-GB alone detected twice as many clinically insignificant cancers as MRI-GB alone (Fig. 2C).

3.5.3. Sensitivity analysis

When regarding the overall PCa detection rates exclusively in publications with low risk of bias and low concerns regarding applicability, which reported on TRUS-GB in conjunction with MRI-GB within the same population ($n = 10$), we found a relative sensitivity of 0.86 (95% CI: 0.74–0.99). When looking at csPCa detection rates in publications with low risk of bias and low concerns regarding applicability ($n = 4$), we found a relative sensitivity of 0.97 (95% CI: 0.71–1.33).

3.6. MRI-TB versus FUS-TB versus COG-TB

3.6.1. Which technique of targeting has the highest overall detection rate of PCa?

Of the included studies that reported on the outcomes of both MRI-GB and TRUS-GB within the same population, seven used COG-TB to perform targeting ($n = 712$), 14 used FUS-TB ($n = 2817$), and three used MRI-TB ($n = 305$). The pooled sensitivity for COG-TB was 0.72 (95% CI: 0.62–0.81). The pooled sensitivity for FUS-TB was 0.81 (95% CI: 0.75–0.85). The pooled sensitivity for MRI-TB was 0.89 (95% CI: 0.78–0.95; Fig. 3A). Based on the above-mentioned pooled sensitivities there is a significant ($p = 0.02$) advantage of using of MRI-TB compared with COG-TB for overall PCa detection. There were no significant differences in the performance of FUS-TB compared with MRI-TB ($p = 0.13$), and FUS-TB compared with COG-TB ($p = 0.11$).

3.6.2. Which technique of targeting has the highest detection rate of csPCa?

Of the included studies that reported on the detection rates of csPCa of both MRI-GB and TRUS-GB within the same population, three used COG-TB to perform targeting ($n = 220$), eight used FUS-TB ($n = 2114$), and two used MRI-TB ($n = 163$). The pooled sensitivity for csPCa for COG-TB was 0.86 (95% CI: 0.69–0.94). The pooled sensitivity for FUS-TB was 0.89 (95% CI: 0.82–0.93). The pooled sensitivity for MRI-TB was 0.92 (95% CI: 0.76–0.98; Fig. 3B). Based on the above-mentioned pooled sensitivities there was no significant advantage of usage of any one technique of MRI-GB for the detection of csPCa; MRI-TB versus FUS-TB ($p = 0.60$), MRI-TB versus COG-TB ($p = 0.42$), FUS-TB versus COG-TB ($p = 0.62$).

3.7. Discussion

3.7.1. Summary of findings

The paradigm on biopsy strategies in men with increased risk for PCa is shifting, and the optimal biopsy strategy is yet to be determined. The optimal biopsy technique presumably has a near 100% detection rate of csPCa, while simultaneously having a low detection rate of clinically insignificant PCa.

Table 1 – Baseline characteristics and applied methodology of included studies

Author, yr of publication	Population investigated	Recruitment criteria	No. of patients	Mean age (yr)	Mean PSA (ng/ml)	MRI used; magnet strength	Coil used (no. channels)	Threshold for target biopsy	Biopsy method; approach	SB and TB cores	Definition of clinically significant PCa
Hambrock et al., 2008 [50]	Negative prior biopsy	Elevated PSA and/or abnormal DRE and abnormal MRI	21	62.0	15.0	Trio Tim (Siemens); 3 Tesla	ERC	In tumour suspicious/abnormal MRI; no threshold defined	In-bore MRI; transrectal	No	No criteria for significance applied
Hambrock et al., 2010 [51]	Negative prior biopsy	Elevated PSA and abnormal MRI	68	63.0	13.0	Trio Tim (Siemens); 3 Tesla	Combined ERC and PPA	In tumour suspicious/abnormal MRI; no threshold defined	In-bore MRI transrectal	No	Epstein criteria
Miyagawa et al., 2010 [52]	Negative prior biopsy	Elevated PSA and abnormal MRI	85	69.0	9.9	Interna pulsar (Philips); 1.5 Tesla	PPA	No threshold defined	MRI/TRUS fusion; transperineal	Yes	No criteria for significance applied
Franiel et al., 2011 [53]	Negative prior biopsy	Elevated PSA and/or abnormal DRE and abnormal MRI	54	68.0	12.1	Avanto (Siemens); 1.5 Tesla	Combined ERC and PPA	PIRADS 2 or higher	In-bore MRI; transrectal	No	No criteria for significance applied
Park et al., 2011 [54]	No prior biopsy	Elevated PSA and/or abnormal DRE	44	63.0	6.1	Interna Achieva (Philips); 3 Tesla	PPA	In tumour suspicious/abnormal MRI; no threshold defined	Cognitive TRUS; transrectal	Yes	No criteria for significance applied
Hadaschik et al., 2011 [29]	Mixed population	Elevated PSA and/or abnormal DRE	95	66.0	8.0	Magnetom Trio (Siemens); 3 Tesla	PPA	Irrespective of MRI findings	MRI/TRUS fusion; transperineal	Yes	No criteria for significance applied
Hoeks et al., 2012 [28]	Negative prior biopsy	Elevated PSA and abnormal MRI	265	66.0	11.4	Magnetom Trio (Siemens) and Magnetom Skyra (Siemens); both 3 Tesla	PPA	In tumour suspicious/abnormal MRI; no threshold defined	In-bore MRI; transrectal	No	d'Amico classification (intermediate and high risk) and Epstein criteria
Portalez et al., 2012 [55]	Negative prior biopsy	Elevated PSA and/or abnormal DRE and abnormal MRI	129	64.7	9.6	Achieva (Philips) and Avanto (Siemens); both 1.5 Tesla	PPA (8)	Irrespective of MRI findings	MRI/TRUS fusion; transrectal	Yes	No criteria for significance applied
Rouse et al., 2011 [56]	Negative or no prior biopsy	Elevated PSA and/or abnormal DRE and abnormal MRI	114	63.6	13.4	Avanto (Siemens); 1.5 Tesla	Unclear	PIRADS 3 or higher	Cognitive TRUS; transrectal	Yes	-Gleason score ≥3 + 4 -or Gleason 3+3 and MMCL ≥3mm
Arsov et al., 2012 [57]	Negative prior biopsy	Elevated PSA and/or abnormal DRE	16	67.0	9.3	Magnetom Trio (Siemens); 3 Tesla	PPA (6)	No threshold defined	Cognitive TRUS; transrectal	Yes	d'Amico classification (intermediate and high risk)
Vourganti et al., 2012 [44]	Negative prior biopsy	Elevated PSA and/or abnormal DRE	195	62.0	9.1	Achieva (Philips); 3 Tesla	Combined ERC and PPA (16)	Irrespective of MRI findings	MRI/TRUS fusion; transrectal	Yes	Gleason score ≥3 + 4
Puech et al., 2013 [34]	Negative or no prior biopsy	Elevated PSA and abnormal MRI	95	65.0	10.1	Gyroscan Intera, (Philips) and Symphony (Siemens); both 1.5 Tesla	PPA	PIRADS 3 or higher	Cognitive TRUS and MRI/TRUS fusion; transrectal	Yes	SB: -Gleason score ≥3+4 -Gleason score = 3 + 3 and MMCL >3mm; TB: Gleason score ≥3+4
Wysock et al., 2013 [42]	Mixed population	Elevated PSA and/or abnormal DRE and abnormal MRI	67	65.0	5.1	Magnetom Trio (Siemens); 3 Tesla	PPA	PIRADS 2 or higher	Cognitive TRUS and MRI/TRUS fusion; transrectal	Yes	Gleason score ≥3 + 4
Nagel et al., 2013 [58]	Negative prior biopsy	Abnormal MRI	88	63.0	11.0	Trio Tim (Siemens); 3 Tesla	PPA	In tumour suspicious/abnormal MRI; no threshold defined	In-bore MRI; transrectal	No	Gleason score ≥3 + 4
Quentin et al., 2013 [59]	Negative or no prior biopsy	Elevated PSA	59	65.0	8.0	Magnetom Trio (Siemens); 3 Tesla	PPA (6)	PIRADS sum score ≥10	In-bore MRI; transrectal	No	No criteria for significance applied
Kasivivanathan et al., 2013 [22]	Mixed population	Elevated PSA and/or abnormal DRE and abnormal MRI	110	63.3	6.7	Avanto (Siemens) and Magnetom Verio (Siemens); 1.5 and 3 Tesla	PPA	PIRADS 3 or higher	Cognitive TRUS; transperineal	Yes	Multiple definitions; applied definition: -Gleason score ≥3 + 4 or Gleason score = 3 + 3 and MCCL >4 mm

Junker et al., 2013 [60]	Negative prior biopsy	Elevated PSA	73	62.0	6.4	Magnetom Skyra (Siemens); 3 Tesla	PPA (18)	PIRADS sum score ≥7	MRI/TRUS fusion; transrectal	Yes	Gleason score ≥4 + 3
Rosenkrantz et al., 2013 [61]	Negative or no prior biopsy	Elevated PSA	42	63.0	7.4	Unknown; 3 Tesla	PPA	In tumour suspicious/abnormal MRI; no threshold defined	Cognitive TRUS; transrectal	Yes	d'Amico classification (intermediate and high risk)
Delongchamps et al., 2013 [62]	No prior biopsy	Elevated PSA and/or abnormal DRE	391	63.9	8.5	Unknown; 1.5 Tesla	Combined ERC and PPA	Sum score of ≥4 and ≥6	Cognitive TRUS and MRI/TRUS fusion; transrectal	Yes	Microfocal disease = Gleason score = 3 + 3 and MCCL <5 mm and single core positive
Fiard et al., 2013 [63]	Negative or no prior biopsy	Elevated PSA and/or abnormal DRE	30	64.0	6.3	Achieva (Philips); 3 Tesla	PPA (32)	PIRADS sum score ≥5	MRI/TRUS fusion; transrectal	Yes	-d'Amico classification (intermediate and high risk) -or Gleason score ≥3 + 4 -or TCCL ≥10 mm
Kuru et al., 2013 [31]	Negative or no prior biopsy	Elevated PSA and/or abnormal DRE	347	65.3	9.9	Magnetom Trio (Siemens); 3 Tesla	PPA	Irrespective of MRI findings	MRI/TRUS fusion; transperineal	Yes	NCCN criteria (intermediate and high risk)
Kaufmann et al., 2015 [64]	Negative prior biopsy	Elevated PSA and abnormal MRI	35	68.0	9.4	Magnetom Espree (Siemens); 1.5 Tesla	ERC	Irrespective of MRI findings	In-bore MRI; transrectal	Yes	d'Amico classification (intermediate and high risk) and Epstein criteria
Penzkofer et al., 2015 [65]	Mixed population	Abnormal MRI	52	65.0	15.3	Signa (GE); 3 Tesla	Combined ERC and PPA	No threshold defined	In-bore MRI; transperineal	No	Gleason score ≥3 + 4
Schimmoller et al., 2014 [66]	Negative or no prior biopsy	Elevated PSA and/or abnormal DRE and abnormal MRI	235	65.7	9.9	Magnetom Trio (Siemens); 3 Tesla	PPA (6)	No threshold defined	In-bore MRI; transrectal	No	Gleason score ≥4 + 3
Shakir et al., 2014 [45]	Negative or no prior biopsy	Elevated PSA and/or abnormal DRE and abnormal MRI	1003	62.1	6.7	Achieva (Philips); 3 Tesla	Combined ERC and PPA (16)	In tumour suspicious/abnormal MRI; no threshold defined	MRI/TRUS fusion; transrectal	Yes	Gleason score ≥4 + 3
Rastinehad et al., 2014 [30]	Negative or no prior biopsy	Elevated PSA and/or abnormal DRE and abnormal MRI	105	65.8	9.2	Magnetom Verio (Siemens); 3 Tesla	Combined ERC and PPA (16)	Low risk using NIH criteria	MRI/TRUS fusion; transrectal	Yes	SB: Epstein criteria (SB) TB: -Gleason score ≥3 + 4 -or MRI lesion >0.2 cc
Mozer et al., 2015 [67]	No prior biopsy	Elevated PSA and abnormal MRI	152	63.0	6.0	Achieva (Philips); 1.5 Tesla	PPA	PIRADS 2 or higher	MRI/TRUS fusion; transrectal	Yes	-Gleason score ≥3 + 4 -or Gleason score = 3 + 3 and MCCL ≥4 mm
Salami et al., 2014 [68]	Negative or no prior biopsy	Elevated PSA and/or abnormal DRE and abnormal MRI	175	64.9	7.1	Magnetom Verio (Siemens); 3 Tesla	Combined ERC and PPA (16)	PIRADS 2 or higher	MRI/TRUS fusion; transrectal	Yes	SB: Epstein criteria TB: -Gleason score ≥3+ 4 -or MRI lesion >0.2 cc
Salami et al., 2015 [69]	Negative prior biopsy	Elevated PSA and/or abnormal DRE and abnormal MRI	140	65.8	9.0	Magnetom Verio (Siemens); 3 Tesla	Combined ERC and PPA (16)	PIRADS 2 or higher	MRI/TRUS fusion; transrectal	Yes	SB: Epstein criteria TB: -Gleason score ≥3+ 4 -or MRI lesion >0.2 cc
Shoji et al., 2015 [70]	No prior biopsy	Elevated PSA and/or abnormal DRE and abnormal MRI	20	70.0	7.4	Signa (GE); 1.5 Tesla	PPA (8)	PIRADS 2 or higher	MRI/TRUS fusion; transperineal	Yes	-Gleason score ≥ 3 + 4 -MCCL >4 mm
Roethke et al., 2014 [27]	Negative or no prior biopsy	Elevated PSA and abnormal MRI	64	64.5	8.3	Magnetom Trio (Siemens); 3 Tesla	PPA	No threshold defined	MRI/TRUS fusion; transperineal	No	Gleason score ≥3 + 4
Ploussard et al., 2014 [71]	Negative or no prior biopsy	Elevated PSA and/or abnormal DRE and abnormal MRI	91	63.0	6.0	Intera (Philips); 1.5 Tesla	PPA	PIRADS 3 or higher	cognitive TRUS; transrectal	Yes	Epstein criteria
Kuru et al., 2014 [72]	Negative prior biopsy	Elevated PSA and abnormal MRI	74	64.0	11.3	Unknown; 3 Tesla	PPA	In tumour suspicious/abnormal MRI; no threshold defined	MRI/TRUS fusion; transperineal	Yes	Gleason score ≥4 + 3
Radtke et al., 2015 [48]	Negative or no prior biopsy	Elevated PSA and/or abnormal DRE	294	64.0	7.3	Unknown (Siemens); 3 Tesla	PPA	PIRADS 2 or higher	MRI/TRUS fusion; transperineal	Yes	Gleason score ≥3 + 4
Iwamoto et al., 2014 [73]	No prior biopsy	Elevated PSA	238	69.2	9.6	Achieva (Philips) and Magnetom Skyra (Siemens); 1.5 and 3 Tesla		In tumour suspicious/abnormal MRI; no threshold defined	Cognitive TRUS; transrectal	Yes	Gleason score ≥3 + 4

Table 1 (*Continued*)

Author, yr of publication	Population investigated	Recruitment criteria	No. of patients	Mean age (yr)	Mean PSA (ng/ml)	MRI used; magnet strength	Coil used (no. channels)	Threshold for target biopsy	Biopsy method; approach	SB and TB cores	Definition of clinically significant PCa
Thompson et al., 2014 [20]	Negative or no prior biopsy	Elevated PSA and/or abnormal DRE	150	62.0	5.6	Unknown; 1.5 and 3.0 Tesla	PPA (32)	PIRADS 3 or higher	Cognitive TRUS and MRI/TRUS fusion; transperineal	Yes	Multiple definitions; applied definition: -Gleason score ≥3 + 4 and >5% grade 4 component and <50% cores positive -or Gleason score ≥3 + 3 and <5% grade 4 component and <30% cores positive -or MCCL ≥8 mm
Pokorny et al., 2014 [23]	No prior biopsy	Elevated PSA and/or abnormal DRE	142	63.0	5.3	Magnetom Skyra (Siemens); 3 Tesla	PPA	PIRADS 3 or higher	In-bore MRI; transrectal	Yes	-Gleason score = 3 + 3 and MCCL ≥6 mm -or Gleason score = 3 + 4 and MCCL ≥4 mm -or Gleason score ≥4 + 3
Jambor et al., 2015 [74]	No prior biopsy	Elevated PSA	53	66.0	7.4	Magnetom Verio (Siemens); 3 Tesla	PPA	PIRADS 4 or higher	Cognitive TRUS; transrectal	Yes	-Gleason score ≥3 + 4 -or Gleason score = 3 + 3 and MCCL ≥3 mm
Boesen et al., 2015 [75]	Negative prior biopsy	Elevated PSA and/or abnormal DRE	83	63.0	11.0	Achieva (Philips); 3 Tesla	PPA (6)	No threshold defined	Cognitive TRUS; transrectal	Yes	Epstein criteria
Habchi et al., 2014 [76]	Mixed population	Elevated PSA and/or abnormal DRE	204	61.8	8.3	Discovery (GE); 3 Tesla	PPA	PIRADS 2 or higher	Cognitive TRUS; transrectal	Yes	Gleason score ≥3 + 4
Sonn et al., 2014 [77]	Negative prior biopsy	Elevated PSA	105	65.0	7.5	Trio Tim (Siemens); 3 Tesla	PPA	PIRADS 2 or higher	MRI/TRUS fusion; transrectal	Yes	-Gleason score ≥3 + 4 -or Gleason score = 3 + 3 and MCCL ≥4 mm
Quentin et al., 2014 [47]	No prior biopsy	Elevated PSA	128	66.1	6.7	Magnetom Trio (Siemens); 3 Tesla	PPA (6)	No threshold defined	In-bore MRI; transrectal	Yes	-Gleason score ≥3 + 4 -or Gleason score = 3 + 3 and TCCL >5 mm
Pepe et al., 2015 [78]	Negative prior biopsy	Elevated PSA	100	64.0	8.6	Achieva (Philips); 3 Tesla	PPA (16)	PIRADS 4 or higher	Cognitive TRUS; transperineal	Yes	-Gleason score ≥ 3 + 4 -or Gleason score = 3 + 3 and TCCL >50%

DRE = digital rectal examination; ERC = Endorectal coil; MMCL = maximum cancer core length; MRI = magnetic resonance imaging; PCa = prostate cancer; PIRADS = prostate imaging reporting and data system; PPA = Pelvic Phased Array; PSA = prostate-specific antigen; SB = systematic biopsy; TB = target biopsy; TCCL = total cancer core length; TRUS = transrectal ultrasound.

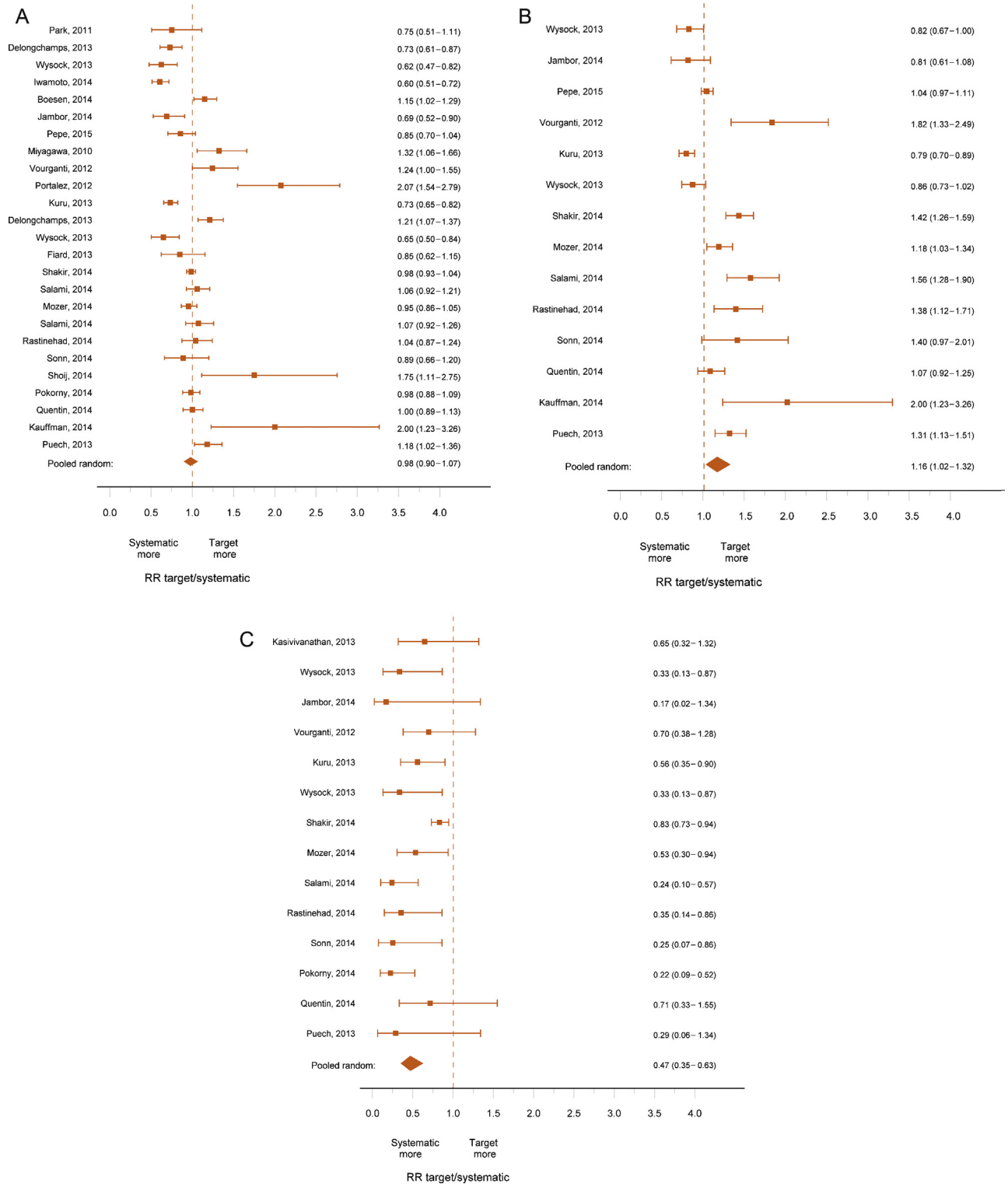

Fig. 2 – (A) Forest plot of pooled relative sensitivity of MRI-guided biopsy (MRI-GB) and transrectal ultrasound-guided biopsy (TRUS-GB) for all prostate cancer (PCa); (B) forest plots of pooled relative sensitivity of MRI-GB and TRUS-GB for clinically significant PCa; (C) forest plots of pooled relative yield of MRI-GB and TRUS-GB for insignificant PCa.
RR = relative risk.

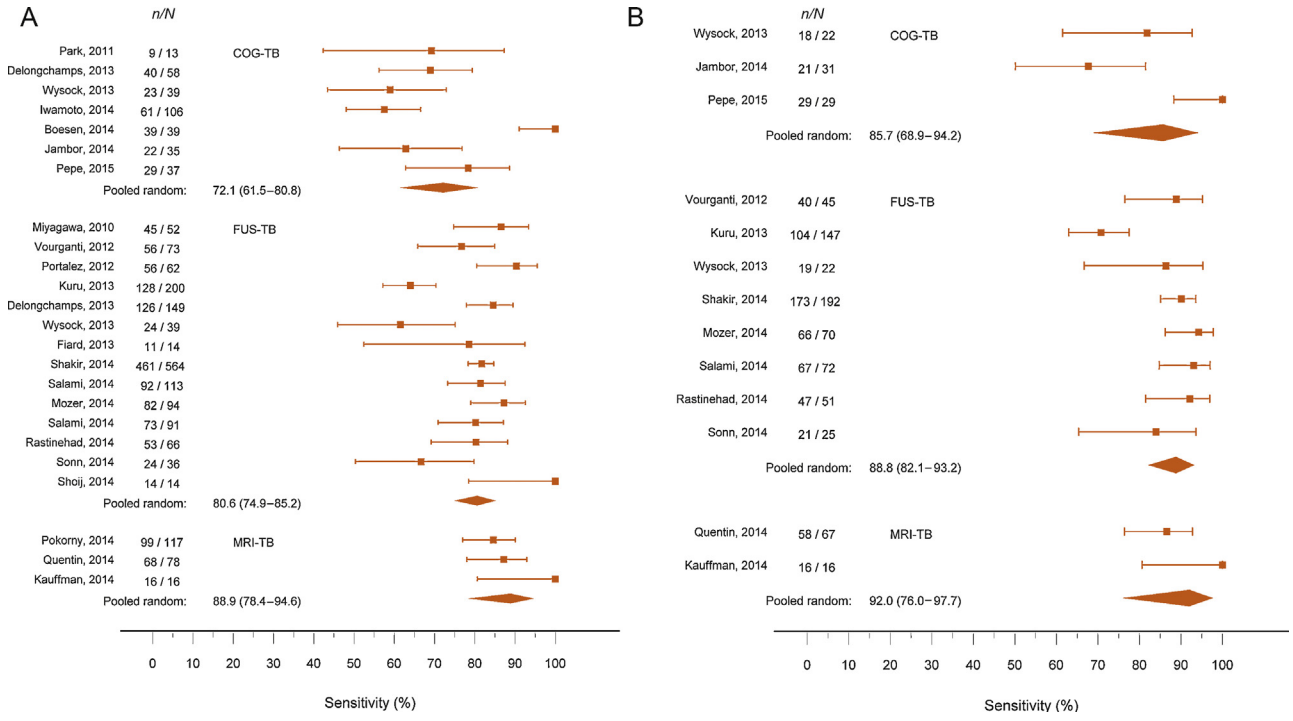

Fig. 3 – (A) Forest plots of pooled sensitivity of cognitive registration transrectal ultrasound-targeted biopsy (COG-TB), magnetic resonance imagimg-TRUS fusion TB (FUS-TB), and MRI-TB for all prostate cancer; (B) forest plots of pooled sensitivity of COG-TB, FUS-TB, and MRI-TB for clinically significant prostate cancer.

The direct comparison of MRI-GB and TRUS-GB within the same population demonstrates that there is no statistically significant difference for overall PCa detection. Though a per core analysis demonstrates a statistically significant increased incidence of PCa in target biopsy cores when compared with systematic biopsy cores, with a relative yield of 3.91 (95% CI: 3.17–4.83). When focussing on the detection of csPCa MRI-GB has a statistically significant advantage over TRUS-GB, with a relative sensitivity of 1.16 (95% CI: 1.02–1.32), indicating that MRI-GB significantly detects more clinically significant cancers than TRUS-GB. Consequently, MRI-GB has a statistically significant lower yield of insignificant PCa compared with TRUS-GB, with a relative yield of 0.47 (95% CI: 0.35–0.63). These results support MRI-GB as a superior alternative to TRUS-GB. These findings are similar to findings of a previous meta-analysis comparing TRUS-GB to MRI-GB in which the authors found a relative sensitivity for MRI-GB of 1.05 (95% CI: 0.94–1.19) for overall PCa, and a relative sensitivity of 1.20 (95% CI: 1.09–1.32) for csPCa [41].

Are we ready to abandon systematic TRUS-GB and completely replace it for MRI-GB? Based on this meta-analysis, omitting TRUS-GB would result in missing 19% of all PCa cases, and 10% of csPCa cases. Simultaneously, by omitting TRUS-GB 50% of the insignificant PCa would not be detected and would thereby decrease overdiagnosis of these tumours. The debate on whether this is acceptable or not is ongoing and a definite conclusion is beyond the scope of this review.

Which technique for MRI-GB should then be preferred? The results of this current meta-analysis indicate that MRI-TB has an advantage over COG-TB in overall PCa detection ($p = 0.02$). There does not seem to be a significant advantage of MRI-TB compared with FUS-TB, or FUS-TB compared with COG-TB for overall PCa detection. When focussing on the detection of csPCa, there does not seem to be a significant advantage of any particular technique, though the number of studies used for this specific meta-analysis was limited. When comparing various techniques of MRI-GB essential components are targeted lesion characteristics, such as PI-RADS classification, lesion size, and lesion location. Of 43 included studies only 5% ($n = 2$) presented data regarding lesion diameter, and 58% ($n = 25$) applied PI-RADS classification. Furthermore the applied threshold for target biopsy will directly impact the found tumour yield, and as mentioned earlier the included studies demonstrate significant heterogeneity regarding applied threshold. Consequently the results of this meta-analysis are indicative at best: the number of randomised controlled trials directly comparing one technique with another is limited. Within the cohort presented in this meta-analysis there were only two studies directly comparing two techniques [34,42]. Both studies were not able to demonstrate significant differences between COG-TB and FUS-TB on overall cancer and clinically significant cancer detection. Although a multivariate analysis in one study demonstrated increased cancer detection in smaller MRI lesions using FUS-TB when directly compared with COG-TB [42].

Importantly, a large randomised controlled trial comparing all three techniques of MRI-GB is underway [43].

3.7.2. Strengths and limitations

The number of studies investigating MRI-GB was quite large, but there was considerable heterogeneity in the applied methodology. The majority of studies report on subsequent cohorts of patients undergoing target biopsy procedures. The number of studies that applied a comparative test (such as TRUS-GB) in conjunction with target biopsy is limited. And finally, the quality of MRI acquisition seems to demonstrate significant heterogeneity, directly influencing the outcome of MRI-GB.

The major strength of this meta-analysis is that all included studies have used MRI acquisition protocols in accordance to the latest imaging guidelines, hereby safeguarding some level of homogeneity in the selection procedure for subsequent MRI-GB. Furthermore, only studies performing both MRI-GB and TRUS-GB within the same population were included in the meta-analysis. As a consequence the number of eligible studies was limited, especially for MRI-TB where lack of simultaneous TRUS-GB seems to be most common.

The heterogeneous usage of definitions for csPCa incorporating PSA (density), clinical stage, and histology among the different series is a major concern for this current meta-analysis and even more so because most definitions have their origin in the systematic biopsy setting. As such they are, at least partially, based on variables such as cancer core length, and number of positive cores and therefore might significantly overestimate the number of detected csPCa in a targeted biopsy setting. Consequently commonly used definitions such as the Epstein criteria seem to become outdated, whereas new generally accepted criteria have yet to be formulated for MRI-GB. Of the 14 studies used for the analysis on csPCa in this systematic review, only three used a definition of csPCa solely based on the presence of a Gleason 4 component on biopsy [42,44,45].

Furthermore, the method of MRI evaluation and the applied threshold for MRI-GB seems to demonstrate heterogeneity. 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 very suspicious findings on MRI. Potentially the PIRADS grading system can solve this problem, but it was only introduced several years ago. Therefore, to date, the number of studies using this grading system is limited. Thirdly, we found significant variation concerning biopsy conduct, especially concerning comparative testing. Not only did the number of cores on TRUS-GB vary, but also whether systematic biopsy was performed prior to or following MRI-GB. Moreover several techniques of FUS-TB are commercially available, and this variation can impact accuracy of targeting. Rigid image fusion (where the MRI prostate contour is projected over the TRUS image, and used to match landmarks during the planning phase of biopsy) is likely to be less accurate when compared to elastic image fusion (where the prostate is contoured on both the MRI and the TRUS image, and the contours are fused correcting for prostate deformation and movement during the entire biopsy procedure) [32]. Finally, the absence of lesion specific descriptive characteristics, such as size, in the majority of studies limits the ability to perform accurate comparison of the various MRI-GB techniques. If only larger lesions are biopsied, this may negatively affect the potential of MRI-TB.

A cursory repeat search on December 15, 2015 identified another four major relevant publications [46–49]. All studies performed MRI-GB in conjunction with TRUS-GB. Three studies used FUS-TB, and one paper used MRI-TB to perform MRI-GB in patients at risk for PCa. The three studies using FUS-TB concluded that MRI-GB detects more csPCa compared with TRUS-GB while decreasing the detection of clinically insignificant PCa [46,48,49]. Although one paper did conclude that omitting TRUS-GB would miss some clinically significant cancers [46]. The fourth paper performed MRI-TB in conjunction with TRUS-GB in biopsy naïve patients. The authors concluded that MRI-GB and TRUS-GB have equivalent high detection yields, although MRI-GB required significantly less biopsy cores compared with TRUS-GB to accomplish this diagnostic yield [47]. These results are in accordance with the findings of this current meta-analysis, and are summarised in Appendix 2.

4. Conclusions

In men at risk for PCa who have tumour suspicious lesions on MRI, subsequent MRI-GB of these lesions demonstrates similar overall tumour detection rates compared with systematic TRUS-GB, although the incidence of PCa is increased in targeted cores when compared with systematic cores. Moreover, the sensitivity of MRI-GB is increased for the detection of csPCa, and decreased for clinically insignificant PCa when compared with TRUS-GB.

Based on the studies included in this meta-analysis MRI-TB demonstrates a superior performance in overall PCa detection when compared with COG-TB. For overall PCa detection and detection of csPCa, FUS-TB has a similar performance compared with MRI-TB. The current number of randomised controlled trials performing a head-to-head comparison of the various techniques for MRI-GB is limited and comparative analysis is restricted by the absence of data on lesion characteristics.

Author contributions: Olivier Wegelin had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Wegelin, van Melick, Somford, Barentsz, Bosch.
Acquisition of data: Wegelin.
Analysis and interpretation of data: Wegelin, van Melick, Somford, Hooft, Reitsma, Barentsz, Bosch.
Drafting of the manuscript: Wegelin, van Melick, Somford, Hooft, Reitsma, Barentsz, Bosch.
Critical revision of the manuscript for important intellectual content: Wegelin, van Melick, Somford, Hooft, Reitsma, Barentsz, Bosch.
Statistical analysis: Wegelin, Reitsma, Hooft.

Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Barentsz, Bosch.
Other: None.

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Appendix 1

Complete search query
Date of search: 27-10-2014
Search performed by: Carla Sloof (c.sloof@antoniusziekenhuis.nl).

PubMed
("Prostate"[Mesh] OR "Prostatic Neoplasms"[Mesh] OR prostat*[tiab]) AND ("Biopsy"[Mesh] OR biops*[tiab]) AND ("Magnetic Resonance Imaging"[Mesh] OR "Image-Guided Biopsy"[Mesh] OR magnetic resonance[tiab] OR MRI*[tiab] OR MR imag*[tiab] OR MR guid*[tiab] OR MR target*[tiab] OR MR-US[tiab] OR MRUS[tiab] OR MR-TRUS[tiab] OR mpMR*[tiab] OR image guid*[tiab] OR imaging guid*[tiab] OR fusion-guid*[tiab] OR multiparametric[tiab] OR image fusion[tiab] OR ultrasound fusion[tiab] OR US fusion[tiab]) *NOT (review[pt] OR case reports[pt]) AND (2004:2014[pdat])*
1138 hits

Embase
'prostate'/de OR 'prostate tumor'/exp OR prostat*:ab,ti AND ('biopsy'/exp OR biops*:ab,ti) AND ('nuclear magnetic resonance imaging'/exp OR 'image guided biopsy'/exp OR 'magnetic resonance':ab,ti OR mri*:ab,ti OR (mr NEXT/1 (imag* OR guid* OR target* OR us OR trus)):ab,ti OR mrus:ab,ti OR mpmr*:ab,ti OR ((image OR imaging OR fusion) NEXT/1 guid*):ab,ti OR multiparametric:ab,ti OR 'image fusion':ab,ti OR 'ultrasound fusion':ab,ti OR 'us fusion':ab,ti) *NOT ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [review]/lim OR 'case report'/de) AND [1–1–2004]/sd*
1378 hits

CENTRAL
prostat* and biops* and ('magnetic resonance' or mri* or (mr next/1 (imag* or guid* or target* or us or trus)) or mrus or mpmr* or ((image or imaging or fusion) next/1 guid*) or multiparametric or 'image fusion' or 'ultrasound fusion' or 'us fusion')
Filters: Publication Year from 2004 to 2014
46 hits

Total hits three databases: 2562 references

Appendix 2

Summary of results of additional papers from cursory repeat search.

Author; yr of publication	Population investigated	No. of patients	Mean age (yr)	Mean PSA (ng/ml)	MRI acquisition according to ESUR guidelines; MRI used	Threshold for target biopsy	Biopsy method; approach	Definition of clinically significant PCa	No. of patients SB No. patients TB	Sensitivity all cancer	Sensitivity significant cancer
Peltier et al., 2015 [46]	No prior biopsy	110	65.1	8.4	Yes; Magnetom Verio (Siemens); 3 Tesla	In tumour suspicious/ abnormal MRI; no threshold defined	MRI/TRUS fusion; transrectal	-Gleason score ≥3 + 4 -or Gleason 3 + 3 and MMCL ≥6 mm	SB: *n* = 110 TB: *n* = 100	SB: 72.5% (50/69) TB: 82.6% (57/69)	SB: 61.5% (32/52) TB: 98.1% (51/52) *p* = 0.0008
Quentin et al., 2014 [47]	No prior biopsy	128	66.1	8.7	Yes; Magnetom Trio (Siemens); 3 Tesla	No threshold defined	In-bore MRI; transrectal	-Gleason score ≥ 3+ 4 -MCCL >5 mm	SB: *n* = 128 TB: *n* = 128	SB: 87.25% (68/78) TB: 87.25% (68/78)	SB: 80.6% (54/67) TB: 86.6% (58/67)
Radtke et al., 2015 [48]	Negative or no prior biopsy	294	64	7.3	Yes; Unknown (Siemens); 3 Tesla	PIRADS 2 or higher	MRI/TRUS fusion; transperineal	-Gleason score ≥3 + 4	SB: *n* = 294 TB: *n* = 196	SB: 90% (135/150) TB: 74.7% (112/150) *p* = 0.001	SB: 79.1% (68/86) TB: 87.2% (75/86)
Siddiqui et al., 2015 [49]	Negative or no prior biopsy	1003	62.1	6.7	Yes; Achieva (Philips); 3 Tesla	In tumour suspicious/ abnormal MRI; no threshold defined	MRI/TRUS fusion; transrectal	-Gleason score ≥4 + 3 -or Gleason score = 3 + 4 and >50% core positivity	SB: *n* = 1003 TB: *n* = 1003	SB: 83.2% (469/564) TB: 81.7% (461/564)	SB: 69.4% (211/304) TB: 81.6% (248/304) *p* < 0.001

ESUR = European Society of Urogenital Radiology; MMCL = maximum cancer core length; MRI = magnetic resonance imaging; PCa = prostate cancer; PIRADS = prostate imaging reporting and data system; SB = systematic biopsy; TB = target biopsy; TCCL = total cancer core length; TRUS = transrectal ultrasound.

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