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Research article

Comparison of PET/MRI with multiparametric MRI in diagnosis of primary prostate cancer: A meta-analysis

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ABSTRACT

Objective: This meta-analysis aimed to compare the diagnostic performance of positron emission tomography (PET)/MRI using various radiotracers with multiparametric (mp) MRI for detection of primary prostate cancer (PCa).

Methods: A systematic literature search up to January 2019 was performed to identify studies that evaluated the diagnostic value of PET/MRI and mpMRI for detection of PCa in the same patient cohorts and had sufficient data to construct 2 × 2 contingency tables for true-positive (TP), false-positive (FP), false-negative (FN), and true-negative (TN) results. The quality of each study was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 tool, and pooled sensitivity (SEN) and specificity (SPE) were calculated. Summary receiver operating characteristic (ROC) curves and area under the curves (AUCs) were used to compare the performances of PET/MRI and mpMRI.

Results: We identified 9 eligible studies that included a total of 353 patients. PET/MRI had a SEN of 0.783 (95% CI, 0.758–0.807) and a SPE of 0.899 (95% CI, 0.879–0.917), and mpMRI had a SEN of 0.603 (95% CI, 0.574–0.631) and a SPE of 0.887 (95% CI, 0.866–0.906). PET/MRI had a higher AUC than mpMRI (0.9311, 95% CI, 0.8990–0.9632 *vs.* 0.8403, 95% CI, 0.7864–0.8942; $P = 0.0036$). There was no notable publication bias, but there was medium heterogeneity in outcomes. The meta-regression analysis showed the major potential cause of heterogeneity was the use of region-based rather than lesion-based analysis.

Conclusion: PET/MRI has very good diagnostic performance and outperforms mpMRI for the diagnosis of primary PCa.

1. Introduction

Prostate cancer (PCa) is the second most common cancer in men, and accounts for about 20% of all cancer diagnoses in men [1]. The current procedure used for diagnosis of primary PCa is transrectal ultrasound (US) -guided biopsy, following detection of elevated serum prostate-specific antigen (PSA) levels. However, the diagnostic accuracy of this approach is suboptimal [2]. Multiparametric magnetic resonance imaging (mpMRI) combining T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI), and dynamic contrast enhanced (DCE) sequences, can overcome the limitations of US-guided biopsy, and the guidelines of several organizations now recommend this as the method of choice for patients with elevated PSA values but negative biopsy results [3,4].

However, mpMRI has limited sensitivity (SEN) for PCa detection, especially in the transitional zone. Moreover, version 2 of the Prostate Imaging Reporting and Data System (PIRADS) provides only moderately reproducible imaging scores for detection of clinically relevant PCa [5]. The use of mpMRI for characterization of suspicious PCa is also limited in some cases, for example, as indeterminate risk of being malignant (PIRADS 3) [6,7].

Additional PET imaging is a promising method that may allow clinicians to overcome these limitations. Previous research has identified several PET ligands for the detection of primary PCa [8], and the most common ones are ^{11}C- and ^{18}F-choline. Several recent studies have described the use of ^{68}Ga-labelled prostate specific membrane antigen ligands (^{68}Ga-PSMA) and found it has favourable biodistribution [9,10]. Other studies have used these radiotracers with PET/MRI for the detection, localization, and characterization of PCa [11–20].

The purpose of this meta-analysis was to compare the diagnostic performance of PET/MRI using different radiotracers with mpMRI in the diagnosis of primary PCa.

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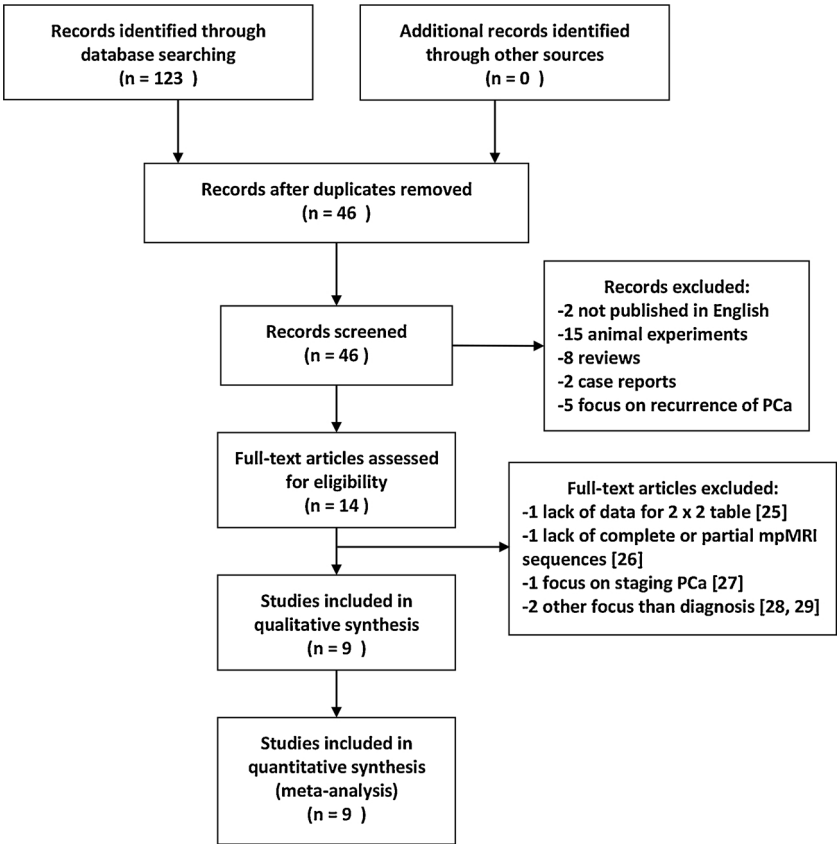

Fig. 1. Procedure used for selection of studies that used two imaging modalities for detection of prostate cancer (PRISMA flow diagram).

2. Material and methods

2.1. Search strategy

Literature searches of the PubMed, Web of Science, and Embase databases up to January 2019 were conducted to identify studies that examined the use of PET/MRI and mpMRI for the diagnosis of primary PCa. The search strategy used the following keywords and syntax: "prostate" AND "PET/MRI OR PET/MR" AND "multiparametric MRI OR mpMRI". The literature search was limited to English language publications and studies of humans. To retrieve additional publications, the reference lists of the initially identified articles were assessed for potentially eligible additional studies. Two reviewers extracted the data independently, and any discrepancies were resolved by discussion.

2.2. Inclusion and exclusion criteria

Studies were eligible for inclusion if all of the following applied: *(i)* PET/MRI and mpMRI were used to detect primary PCa in the same population; *(ii)* sufficient raw data was provided for completion of a 2×2 contingency table; *(iii)* the mpMRI protocols consisted of the T2WI, DWI, and DCE sequences. Publications were excluded if they were reviews, proceedings, case reports, letters, or commentaries.

2.3. Data extraction and quality assessment

We assessed all included articles to extract the information needed for the meta-analysis. For building the 2×2 contingency tables, we extracted or calculated true-positive (TP), false-positive (FP), false-negative (FN), and true-negative (TN) results of PET/MRI and mpMRI in the detection of PCa. In addition, the following information was extracted from each study: author, country, year of publication, study design, reference standard, number of patients, MRI field strength, estimation method (region-based analysis, in which the prostate was divided into segments according to anatomical landmarks, and recording the presence of lesions in each sextant; and lesion-based analysis, which only examined targeted biopsy findings), manufacturer of the PET/MRI scanner, radiotracer used for PET/MRI, and interpretation of mpMRI. Quality assessment of the included studies was performed using the Quality Assessment of Diagnostic Accuracy Studies tool-2 ($QUADAs^{-2}$) [21]. The data extraction and quality evaluation were performed independently by two reviewers, and differences were resolved by discussion.

2.4. Statistical analysis

The pooled sensitivities, specificities, and 95% confidence intervals (CIs) were calculated using random-effect analysis. The pooled positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) were also obtained. Summary receiver operating characteristic (ROC) curves were constructed, and the areas under the curves (AUCs) were calculated. The Z test was used for direct comparisons of the diagnostic accuracy of PET/MRI and mpMRI studies.

The heterogeneity (variation in outcomes) among studies was assessed using the I^2 value, calculated from the Q statistic of the chi-square test (25–50%, low heterogeneity; 51–75%, medium heterogeneity; greater than 75%, high heterogeneity) [22]. To identify potential sources of heterogeneity, subgroup analysis and meta-regression analysis were performed. A threshold effect was identified by a strong positive correlation between the $\log_{10}$-transformed values of SEN and (1 – specificity [SPE]), and a P value less than 0.05 indicated a significant threshold effect [23]. Publication bias was assessed using Deeks' funnel plot asymmetry test, and a P value above 0.05 suggested the absence of publication bias [24]. All statistical analyses were performed using Meta-DiSc Version 1.4, Review Manager Version 5.3, and Stata Version 12.0.

Table 1
Characteristics of the 9 studies included in the meta-analysis.

Authors	Nation	Year	Study design	Field strength	Estimation method	PET/MRI scanner[a]	Radiotracer of PET	Report of mpMRI[b]	Reference standard	No. of patients
Albayati et al. [11]	Germany	2018	retro	3.0 T	lesion-based	Siemens AG	^{68}Ga-PSMA	PI-RADS	pathology	22
Eiber et al. [12]	Germany	2016	retro	3.0 T	region-based	Siemens Biograph	^{68}Ga-PSMA	PI-RADS	pathology	66
Taneja et al. [13]	India	2018	retro	3.0 T	lesion-based	Siemens Biograph	^{68}Ga-PSMA	PI-RADS	pathology	35
Hicks et al. [14]	USA	2018	retro	3.0 T	region-based	GE Signa	^{68}Ga-PSMA	PI-RADS*	pathology	32
Jambor et al. [15]	Finland	2017	pro	3.0 T	region-based	Phillips Ingenuity	^{18}F-FACBC	PI-RADS	pathology	26
Jena et al. [16]	India	2018	retro	3.0 T	lesion-based	Siemens Biograph	^{68}Ga-PSMA	PI-RADS	pathology	82
Lee et al. [17]	Korea	2016	pro	3.0 T	region-based	Siemens Biograph	^{18}F-choline	PI-RADS	pathology	31
Park et al. [18]	USA	2018	pro	3.0 T	region-based	GE Signa	^{68}Ga-PSMA	PI-RADS	pathology	33
Perrot et al. [19]	Switzerland	2014	pro	3.0 T	region-based	Philips Ingenuity	^{18}F-fluorocholine	parameter	pathology	26

FACBC: fluciclovine; PI-RADS: Prostate Imaging Reporting and Data System (version 2), with lesions scored as PI-RADS 3 negative for PCa; PI-RADS*: PI-RADS 3 positive for PCa; parameter: quantitative parameters (*e.g.*, apparent diffusion coefficient) of T2WI, DWI, and DCE sequences; PSMA: prostate-specific membrane antigen; pro: prospective; retro: retrospective.

[a] All data of PET/MR and mpMRI were acquired in the same integrated PET/MRI scanner, except for Phillips Ingenuity.

[b] The mpMRI protocols mainly consisted of T2WI, DWI, and DCE sequences.

3. Results

3.1. Literature search

The literature search led to the initial identification of 123 abstracts. One hundred and nine of these studies were eliminated before the full text assessment. We performed full text assessments of the remaining 14 studies, and eliminated 5 of them for the following reasons: lack of sufficient data to build a 2 × 2 contingency table (n = 1) [25], lack of mpMRI sequences (n = 1) [26], focus on PCa staging (n = 1) [27], and no focus on diagnosis (n = 2) [28,29] (Fig. 1 and Table 1). The quality of the 9 included studies, in terms of risk of bias and applicability concerns, was good according to QUADAs^{-2} results (Fig. 2).

3.2. Quantitative synthesis

The absence of a threshold effect was indicated by the correlation coefficients for $\log_{10}$(SEN) *vs.* $\log_{10}$(1 – SPE) in the PET/MRI studies (P = 0.668) and the mpMRI studies (P = 0.224). Because there was medium heterogeneity in the PET/MRI studies (I^2 of DOR = 70.5%) and the mpMRI studies (I^2 of DOR = 66.7%), we used random-effects coefficient binary regression models to pool the SEN, SPE, PLR, and NLR outcomes. PET/MRI had a SEN of 0.783 (95% CI, 0.758–0.807) and a SPE of 0.899 (95% CI, 0.879–0.917), whereas mpMRI had a SEN of 0.603 (95% CI, 0.574–0.631) and a SPE of 0.887 (95% CI, 0.866–0.906) (Table 2, Fig. 3). PET/MRI had a significantly higher AUC (0.9311, 95% CI, 0.8990–0.9632) than mpMRI (0.8403, 95% CI, 0.7864–0.8942, P = 0.0036; Table 2, Fig. 4).

3.3. Meta-regression and subgroup analysis

The meta-regression analysis showed that the estimation method (region-based *vs.* lesion-based analysis) contributed significantly to the heterogeneity of the included studies (P = 0.0280). Thus, we performed subgroup analysis of studies that differed in design, radiotracer, and estimation method (Table 3). The results of this analysis indicated that studies which used ^{68}Ga-PSMA had higher AUC values than studies which used other radiotracers (AUC = 0.94 *vs.* 0.88, P = 0.6074), but without significance. The lesion-based studies had higher AUC values than the region-based studies (0.96 *vs.* 0.86, P = 0.3035 for PET/MRI; 0.82 *vs.* 0.77, P = 0.9013 for mpMRI), but without significance. The prospective studies had lower AUC values than the retrospective studies (0.90 *vs.* 0.95, P = 0.5366 for PET/MRI; 0.78 *vs.* 0.83, P = 0.1606 for mpMRI), but without significance.

3.4. Publication bias

The Deeks' funnel plot asymmetry test indicated no statistical evidence of publication bias in the PET/MRI studies (P = 0.432) or the mpMRI studies (P = 0.932) (Fig. 5).

4. Discussion

This meta-analysis compared the diagnostic performance of PET/MRI with mpMRI in the detection of primary PCa. To our knowledge, no previous meta-analysis has previously addressed this topic. We demonstrated that PET/MRI was significantly better than mpMRI in the diagnosis of PCa. In particular, the AUC was greater for PET/MRI than mpMRI (0.9311, 95% CI, 0.8990–0.9632 *vs.* 0.8403, 95% CI, 0.7864–0.8942; P = 0.0036).

Many researchers have used mpMRI, which combines T2WI, DWI, and DCE perfusion imaging with PI-RADS (version 2), for detection of clinically significant cancers [17]. Nevertheless, this method has a limited ability to detect tumours in the transition zone, due to the complex morphology of this region, with features such as a heterogeneous background signal and multinodularity [11]. Additionally, the

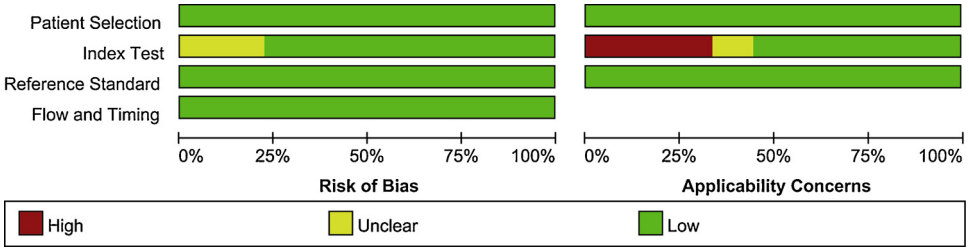

Fig. 2. Quality assessment of the included studies (QUADAs-2).

Table 2
Diagnostic performances of the 9 studies (pooled data) that used PET/MRI and mpMRI for detection of prostate cancer.

Parameter	PET/MRI	95% CI	mpMRI	95% CI	*P* Value
No. of TP results	887	…	683	…	…
No. of FP results	102	…	114	…	…
No. of FN results	246	…	450	…	…
No. of TN results	906	…	894	…	…
Sensitivity (%)	78.3	75.8, 80.7	60.3	57.4, 63.1	…
Specificity (%)	89.9	87.9, 91.7	88.7	86.6, 90.6	…
PLR	8.064	5.168, 12.583	3.986	2.642, 6.013	…
NLR	0.221	0.174, 0.280	0.410	0.321, 0.524	…
DOR	42.121	21.527, 82.417	11.477	6.495, 20.281	…
AUC	0.9311	0.8990, 0.9632	0.8403	0.7864, 0.8942	**0.0036**

AUC: area under the summary receiver operating characteristic curve; CI: confidence interval; FN: false-negative, FP: false-positive, TN: true-negative, TP: true-positive, PLR: positive likelihood ratio; NLR: negative likelihood ratio; DOR: diagnostic odds ratio.

diagnostic accuracy of mpMRI in the evaluation of the peripheral zone can be limited because this method only provides limited discrimination of cancer from prostatitis or thinly scattered tumours of the peripheral zone, and does not provide significant differences in T2 values [30].

Molecular imaging with positron emission tomography (PET) is a promising diagnostic approach that can overcome the limitations of mpMRI [16]. Several studies have compared the performance of PET/MRI with mpMRI for the detection of PCa, but the results have been discordant [11,15]. Our meta-analysis indicated that PET/MRI had a better diagnostic performance than mpMRI, with an especially notable improvement of SEN (0.783 *vs.* 0.603). A previous study [11] also showed that PET/MRI was particularly valuable for further characterization of PIRADS 3 results of mpMRI, in that it significantly improved the SEN (PIRADS 3 was classified as benign when calculating statistical outcomes). In particular, for 15 lesions that PIRADS 3 classified as indeterminate, additional PET led to a shift downwards in 6 lesions, and to a shift upwards in 7 lesions (subsequently confirmed by pathology). Eiber et al. [12] showed that PET imaging successfully detected tumor involvement that had negative results (19% of segments) in mpMRI. These results are in line with our results.

Recent studies have used PSMA for the diagnosis of PCa. PSMA is a transmembrane protein that has significantly greater expression in prostate cancer tissue than benign prostate tissue [18]. Several studies have described the value of ^{68}Ga-PSMA in different clinical scenarios. All of them showed that ^{68}Ga-PSMA had a higher diagnostic efficacy than PET with other tracers (*e.g.*, ^{18}F-choline, ^{18}F-FDG) [12,17,31]. This agrees with the results of our meta-analysis. Although studies using ^{68}Ga-PSMA had a higher AUC (0.94) than studies that used other radiotracers, including ^{18}F-FACBC, ^{18}F-choline, and ^{18}F-fluorocholine (0.88), subgroup analysis indicated this difference was not significant. This might be because of the small number of studies that used other radiotracers. Moreover, the subgroup analysis indicated that lesion-based studies had better diagnostic performance than region-based studies, although this difference was also not significant. This may be

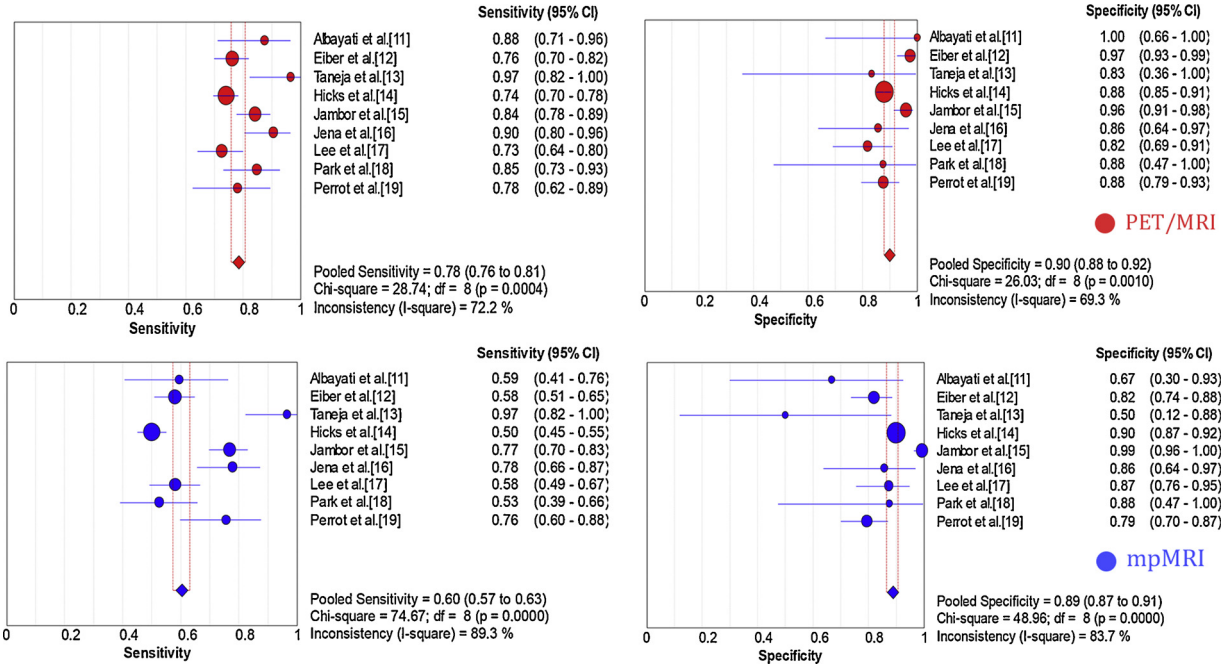

Fig. 3. Sensitivity and specificity of the included studies (Forest plot).

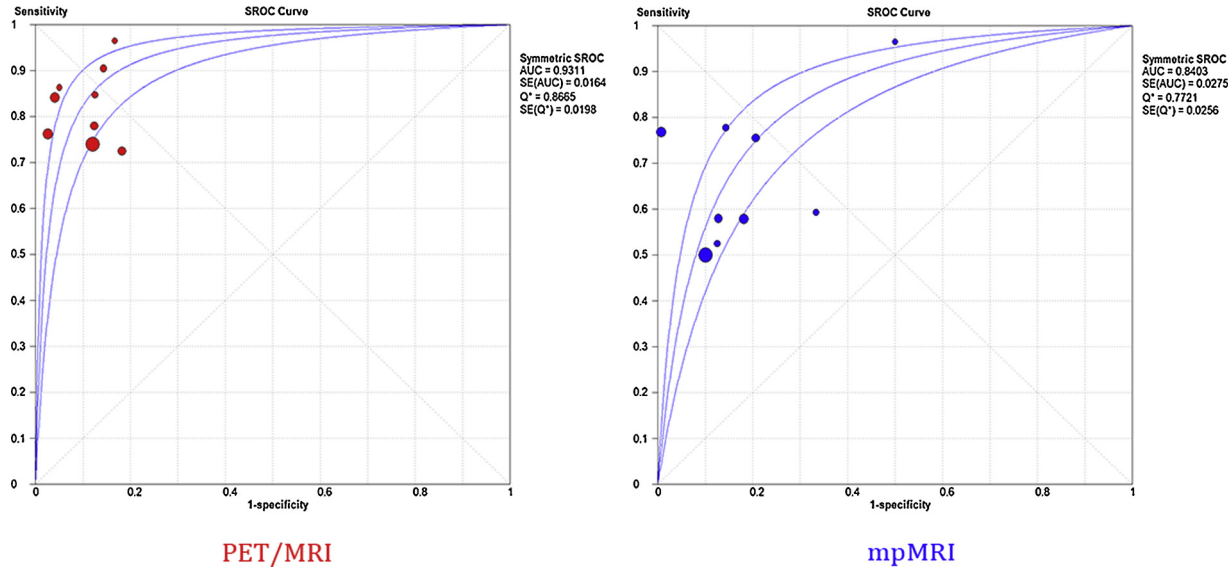

Fig. 4. Summary receiver operating characteristic curves of PET/MRI (left) and mpMRI (right) in the diagnosis of prostate cancer.

explained, at least in part, by the involvement of the whole prostate gland in region-based analysis. Dividing the prostate into sextants can lead to inappropriate assignments of tumor foci on the boundaries between sextants, and does not allow a lesion-by-lesion comparison [12]. Our subgroup analysis indicated that all prospective studies used region-based analysis, and this may have decreased their diagnostic performance relative compared to the retrospective studies.

We examined the sources of heterogeneity among the studies and their quantitative effects on diagnostic performance by performing meta-regression and subgroup analyses. The results indicated that the estimation method (region-based *vs.* lesion-based) contributed significantly to the heterogeneity of studies. In addition, one included study [19] used quantitative parameters (*e.g.*, apparent diffusion coefficient [ADC]) of T2WI, DWI, and DCE sequences to report outcomes of mpMRI, and this contributed to heterogeneity. Another included study [14] used PIRADS 3 to define positive PCa, which could also contribute to heterogeneity.

There were some limitations in our meta-analysis. First, the number of the included studies was small. This is because we only included studies that used PET/MRI and mpMRI for detection of PCa within the same patient cohorts. In addition, studies without sufficient data to construct a 2 × 2 contingency table for TP, FP, FN, and TN results were not included, even if they included both imaging modalities. A second limitation is that we only compared the diagnostic value of PET/MRI and mpMRI in PCa detection, but were unable to consider other important problems, such as tumour grade or aggressiveness, because there were insufficient studies of these topics for reliable data-synthesis.

5. Conclusions

In conclusion, our results demonstrate that PET/MRI had a better diagnostic performance than mpMRI in the diagnosis of primary PCa, in that it provided better discrimination of benign and malignant lesions and improved diagnostic accuracy.

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Guarantor

The scientific guarantor of this publication is Bin Song.

Conflict of interest

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry

No complex statistical methods were necessary for this paper.

Table 3
Subgroup analysis of studies that differed in design, radiotracer, and estimation method.

Characteristic	No. of Studies	PET/MRI			*P* value[a]	mpMRI			*P* value[a]
		SEN	SPE	AUC		SEN	SPE	AUC	
Study design					0.1201				0.1124
Prospective	4	80%	91%	0.90		65%	92%	0.78	
Retrospective	5	85%	92%	0.95		71%	80%	0.83	
Radiotracer					0.0691				…
^{68}Ga-PSMA	6	84%	91%	0.94		…	…	…	
Others	3	78%	90%	0.88		…	…	…	
Estimation method					**0.0280**				0.2014
Lesion-based	3	91%	89%	0.96		82%	74%	0.82	
Region-based	6	77%	92%	0.86		61%	90%	0.77	

AUC: area under the curve; Others: other radiotracers including ^{18}F-FACBC, ^{18}F-choline, and ^{18}F-fluorocholine; SEN: Sensitivity; SPE: Specificity.
[a] *P* values were calculated by meta-regression analysis.

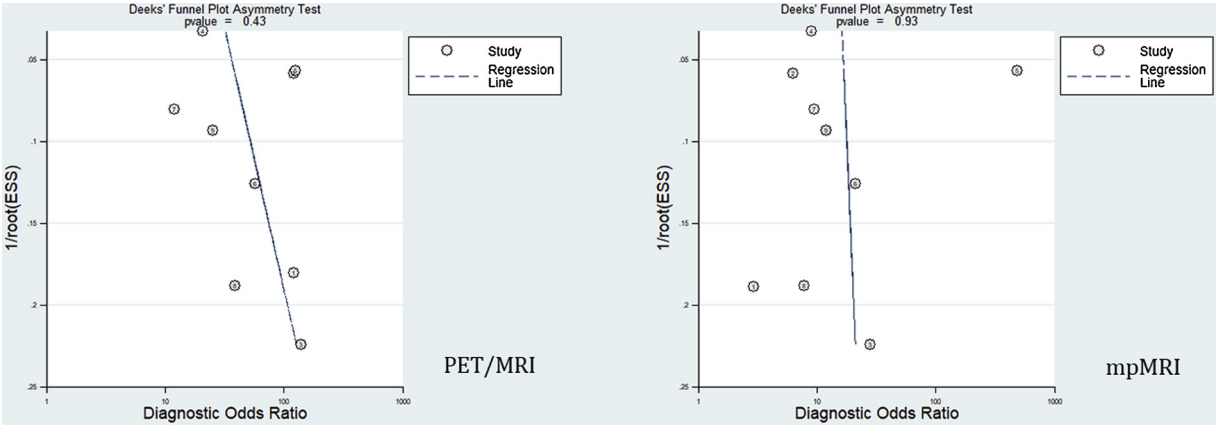

Fig. 5. Deeks funnel plot asymmetry test for publication bias of the PET/MRI studies (left) and mpMRI studies (right).

Informed consent

Written informed consent was waived.

Ethical approval

Institutional Review Board approval was waived.

Study subjects or cohorts overlap

This manuscript has not been published or presented elsewhere in part or in entirety.

Methodology

Meta-analysis.

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