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Review – Priority Article

Editorial by Jochen Walz on pp. 401–402 of this issue

Diagnostic Performance of Prostate-specific Membrane Antigen Positron Emission Tomography–targeted biopsy for Detection of Clinically Significant Prostate Cancer: A Systematic Review and Meta-analysis

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Abstract

Context: Prostate-specific membrane antigen positron emission tomography (PSMA-PET) has fgained acceptance as a staging tool for prostate cancer (PCa). Recent reports suggest an association between PSMA PET and detection of clinically significant PCa (csPCa) on prostate biopsy.

Objective: To assess the diagnostic accuracy of PSMA PET–targeted biopsy (PSMA-PET-TB) for csPCa detection.

Evidence acquisition: We searched PubMed, Web of Science, and Scopus in December 2021 to identify studies assessing the accuracy of PSMA-PET-TB for csPCa detection. A diagnostic meta-analysis was performed to calculate pooled sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of PSMA-PET-TB alone

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and in combination with magnetic resonance imaging (MRI)-TB for detecting csPCa.

Evidence synthesis: Overall, five prospective studies involving 497 patients were eligible for this meta-analysis. For csPCa detection, PSMA-PET-TB had pooled sensitivity, specificity, PPV, and NPV of 0.89 (95% confidence interval [CI] 0.85–0.93), 0.56 (95% CI 0.29–0.80), 0.69 (95% CI 0.58–0.79), and 0.78 (95% CI 0.50–0.93), respectively. Among the three studies assessing the PSMA-PET + MRI-TB strategy, the pooled sensitivity, specificity, PPV, and NPV for csPCa detection were 0.91 (95% CI 0.77–0.97), 0.64 (95% CI 0.40–0.82), 0.75 (95% CI 0.56–0.87), and 0.85 (95% CI 0.62–0.95), respectively. For lesions with a Prostate Imaging-Reporting and Data System (PI-RADS) score of 3, the sensitivity, specificity, PPV, and NPV were 0.69, 0.73, 0.48, and 0.86, respectively.

Conclusions: PSMA-PET-TB appears to have favorable diagnostic accuracy for csPCa detection and combination with MRI seems to improve this. According to our meta-analysis, PSMA-PET has promising clinical application for detection of csPCa, namely in the case of PI-RADS 3 lesions. Further prospective studies are needed to explore the true clinical utility of a PSMA-PET-based diagnostic pathway.

Patient summary: Prostate-specific membrane antigen positron emission tomography (PSMA-PET) is a promising imaging method for detecting clinically significant prostate cancer and seems to have additional value to magnetic resonance imaging (MRI) for detection.

Abbreviations: csPCa, clinically significant Prostate Cancer; PSMA, Prostate-Specific Membrane Antigen; PET, Positron Emission Tomography; mpMRI, multiparametric Magnetic Resonance Imaging; TB, Targeted Biopsy; PI-RADS, Prostate Imaging–Reporting and Data System; ISUP, International Society of Urological Pathology; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analyses; CI, Confidence Intervals; HR, Hazard Ratio; IQR, Interquartile Range; SROC, Summary Receiver Operating Characteristic Curve; AUC, Area Under the Curve; PPV, Positive Predictive Value; NPV, Negative Predictive Value; DOR, Diagnostic Odds Ratio.

1. Introduction

Multiparametric magnetic resonance imaging (mpMRI) of the prostate has changed the diagnostic pathway for prostate cancer (PCa). Prostate mpMRI assessed according to the most commonly used Prostate Imaging-Reporting and Data System (PI-RADS) classification achieves a negative predictive value (NPV) of >80% and a positive predictive value (PPV) of approximately 50% for detection of clinically significant PCa (csPCa) [1–6]. However, these data indicate that every fifth case of csPCa is missed by MRI, and 50% of patients with positive MRI undergo unnecessary, unpleasant, and complication-related prostate biopsies. Furthermore, the diagnostic performance estimates reported for csPCa vary largely for mpMRI, with sensitivity ranging from 58% to 96%, specificity from 23% to 87%, PPV from 38% to 93%, and NPV from 63% to 98%. This variability has been assessed over all PI-RADS scores, and particularly for PI-RADS 3 lesions [7,8]. Moreover, the diagnostic accuracy of mpMRI is reader- and scanner-dependent, with high inter-reader variability. Thus, there is a need for further improvement of the diagnostic pathway for detecting csPCa.

Prostate-specific membrane antigen positron emission tomography (PSMA-PET) has recently gained wide acceptance for staging in PCa owing to its high performance for detecting metastases and identifying recurrent lesions [9–12]. PSMA is overexpressed in malignant prostate cells and more aggressive disease generally presents with higher PSMA overexpression [13]. Several studies have reported on the potential of PSMA-PET for detecting csPCa and thereby improving the diagnostic pathway [14–16]. However, owing to differences in study design and the heterogeneous results obtained, single-center studies have not provided strong evidence regarding the usefulness of PSMA-PET in the diagnosis of csPCa. In this systematic review and meta-analysis, we evaluated the diagnostic performance of PSMA-PET–targeted biopsy (PSMA-PET-TB) for detection of csPCa. We also assessed the additional value of hybrid imaging with PSMA-PET/MRI compared to PET/computed tomography (CT).

2. Evidence acquisition

2.1. Protocol

A protocol for this study was registered a priori on the International Prospective Register of Systematic Reviews (CRD42021286927).

2.2. Search strategy

The systematic review and meta-analysis were performed according to the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy (PRISMA-DTA) statement [17].

A literature search was conducted in the PubMed, Web of Science, and Scopus databases in December 2021. The search terms were as follows: (“prostate” OR “prostatic”) AND (“cancer” OR “neoplasm” OR “malignancy”) AND (“PSMA” OR “prostate specific membrane antigen”) AND (“PET” OR “positron emission tomography”) AND (“biopsy” OR “biopsies” OR “puncture”) AND (”target” OR ”targeted” OR ”guided” OR “fusion”).

Initial screening was performed independently by two investigators (TK and TY) based on the titles and abstracts to identify ineligible reports. Potentially relevant reports

were subjected to a full article review and excluded with reasons. Any discrepancies were resolved at the authors' consensus meeting.

2.3. Inclusion and exclusion criteria

Studies were included if they investigated patients with elevated prostate-specific antigen (PSA) who were suspected of harboring PCa (Patients) and positive PSMA PET (Intervention) was compared to negative PSMA PET (Comparison) to assess the sensitivity, specificity, PPV, and NPV for csPCa diagnosis (Outcomes) in observational studies. We selected studies that reported on the diagnostic accuracy of PSMA-PET-TB for csPCa and used systematic biopsy and image-targeted biopsy as the reference test. Only studies with sufficient data to reconstruct 2 × 2 contingency tables regarding sensitivity and specificity for csPCa were included. There was no restriction related to the background for prostate biopsy (biopsy-naïve or repeat biopsy setting, including previously negative biopsy, active surveillance [AS], and previously positive biopsy referred for focal therapy), the imaging modalities for PSMA-PET (CT or MRI), the type of PSMA ligand, or the sample size.

We excluded review articles, letters, editorials, conference abstracts, case reports, and articles not published in English. Studies with insufficient data to produce 2 × 2 contingency tables were also excluded.

2.4. Study eligibility

The following data were independently extracted by two investigators (T.K. and T.Y.): author names, publication year, type of study, number of patients, patient characteristics (age, PSA at the time of PET, PCa classification according to International Society of Urological Pathology), imaging characteristics (radiotracer used for PSMA-PET, PSMA-PET modalities, PI-RADS score), definition of csPCa, and definition of PSMA-PET positivity. If data for both PSMA-PET-TB and PSMA-PET + MRI targeted biopsy (PSM-PET/MRI-TB) were available, these data were extracted separately, and the definition of PSMA-PET/MRI positivity was also extracted. In this study, PSMA-PET/MRI included use of an integrated PET/MRI scanner or post hoc image fusion of MRI and PSMA-PET data.

Using histopathology for systematic and targeted biopsy as the reference standard, the numbers of true positives, false positives, true negatives, and false negatives on per-patient analysis for each study were extracted. Subsequently, the sensitivity, specificity, PPV, NPV, and diagnostic odds ratio (DOR) for each study were calculated. Any discrepancies were resolved at the authors' consensus meeting.

2.5. Quality assessment and risk of bias

The risk of bias and applicability were evaluated independently by two authors using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [18]. We defined PSMA-PET-TB results as the index test and histopathology findings as the reference standard. We assessed four domains: patient selection, index text, reference standard, and flow and timing, and judged their risk of bias as low, high, or unclear.

2.6. Statistical analyses

All analyses were performed using R v4.0 (R Foundation for Statistical Computing, Vienna, Austria) and the statistical significance level was set at $p < 0.05$. Pooled sensitivity, specificity, PPV, NPV, and DOR values were calculated using the *mada* and *meta* packages for R. Forest plots with 95% confidence interval (CI) were constructed. The Cochrane Q test and the I^2 statistic were used to evaluate heterogeneity. Significant heterogeneity was indicated by $p < 0.05$ for the Cochrane Q test and $I^2 > 50\%$. We developed a hierarchical summary receiver operating characteristic (SROC) curve and calculated the area under the curve (AUC) to examine the diagnostic accuracy of PSMA-PET-TB and PSMA-PET/MRI-TB. To consider prostate biopsy heterogeneity, subgroup analysis was carried out separately for studies in the biopsy-naïve setting and others (including repeat biopsy or both biopsy-naïve and repeat biopsy).

3. Evidence synthesis

3.1. Study selection and characteristics

The PRISMA flowchart is presented in Figure 1. In total, we included five prospective cohort studies involving 497 patients who underwent PSMA-PET-TB [19–23]. Two studies included only biopsy-naïve patients [19,20] and the remaining three studies included patients undergoing repeat biopsy or both biopsy-naïve and repeat-biopsy patients [21–23]. The characteristics of these studies are presented in Tables 1 and 2. Three of the studies used MRI and assessed PSMA-PET/MRI-TB. The pooled PSMA-PET positivity rate for all five studies was 66.5% and the pooled cancer prevalence was 59.5% for any PCa and 45.7% for csPCa. According to QUADAS-2 assessment, one study was considered as having low risk of bias and the other four were considered as having moderate risk. Regarding applicability, three studies were considered as having low and two as having moderate concerns (Supplementary Fig. 1).

3.2. Outcomes

3.2.1. Meta-analysis of the diagnostic performance of PSMA-PET-TB for csPCa

Data for the diagnostic meta-analysis were available from five studies involving 497 patients who underwent PSMA-PET-TB. Forest plots (Fig. 2) revealed pooled sensitivity, specificity, PPV, NPV, and DOR of 0.89 (95% CI 0.85–0.93), 0.56 (95% CI 0.29–0.80), 0.69 (95% CI 0.58–0.79), 0.78 (95% CI 0.50–0.93), and 10.50 (95% CI 2.59–42.57), respectively. SROC curve analysis revealed an AUC of 0.88 for PSMA-PET-TB detection of csPCa (Supplementary Fig. 2). In the subgroup analysis of two studies involving 393 biopsy-naïve patients, the pooled sensitivity, specificity, PPV, and NPV were 0.90 (95% CI 0.84–0.93), 0.71 (95% CI 0.21–0.96), 0.86 (95% CI 0.37–0.99), and 0.79 (95% CI 0.69–0.86), respectively. There were no significant differences in diagnostic performance between the biopsy-naïve setting and the setting that included repeat biopsy.

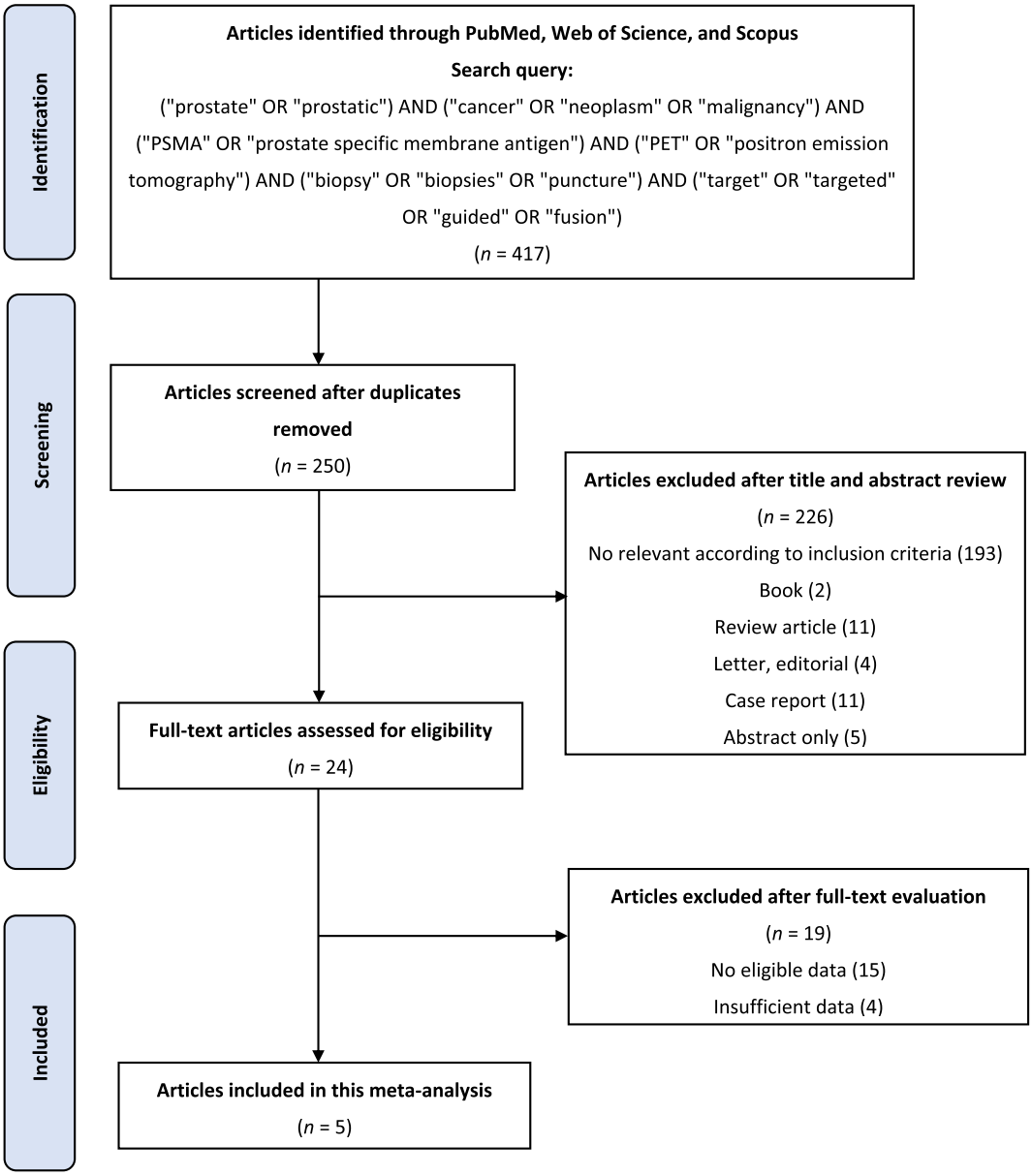


Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart detailing the article selection process.

3.2.2. Comparison of diagnostic performance of PSMA-PET-TB in addition to MRI-TB for csPCa

Three studies involving 424 patients who underwent combined PSMA-PET-TB and MRI-TB assessed the diagnostic performance of each modality (PSMA-PET, MRI, and PSMA-PET/MRI). Results for the pooled sensitivity, specificity, PPV, NPV, and DOR for each modality are shown in Supplementary Table 1.

The pooled sensitivity, specificity, PPV, NPV, and DOR for PSMA-PET/MRI-TB were 0.91 (95% CI 0.77–0.97), 0.64 (95% CI 0.40–0.82), 0.75 (95% CI 0.56–0.87), 0.85 (95% CI 0.62–0.95), and 19.04 (95% CI 9.54–38.02), respectively. There was a trend for better performance over PSMA-PET-TB and MRI-TB alone (Fig. 3 and Supplementary Fig. 3). The pooled DOR was significantly higher with PSMA-PET/MRI-TB than with MRI-TB alone ($p = 0.01$) but was not significantly different compared to PSMA-PET-TB alone ($p = 0.13$; Supplementary Fig. 4). The AUC was 0.88 for PSMA-PET-TB, 0.81 for MRI-TB, and 0.87 for PSMA-PET/MRI-TB (Supplementary Fig. 5).

3.2.3. PSMA-PET-TB for csPCa diagnosis in patients with a PI-RADS 3 lesion

Three studies involving 175 patients evaluated the diagnostic performance of PSMA-PET-TB for csPCa detection in PI-RADS 3 lesions. Overall, 34% (60/175) of these patients had PI-RADS 3 lesions, of whom 27% (16/60) harbored csPCa. The pooled sensitivity, specificity, PPV, and NPV were 0.69, 0.73, 0.48, and 0.86, respectively (Fig. 4).

3.3. Discussion

In the present study, our aim was to summarize the weak but accumulating evidence assessing whether PSMA-PET can improve diagnostic performance in the

Table 1 – Study design and patient characteristics

Study	Design	Reference standard	Patients (*n*)	Study population	Age (yr)	PSA (ng/ml)	Prostate volume (ml)	csPCa definition	csPCa prevalence
Emmett 2021 [19]	PS	SB + TB	291	Bx-naïve	64 (58–70)[a]	5.6 (4.2–7.5)[a]	40 (29–55)[a]	ISUP ≥ 2	74% (163/291)
Ferraro 2021 [20]	PS	SB + TB (RP if available)	42	Bx-naïve	65 (59–68) [a]	8 (7–11)[a]	ND	(GG ≥3 or TCL ≥6 mm) or GG ≥2[d]	73% (31/42)
Liu 2020 [21]	PS	SB + TB	31	Previous negative Bx	65 (53–81)[b]	18 (5.5–49.8)[b]	ND	GG ≥2	39% (12/31)
Margel 2021 [22]	PS	SB + TB	78	Bx-naïve + previous negative Bx + AS	67 (62–71)[a]	6.7 (6–9.6)[a]	61 (42.8–82.5)[a]	GG ≥2	32% (25/78)
Metser 2021 [23]	PS	SB + TB	55	Previous negative Bx + previous positive Bx and considered for FAB	65 (49–83)[c]	8.8 (1.1–25.0)[c]	ND	GG ≥2 or TCL ≥6 mm	74.5% (41/55)

PSA = prostate-specific antigen at prostate-specific membrane antigen positron emission tomography; PS = prospective study; csPCa = clinically significant prostate cancer; SB = systematic biopsy, TB = targeted biopsy; RP = radical prostatectomy; Bx = biopsy; AS = active surveillance; FAB = focal ablative therapy; GG = International Society of Urological Pathology grade group; TCL = tumor core length; ND = no data.

[a] Median (interquartile range).

[b] Median (range).

[c] Mean (range).

[d] This study used data for csPCa defined as GG ≥2 for calculating diagnostic performance.

Table 2 – Imaging characteristics

Study	PET positive	Fusion software	PSMA ligand	Mean dose	Mean SUVmax		Definition of imaging positivity	
					csPCa	ROI	PSMA-PET	PSMA-PET/MRI
Emmett [19]	73% (211/291)	ND (cognitive)	^{68}Ga-PSMA-11	1.8–2.2 MBq/kg	7.0 (5.2–13.4)	6.5 (5.2–9.0)	SUVmax ≥4	Positive PSMA or PI-RADS 4/5
Ferraro [20]	67% (28/42)	BiopSee	^{68}Ga-PSMA-11	85 MBq	ND	ND	Focal uptake higher than local background	ND
Liu [21]	58% (18/31)	Brilliance Workstation	^{68}Ga-PSMA-617	206.09 MBq	ND	5.6 (2.9–31.0)	Focal uptake higher than liver background	ND
Margel [22]	54% (42/78)	Navigo, Bio-Jet	^{68}Ga-PSMA	74–148 MBq	ND	ND	SUVmax ≥2.5	Positive PSMA and PI-RADS ≥3
Metser [23]	89% (49/55)	Artemis	^{18}F-DCFPyL	329.5 (301–350) MBq	10.4 (2.1–37.7)	ND	Focal uptake higher than local background	PROMISE classification

csPCa = clinically significant prostate cancer; ROI = region of interest; SUVmax = maximum standardized uptake value; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging-Reporting and Data System; ND = no data; PROMISE = Prostate Cancer Molecular Imaging Standardized Evaluation [33].

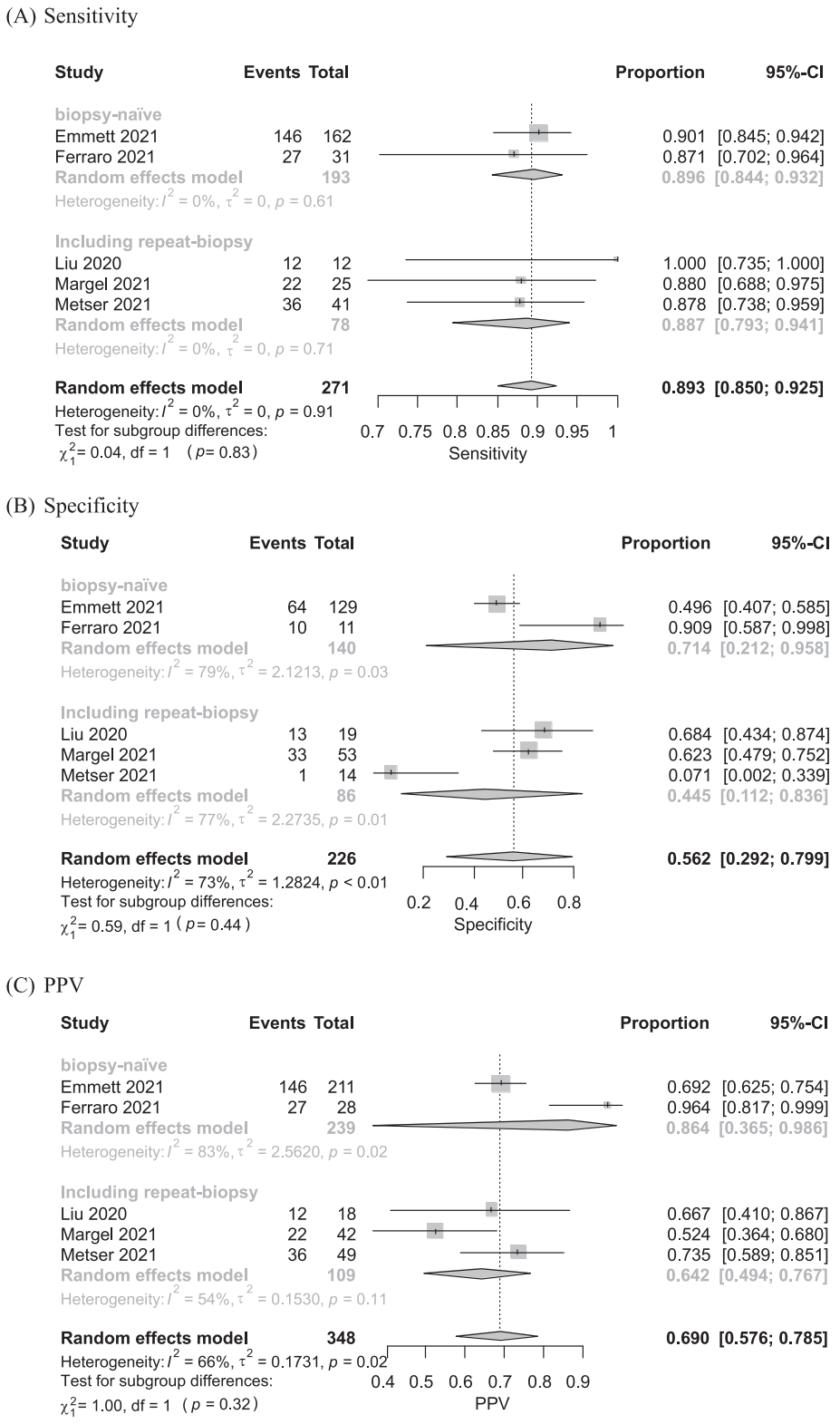


Fig. 2 – Forest plots for the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic odds ratio (DOR) of prostate-specific membrane antigen positron emission tomography–targeted biopsy for detection of clinically significant prostate cancer. CI = confidence interval; df = degrees of freedom.

primary diagnosis setting [14,24–26]. To this end, we evaluated the performance of PSMA-PET-TB for diagnosing csPCa.

We found that PSMA-PET-TB has a favorable diagnostic performance for csPCa detection that is comparable to that of MRI-TB [6]. Moreover, it seems to have additional value

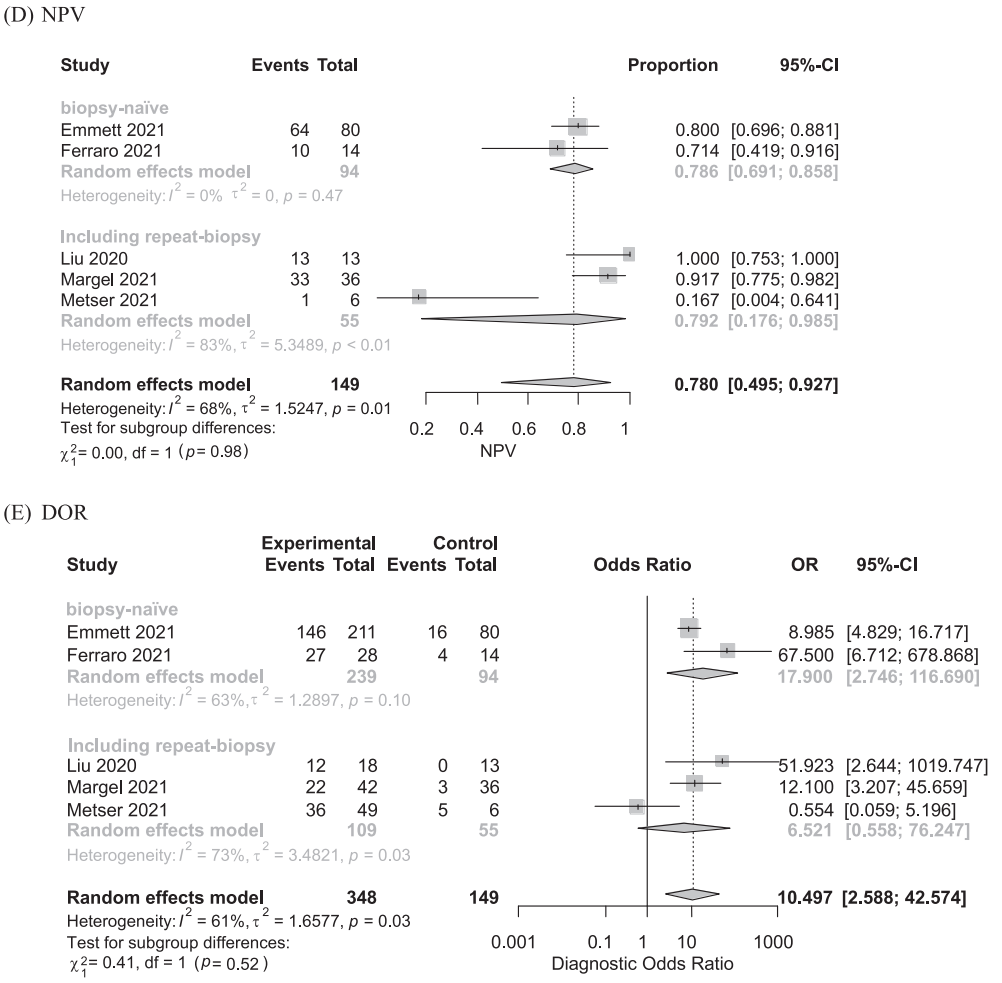


Fig. 2 (*continued*)

on MRI-TB and, therefore, could have clinical utility in selected patients with suspected csPCa with equivocal lesions (PI-RADS 3).

In the present meta-analysis, three studies assessed the diagnostic performance of both MRI-TB and PSMA-PET-TB. There was a trend for better diagnostic performance for csPCa detection with the PSMA-PET/MRI-TB combination than with PSMA-PET-TB or MRI-TB alone. According to these results, PSMA-PET-TB has added value over MRI-TB for detecting csPCa. Both PSMA-PET and MRI have the potential to detect csPCa cases that were missed by the other modality. We can expect a synergistic effect when PSMA-PET and MRI are combined for imaging-targeted biopsy of lesions. Several studies support this combined approach using whole-mount histology of the radical prostatectomy specimen as the reference [14,24,25,27,28]. For example, Scheltema et al. [28] assessed PSMA-PET combined with MRI and observed higher diagnostic accuracy for csPCa in comparison to MRI or PSMA-PET alone, with sensitivity, specificity, NPV, and PPV, reaching 0.92, 0.90, 0.96, and 0.81, respectively.

PI-RADS 3 lesions on MRI are still recognized as equivocal for the presence of csPCa and therefore not all of these lesions are biopsied. A meta-analysis revealed that the prevalence of PI-RADS 3 cases was 17.3%, with similar rates of csPCa (19%) and insignificant PCa (17%) cases [29]. Anconina et al. [30] reported that PSMA uptake in PI-RADS 3 lesions was associated with csPCa detection. Furthermore, Margel et al. [22] showed that, according to decision curve analysis, implementation of PSMA-PET increased the net benefit of MRI for PI-RADS 3 lesions. In the present review, among three studies on csPCa in patients with PI-RADS 3 lesions, PSMA-PET-TB had sensitivity of 69% and specificity of 73% for csPCa detection. Although our results should be interpreted with caution, mostly because of the small sample size, our findings show promising diagnostic estimates for the combined detection strategy. Radiologist experience and high-quality imaging could reduce the identification of equivocal PI-RADS 3 lesions. Moreover, clinical factors and biomarkers such as PSA density could help to improve risk stratification for patients with equivocal MRI lesions; considering the current evidence, PSMA-PET could be a valuable tool in this setting in the future. Adding quantitative assessment using the maximum standardized uptake value (SUVmax) on PSMA-PET over MRI might help in more efficient detection of csPCa and reduce unnecessary biopsies, especially for PI-RADS 3 lesions.

Despite the benefits of PSMA-PET, it has some limitations. First, PSMA-PET can yield some false-positive and false-negative results, although it is more accurate than

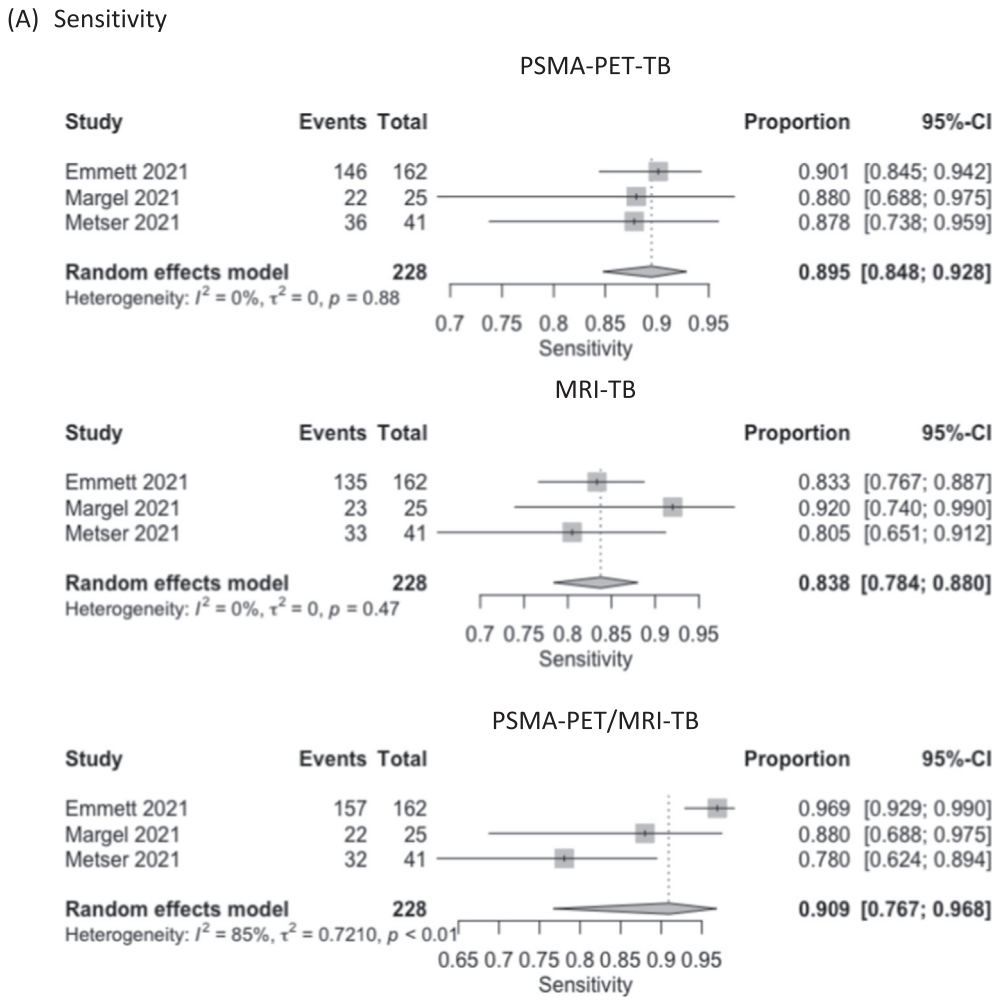


Fig. 3 – Forest plots of the sensitivity and specificity of PSMA-PET-TB, MRI-TB, and PSMA-PET/MRI-TB for detection of clinically significant prostate cancer. CI = confidence interval; MRI = magnetic resonance imaging; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; TB = targeted biopsy.

choline-PET for detecting PCa [26]. PSMA overexpression is sometimes observed in benign conditions including prostatitis, granulomatous diseases, and benign prostatic hyperplasia [31,32], while there is a lack of PSMA expression in approximately 5% of PCa cases [33]. Second, interpretation of PSMA-PET, similar to MRI, widely varies by threshold, and there is a lack of quantitative standards such as PI-RADS. In the present meta-analysis, only one study applied central reading and referred to a standardized reporting system [19], which might have contributed to the low specificity. Finally, some csPCa cases can be missed during imaging cognition or fusion for biopsy execution (fusion error), as reported for MRI-TB [34,35]. These, among other reasons, could explain the lack of significant AUC difference between PSMA-PET/MRI-TB and PSMA-PET-TB alone in our study. Nevertheless, before broad implementation of PSMA-PET-TB in the diagnostic setting, standardization and assessment of its cost-effectiveness are required. Therefore, mpMRI before biopsy and MRI-TB should still be recommended for patients in the biopsy-naïve setting on the basis of level 1 evidence [1]. PSMA-PET-TB could play a role, combined with MRI-TB, in patients with persistent csPCa suspicion despite negative biopsy and in equivocal cases such as PI-RADS 3 lesions. Several studies have suggested an optimal SUVmax threshold for PSMA-PET [15,36,37]. It is expected that establishing a well-defined and standardized quantitative reporting system for PSMA-PET findings, as well as a central reading system and reader experience, will improve the diagnostic performance for csPCa. More studies are needed to assess the utility of PSMA-PET-TB in the PCa diagnostic pathway in comparison to MRI-TB with consideration of the additional workload and cost-effectiveness.

Our study has several limitations. First, despite very promising pooled findings, the number and strength of the studies included still limit the broad implementation of PSMA-PET in clinical practice. Second, the studies analyzed differed in their definitions for csPCa and imaging positivity, as well as the PSMA-PET ligands used. Third, there were differences in terms of study populations; two studies evaluated only biopsy-naïve patients, while the other studies included both biopsy-naïve patients and those undergoing

(B) Specificity

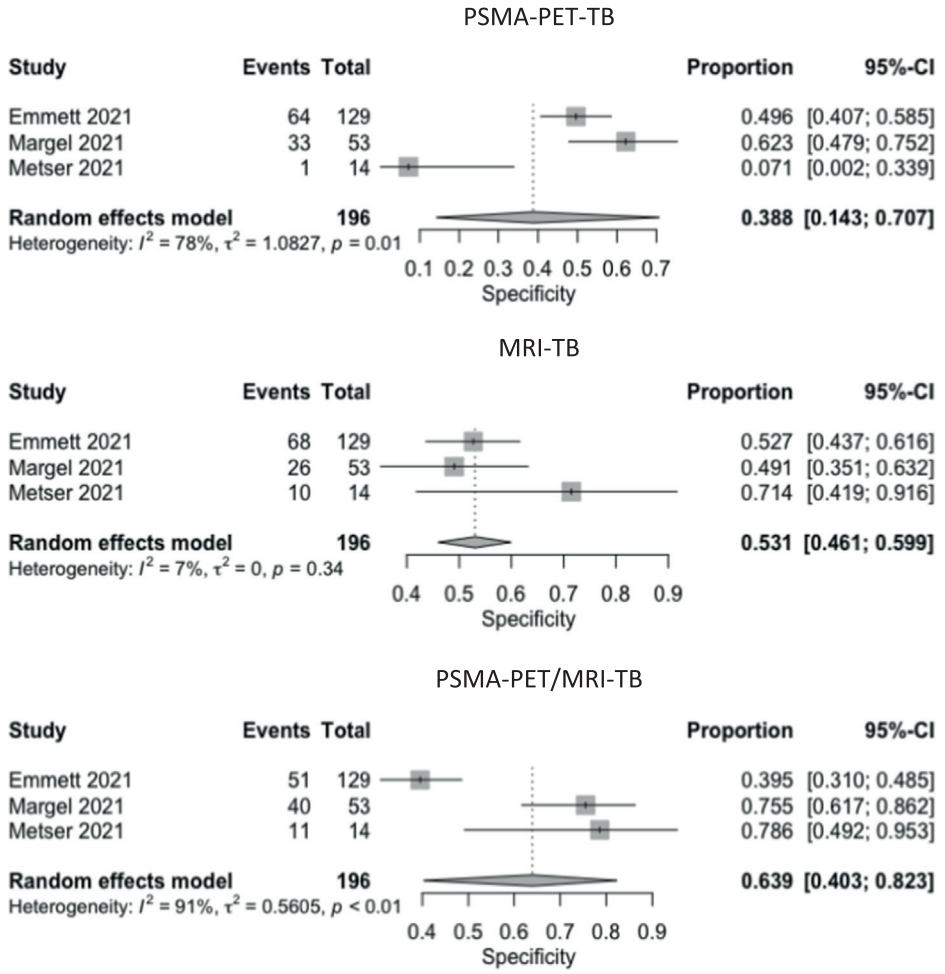
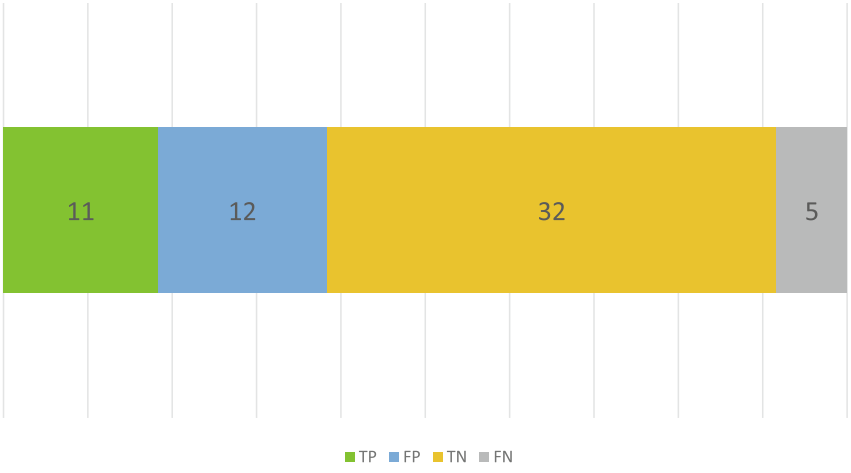


Fig. 3 (*continued*)



Sensitivity	Specificity	PPV	NPV
0.69	0.73	0.48	0.86

Fig. 4 – Diagnostic performance for detection of clinically significant prostate cancer for lesions with a Prostate Imaging-Reporting and Data System (PI-RADS) score of 3. PPV = positive predictive value; NPV = negative predictive value; TP = true positive; FP = false positive; TN = true negative; FP = false positive.

repeat biopsy. Some of the repeat biopsy settings even included patients on AS and patients undergoing staging for local therapy. Although the subgroup analysis showed no significant differences between the biopsy-naïve-alone setting and the studies that included both biopsy-naïve and repeat-biopsy patients, we could not clearly separate the repeat-biopsy-alone setting for selective analysis. Further, most of the biopsy-naïve cohort came from one study. These heterogeneities and sample size bias across the studies included may also limit the generalizability of PSMA-PET-TB implementation as a primary diagnostic tool. In addition, two studies showed high csPCa prevalence (>70%), introducing a possible selection bias that might contribute to the heterogeneity. Finally, we could not assess the diagnostic performance of TB without including systematic biopsy as in current practice. It is therefore difficult to assess the potential of PSMA-PET-TB for decreasing the number of biopsy cores.

4. Conclusions

Despite limitations such as the small sample size and heterogeneity, this meta-analysis showed that PSMA-PET-TB has promising diagnostic estimates for detection of csPCa. Furthermore, it might provide additional value to mpMRI, especially for PI-RADS 3 lesions. At present, PSMA-PET for diagnostic use should be considered in combination with mpMRI only for selected patients, while mpMRI before prostate biopsy and MRI-TB should be recommended. In the future, PSMA-PET may allow for more precise risk stratification for patients with csPCa suspicion. Further well-designed large-scale studies are warranted to standardize PSMA-PET recommendations for PCa detection.

Author contributions: Tatsushi Kawada 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: Kawada.
Acquisition of data: Kawada, Yanagisawa.
Analysis and interpretation of data: Kawada, Yanagisawa, Rajwa.
Drafting of the manuscript: Kawada, Yanagisawa, Rajwa.
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Appendix A. Supplementary data

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References

[1] Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med 2018;378:1767–77. https://doi.org/10.1056/NEJMoa1801993.
[2] van der Leest M, Cornel E, Israël B, et al. Head-to-head comparison of transrectal ultrasound-guided prostate biopsy versus multiparametric prostate resonance imaging with subsequent magnetic resonance-guided biopsy in biopsy-naïve men with elevated prostate-specific antigen: a large prospective multicenter clinical study. Eur Urol 2019;75:570–8. https://doi.org/10.1016/j.eururo.2018.11.023.
[3] Elkhoury FF, Felker ER, Kwan L, et al. Comparison of targeted vs systematic prostate biopsy in men who are biopsy naive: the Prospective Assessment of Image Registration in the Diagnosis of Prostate Cancer (PAIREDCAP) study. JAMA Surg 2019;154:811–8. https://doi.org/10.1001/jamasurg.2019.1734.
[4] Rouvière O, Puech P, Renard-Penna R, et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. Lancet Oncol 2019;20:100–9. https://doi.org/10.1016/s1470-2045(18)30569-2.
[5] Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS Prostate Imaging-Reporting and Data System: 2015, version 2. Eur Urol 2016;69:16–40. https://doi.org/10.1016/j.eururo.2015.08.052.
[6] Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017;389:815–22. https://doi.org/10.1016/s0140-6736(16)32401-1.
[7] Fütterer JJ, Briganti A, De Visschere P, et al. Can clinically significant prostate cancer be detected with multiparametric magnetic resonance imaging? A systematic review of the literature. Eur Urol 2015;68:1045–53. https://doi.org/10.1016/j.eururo.2015.01.013.
[8] Park KJ, Choi SH, Lee JS, Kim JK, Kim MH, Jeong IG. Risk stratification of prostate cancer according to PI-RADS® version 2 categories: meta-analysis for prospective studies. J Urol 2020;204:1141–9. https://doi.org/10.1097/ju.0000000000001306.
[9] Perera M, Papa N, Christidis D, et al. Sensitivity, specificity, and predictors of positive ^{68}Ga-prostate-specific membrane antigen positron emission tomography in advanced prostate cancer: a systematic review and meta-analysis. Eur Urol 2016;70:926–37. https://doi.org/10.1016/j.eururo.2016.06.021.
[10] Grubmüller B, Baltzer P, Hartenbach S, et al. PSMA ligand PET/MRI for primary prostate cancer: staging performance and clinical impact. Clin Cancer Res 2018;24:6300–7. https://doi.org/10.1158/1078-0432.Ccr-18-0768.
[11] Grubmüller B, Rasul S, Baltzer P, et al. Response assessment using [^{68}Ga]Ga-PSMA ligand PET in patients undergoing systemic therapy for metastatic castration-resistant prostate cancer. Prostate 2020;80:74–82. https://doi.org/10.1002/pros.23919.
[12] Grubmüller B, Baltzer P, D'Andrea D, et al. ^{68}Ga-PSMA 11 ligand PET imaging in patients with biochemical recurrence after radical prostatectomy — diagnostic performance and impact on therapeutic decision-making. Eur J Nucl Med Mol Imaging 2018;45:235–42. https://doi.org/10.1007/s00259-017-3858-2.
[13] Roberts MJ, Morton A, Donato P, et al. ^{68}Ga-PSMA PET/CT tumour intensity pre-operatively predicts adverse pathological outcomes and progression-free survival in localised prostate cancer. Eur J Nucl Med Mol Imaging 2021;48:477–82. https://doi.org/10.1007/s00259-020-04944-2.
[14] Rhee H, Thomas P, Shepherd B, et al. Prostate specific membrane antigen positron emission tomography may improve the diagnostic accuracy of multiparametric magnetic resonance imaging in

localized prostate cancer. J Urol 2016;196:1261–7. https://doi.org/10.1016/j.juro.2016.02.3000.
[15] Hoffmann MA, Miederer M, Wieler HJ, Ruf C, Jakobs FM, Schreckenberger M. Diagnostic performance of ^{68}gallium-PSMA-11 PET/CT to detect significant prostate cancer and comparison with ^{18}FEC PET/CT. Oncotarget 2017;8:111073–83. https://doi.org/10.18632/oncotarget.22441.
[16] Zhang J, Shao S, Wu P, et al. Diagnostic performance of ^{68}Ga-PSMA PET/CT in the detection of prostate cancer prior to initial biopsy: comparison with cancer-predicting nomograms. Eur J Nucl Med Mol Imaging 2019;46:908–20. https://doi.org/10.1007/s00259-018-4255-1.
[17] McInnes MDF, Moher D, Thombs BD, et al. Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy studies: the PRISMA-DTA statement. JAMA 2018;319:388–96. https://doi.org/10.1001/jama.2017.19163.
[18] Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529–36. https://doi.org/10.7326/0003-4819-155-8-201110180-00009.
[19] Emmett L, Buteau J, Papa N, et al. The additive diagnostic value of prostate-specific membrane antigen positron emission tomography computed tomography to multiparametric magnetic resonance imaging triage in the diagnosis of prostate cancer (PRIMARY): a prospective multicentre study. Eur Urol 2021;80:682–9. https://doi.org/10.1016/j.eururo.2021.08.002.
[20] Ferraro DA, Becker AS, Kranzbühler B, et al. Diagnostic performance of ^{68}Ga-PSMA-11 PET/MRI-guided biopsy in patients with suspected prostate cancer: a prospective single-center study. Eur J Nucl Med Mol Imaging 2021;48:3315–24. https://doi.org/10.1007/s00259-021-05261-y.
[21] Liu C, Liu T, Zhang Z, et al. ^{68}Ga-PSMA PET/CT combined with PET/ultrasound-guided prostate biopsy can diagnose clinically significant prostate cancer in men with previous negative biopsy results. J Nucl Med 2020;61:1314–9. https://doi.org/10.2967/jnumed.119.235333.
[22] Margel D, Bernstine H, Groshar D, et al. Diagnostic performance of ^{68}Ga prostate-specific membrane antigen PET/MRI compared with multiparametric MRI for detecting clinically significant prostate cancer. Radiology 2021;301:379–86. https://doi.org/10.1148/radiol.2021204093.
[23] Metser U, Ortega C, Perlis N, et al. Detection of clinically significant prostate cancer with ^{18}F-DCFPyL PET/multiparametric MR. Eur J Nucl Med Mol Imaging 2021;48:3702–11. https://doi.org/10.1007/s00259-021-05355-7.
[24] Eiber M, Weirich G, Holzapfel K, et al. Simultaneous ^{68}Ga-PSMA HBED-CC PET/MRI improves the localization of primary prostate cancer. Eur Urol 2016;70:829–36. https://doi.org/10.1016/j.eururo.2015.12.053.
[25] Zamboglou C, Drendel V, Jilg CA, et al. Comparison of ^{68}Ga-HBED-CC PSMA-PET/CT and multiparametric MRI for gross tumour volume detection in patients with primary prostate cancer based on slice by slice comparison with histopathology. Theranostics 2017;7:228–37. https://doi.org/10.7150/thno.16638.
[26] Evangelista L, Zattoni F, Cassarino G, et al. PET/MRI in prostate cancer: a systematic review and meta-analysis. Eur J Nucl Med Mol Imaging 2021;48:859–73. https://doi.org/10.1007/s00259-020-05025-0.
[27] Chen M, Zhang Q, Zhang C, et al. Combination of ^{68}Ga-PSMA PET/CT and multiparametric MRI Improves the detection of clinically significant prostate cancer: a lesion-by-lesion analysis. J Nucl Med 2019;60:944–9. https://doi.org/10.2967/jnumed.118.221010.
[28] Scheltema MJ, Chang JI, Stricker PD, et al. Diagnostic accuracy of ^{68}Ga-prostate-specific membrane antigen (PSMA) positron-emission tomography (PET) and multiparametric (mp)MRI to detect intermediate-grade intra-prostatic prostate cancer using whole-mount pathology: impact of the addition of ^{68}Ga-PSMA PET to mpMRI. BJU Int 2019;124(Suppl 1):42–9. https://doi.org/10.1111/bju.14794.
[29] Maggi M, Panebianco V, Mosca A, et al. Prostate Imaging Reporting and Data System 3 category cases at multiparametric magnetic resonance for prostate cancer: a systematic review and meta-analysis. Eur Urol Focus 2020;6:463–78. https://doi.org/10.1016/j.euf.2019.06.014.
[30] Anconina R, Hawsawy A, Ortega C, Veit-Haibach P, Ghai S, Metser U. Detection of clinically significant prostate cancer with ^{18}F-DCFPyL (PSMA) PET/MR compared to mpMR alone: preliminary results of a prospective trial. J Nucl Med 2019;60(Suppl 1):1574.
[31] Bodar YJL, Jansen BHE, van der Voorn JP, et al. Detection of prostate cancer with ^{18}F-DCFPyL PET/CT compared to final histopathology of radical prostatectomy specimens: is PSMA-targeted biopsy feasible? The DeTeCT trial. World J Urol 2021;39:2439–46. https://doi.org/10.1007/s00345-020-03490-8.
[32] Pizzuto DA, Müller J, Mühlematter U, et al. The central zone has increased ^{68}Ga-PSMA-11 uptake: “Mickey Mouse ears” can be hot on ^{68}Ga-PSMA-11 PET. Eur J Nucl Med Mol Imaging 2018;45:1335–43. https://doi.org/10.1007/s00259-018-3979-2.
[33] Minner S, Wittmer C, Graefen M, et al. High level PSMA expression is associated with early PSA recurrence in surgically treated prostate cancer. Prostate 2011;71:281–8. https://doi.org/10.1002/pros.21241.
[34] Bratan F, Niaf E, Melodelima C, et al. Influence of imaging and histological factors on prostate cancer detection and localisation on multiparametric MRI: a prospective study. Eur Radiol 2013;23:2019–29. https://doi.org/10.1007/s00330-013-2795-0.
[35] Stabile A, Giganti F, Kasivisvanathan V, et al. Factors influencing variability in the performance of multiparametric magnetic resonance imaging in detecting clinically significant prostate cancer: a systematic literature review. Eur Urol Oncol 2020;3:145–67. https://doi.org/10.1016/j.euo.2020.02.005.
[36] Lopci E, Lughezzani G, Castello A, et al. Prospective evaluation of ^{68}Ga-labeled prostate-specific membrane antigen ligand positron emission tomography/computed tomography in primary prostate cancer diagnosis. Eur Urol Focus 2021;7:764–71. https://doi.org/10.1016/j.euf.2020.03.004.
[37] Eiber M, Herrmann K, Calais J, et al. Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE): proposed miTNM classification for the interpretation of PSMA-ligand PET/CT. J Nucl Med 2018;59:469–78. https://doi.org/10.2967/jnumed.117.198119.