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Review – Prostate Cancer

Head-to-head Comparison of the Diagnostic Accuracy of Prostate-specific Membrane Antigen Positron Emission Tomography and Conventional Imaging Modalities for Initial Staging of Intermediate- to High-risk Prostate Cancer: A Systematic Review and Meta-analysis

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Abstract

Context: Whether prostate-specific membrane antigen positron emission tomography (PSMA-PET) should replace conventional imaging modalities (CIM) for initial staging of intermediate-high risk prostate cancer (PCa) requires definitive evidence on their relative diagnostic abilities.

Objective: To perform head-to-head comparisons of PSMA-PET and CIM including multiparametric magnetic resonance imaging (mpMRI), computed tomography (CT) and bone scan (BS) for upfront staging of tumour, nodal, and bone metastasis.

Evidence acquisition: A search of the PubMed, EMBASE, CENTRAL, and Scopus databases was conducted from inception to December 2021. Only studies in which patients underwent both PSMA-PET and CIM and imaging was referenced against histopathology or composite reference standards were included. Quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) checklist and its extension for comparative reviews (QUADAS-C). Pairwise comparisons of the sensitivity and specificity of PSMA-PET versus CIM were performed by adding imaging modality as a covariate to bivariate mixed-effects meta-regression models. The likelihood ratio test was applied to determine whether statistically significant differences existed.

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Positron emission tomography
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Evidence synthesis: A total of 31 studies (2431 patients) were included. PSMA-PET/MRI was more sensitive than mpMRI for detection of extra-prostatic extension (78.7% versus 52.9%) and seminal vesicle invasion (66.7% versus 51.0%). For nodal staging, PSMA-PET was more sensitive and specific than mpMRI (73.7% versus 38.9%, 97.5% versus 82.6%) and CT (73.2% versus 38.5%, 97.8% versus 83.6%). For bone metastasis staging, PSMA-PET was more sensitive and specific than BS with or without single-photon emission computerised tomography (98.0% versus 73.0%, 96.2% versus 79.1%). A time interval between imaging modalities >1 month was identified as a source of heterogeneity across all nodal staging analyses.
Conclusions: Direct comparisons revealed that PSMA-PET significantly outperforms CIM, which suggests that PSMA-PET should be used as a first-line approach for the initial staging of PCa.
Patient summary: We reviewed direct comparisons of the ability of a scan method called PSMA-PET (prostate-specific membrane antigen positron emission tomography) and current imaging methods to detect the spread of prostate cancer outside the prostate gland. We found that PSMA-PET is more accurate for detection of the spread of prostate cancer to adjacent tissue, nearby lymph nodes, and bones.

1. Introduction

Approximately 30% of patients diagnosed with prostate cancer (PCa) undergo definitive treatment with curative intent [1], but 20–50% experience biochemical recurrence (BCR) within 10 yr [2–4]. This is attributed in part to the limitations of current conventional imaging modalities (CIMs) such as computed tomography (CT), magnetic resonance imaging (MRI), and bone scan (BS) in the detection of locally advanced or metastatic PCa.

A superior imaging modality with reliable exclusion of metastases can crucially alter oncological outcomes for a patient with PCa, shift the cost-benefit analysis of definitive therapy, and potentially spare patients the morbidity of unnecessary treatments. The high target-to-background prostate-specific membrane antigen (PSMA) expression levels on PSMA positron emission tomography (PSMA-PET), by providing greater delineation of whole-body tumour burden [5], has the potential to overcome the inherent limitations of CIMs. However, PSMA-PET remains a second line to CIM as it is not without limitations: although multiple studies [6–9] have demonstrated high specificity, the sensitivity reported is variable. In addition, there are concerns about tracer uptake by nonprostatic malignancies and benign lesions [10], potentially resulting in overtreatment of patients with localised or oligometastatic disease [11]. Moreover, although data on cost savings are available [12], widespread use of PSMA-PET can be a resource-intensive endeavour. Thus, before PSMA-PET can be introduced into the primary staging pathway, definitive evidence on its relative diagnostic accuracy in comparison to CIM is necessary.

Previous reviews have indirectly compared PSMA-PET to CIM for the staging of nodal and bone metastases [13,14] but lacked high-quality direct comparative studies between the two approaches, resulting in weaker conclusions owing to the possibility of bias due to confounding. Therefore, the aim of this systematic review and meta-analysis (SRMA) was to assess all current literature on direct head-to-head comparisons between the two imaging approaches for primary staging of local invasion, lymph node involvement, and bone metastasis in PCa.

2. Evidence acquisition

This SRMA is reported in accordance with Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The population, index test, and target condition (PIT) approach was used to define study eligibility according to the Cochrane Handbook for Systemic Reviews of Diagnostic Test Accuracy (DTA) [15]. This review was registered in the international prospective register of systemic reviews (PROSPERO, ID CRD42022337624)

2.1. Search strategy and selection criteria

A systematic review of the literature was conducted using the PubMed, EMBASE, Cochrane library CENTRAL, and Scopus databases for articles published from inception to December 21, 2021. We combined search terms for the index imaging technique (“prostate specific membrane antigen” OR “PSMA” AND “positron emission tomography” OR “PET”) and disease (“prostate cancer” OR “prostate neoplasm” OR “prostate malignancy”; Supplementary Table 1) Bibliographies in the articles retrieved were screened for relevant studies not included in the database search. Two independent reviewers (K.M.C. and W.Z.S.) screened all titles and abstracts and also performed full-text review of potentially eligible studies. Discrepancies were resolved by a third reviewer (L.H.J.). Reasons for exclusion at this stage were recorded. Case reports, conference abstracts, and editorials were excluded as the study methodological quality could not be assessed.

Studies were included if: (1) primary staging was performed in patients with biopsy-proven PCa before definitive therapy; (2) both PSMA-PET/CT or PET/MRI and CIM were performed in the same patient population; (3) either histopathological results from radical prostatectomy (RP) and pelvic lymph node dissection (PLND), or a composite

reference standard (CRS) based on clinical parameters, imaging findings, or histopathological evidence available on follow-up were used as the reference; and (4) the number of true-positive, false-positive (FP), false-negative, and true-negative findings were reported or could be calculated for the construction of 2 × 2 tables.

2.2. Quality assessment

The methodological quality of all studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) checklist (Supplementary Appendix 1) and its extension for comparative reviews (QUADAS-C), consisting of four domains: patient selection, index test, reference standard, and flow and timing. Each domain was assessed for risk of bias (RoB) and the first three domains were evaluated for applicability concerns. For the patient selection domain, studies that did not specify consecutive or randomised patient recruitment were deemed at high RoB. For the index test domain, studies in which readers of PSMA-PET or CIM were not blinded to the corresponding results of the other imaging modality were deemed at high RoB. For the reference standard domain, since all studies referenced imaging findings against histopathology or CRS, as per our inclusion criteria, all studies were deemed at low RoB. Studies that did not report the time interval between PSMA-PET and CIM were deemed at high RoB for the flow and timing domain. When studies failed to provide sufficient information required for comprehensive assessment of any of the four domains, they were regarded as having unclear RoB. All papers were independently evaluated by two review authors (K.M.C. and W.Z.S.) and disagreements were resolved by a third author (L.H.J.).

2.3. Outcomes

The primary outcome of this analysis was direct pairwise comparison of the sensitivity and specificity of PSMA-PET and CIM in the primary staging of PCa. The unit of analysis was the patient and the difference in accuracy was expressed as absolute differences in sensitivity and specificity for the following comparisons: (1) PSMA-PET versus multiparametric MRI (mpMRI) for local tumour staging; (2) PSMA-PET versus mpMRI for nodal staging; (3) PSMA-PET versus abdominopelvic CT for nodal staging; and (4) PSMA-PET versus BS for bone metastasis staging. As a secondary outcome, a lesion level analysis was conducted for nodal staging comparing PSMA-PET and mpMRI.

2.4. Data extraction and analysis

From the studies included, the following information was extracted: (1) study population characteristics; (2) PSMA-PET and CIM parameters; (3) study design details, including blinding of PSMA-PET readers to the CIM results and vice versa; (4) how histopathological reference standards or CRS were defined and derived; and (5) the time interval between PSMA-PET and CIM.

The bivariate model [16] was used for meta-analysis to estimate summary sensitivities and specificities with their 95% confidence intervals (CIs). To perform pairwise comparisons between PSMA-PET and CIM, a covariate for imaging modality was added to the bivariate model (ie, bivariate meta-regression) to assess differences in sensitivity and specificity. The impact of imaging modality on the variability of sensitivity and specificity was also investigated, with separate variance terms included for each test where required. The statistical significance of differences in test performance was assessed using likelihood ratio tests comparing models with and without covariate terms for imaging modality [17]. The absolute differences in sensitivity and specificity between imaging modalities were also computed and their 95% CIs were computed using the delta method. Given the complexity of the bivariate model, in cases for which few studies were available, we simplified the model by removing the correlation parameter or assumed fixed effects for sensitivity and/or specificity [18].

Formal data analysis was undertaken with RStudio version 1.3 (RStudio, Boston, MA, USA). Bivariate meta-regression was carried out by fitting the generalised linear mixed model using the *glmer* function in the R package *lme4* [19]. Coupled forest plots and linked summary receiver operating characteristic (SROC) plots of paired data comparing PSMA-PET versus CIM were generated in Review Manager 5, with parameter estimates derived from the bivariate analysis.

When possible, heterogeneity was investigated visually on forest plots and in ROC space, and formally by adding covariate terms to a bivariate model for factors that could potentially influence the accuracy of the imaging modalities. These included: (1) study design (prospective vs retrospective); (2) PSMA-PET scanner (PET/CT vs PET/MRI); and (3) the time interval between PSMA-PET and CIM ($\leq$1 mo vs >1 mo). We used a cutoff of 1 mo on the basis of the spread of time intervals reported in the studies included, since no previous comparative study had established a significant threshold for the time interval between difference imaging modalities.

Post hoc sensitivity analyses were performed to examine the robustness of our findings by restricting the analyses to (1) studies that used PSMA-PET radioligands with US Food and Drug Administration (FD) approval (^{68}Ga-PSMA-11 and ^{18}FCDPyL); (2) studies that only used histopathology as the reference standard; and (3) studies that only included patients with intermediate to high risk PCa.

Assessment of publication bias via the Deeks test [18] was not undertaken because of the heterogeneity observed, as this approach has low power for detecting funnel plot asymmetry when there is heterogeneity [20].

3. Data synthesis

3.1. Study selection

The search identified 3473 titles after removal of duplicates, of which 3346 were excluded after title and/or abstract review. Figure 1 is flowchart illustrating the selection process. At the end of the process, 32 studies were included for the systematic review and meta-analysis.

3.2. Characteristics of included studies

In total, 31 studies were included. In 23 tumour and nodal staging studies, patients underwent RP and/or PLND, while

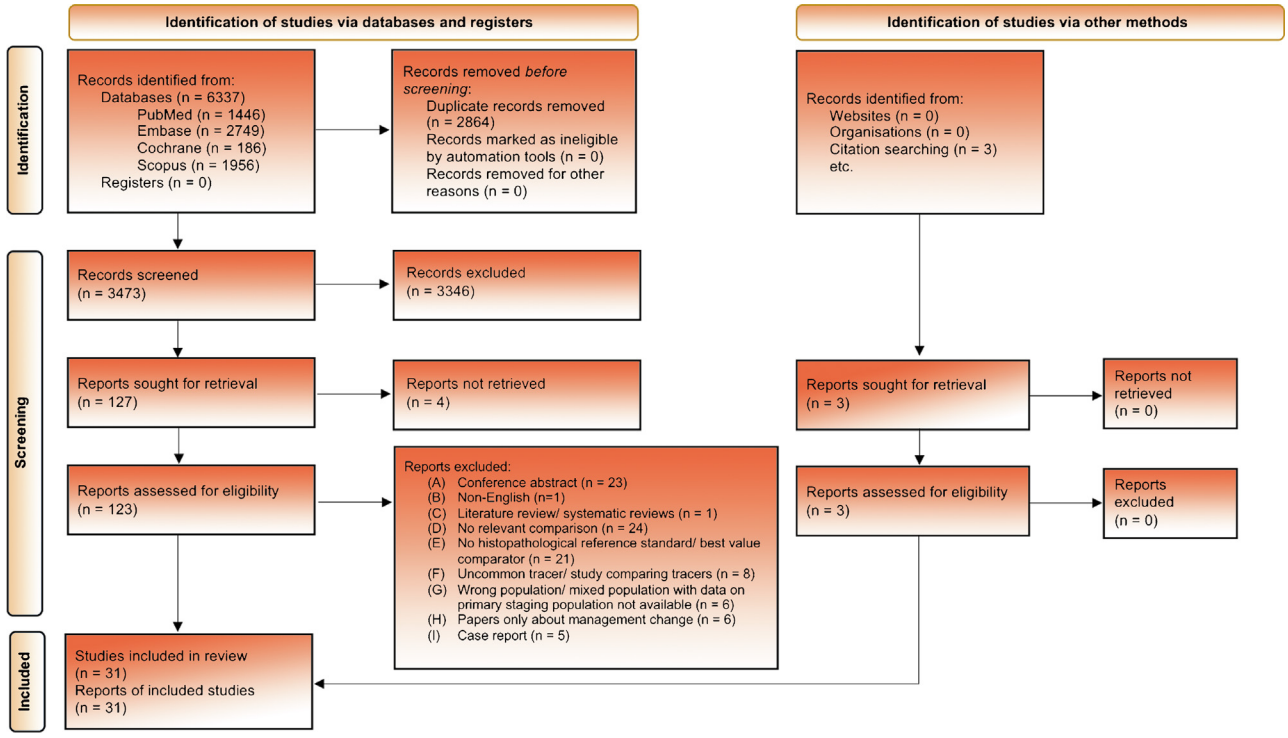

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the study selection process.

in three studies a combination of histopathology and a predefined CRS was used for reference. All six studies on bone metastasis staging used a CRS as the reference standard, of which two included histopathology, five used a combination of clinical, biochemical, and radiological findings, and one used only follow-up radiological findings to define the CRS. In 25, five, and two studies, patients underwent PSMA-PET/CT, PSMA-PET/MRI, or both, respectively. The majority of the studies used FDA-approved PSMA-PET radioligands (n = 27 ^{68}Ga-PSMA-11 and n = 2 ^{18}F-DCFPyL), while ^{18}F-PSMA-1007, ^{18}F-rhPSMA-17, and ^{68}Ga-PSMA-I/T were each used in one study. Most studies included only patients with intermediate- to high-risk PCa; cases with low-risk disease constituted only 2.2% (14/632) and 0.4% (8/1877) of patients in the tumour and nodal staging analyses, respectively. Table 1 summarises the study and patient characteristics [9,21–50]. Technical characteristics of the PSMA-PET imaging are summarised in Supplementary Table 2.

3.3. RoB and applicability concerns

Supplementary Table 3 and Supplementary Figure 1 summarise findings from the QUADAS-2 and QUADAS-C assessments. Methodological quality varied. Of the studies comparing PSMA-PET to mpMRI, CT, and BS, 38%, 17%, and 50%, respectively, were deemed at low RoB in all four QUADAS-2 domains. Of the studies comparing PSMA-PET to mpMRI, CT, and BS, 21%, 17%, and 50%, respectively, were deemed at low RoB in all four QUADAS-C domains. The main RoB arose from patient selection, as 13 (41%) retrospective studies did not use consecutive or random patient enrolment, and from flow and timing, as seven (22%) studies did not report the time interval between PSMA-PET and CIM. Applicability was generally considered a low concern across all studies for both index tests and the reference standard owing to well-defined patient cohorts and clear methodological interpretation of the imaging tests.

3.4. Local tumour staging

Supplementary Figures 2–5 show coupled forest plots for patient level analysis of PSMA-PET/MRI versus mpMRI for detection of extraprostatic extension (EPE; four studies, 210 patients) and seminal vesicle invasion (SVI; three studies, 175 patients) and for PSMA-PET/CT versus mpMRI for EPE (five studies, 228 patients) and SVI (eight studies, 518 patients).

Pairwise comparisons indicated that PSMA-PET/MRI was significantly more sensitive than mpMRI, with an absolute difference of 25.8 percentage points (95% CI 13.2–38.5; $p < 0.001$) for EPE detection and 15.7 percentage points (95% CI 7.6–23.8; $p = 0.02$) for SVI detection. By contrast, PSMA-PET/CT appeared to be less sensitive than mpMRI, with an absolute difference of −9.6 percentage points (95% CI −32.1 to 12.9; $p = 0.2$) for EPE detection and −16.9 percentage points (95% CI −33.5 to −0.3; $p = 0.1$) for SVI detection (Table 2).

3.5. Nodal staging

Figure 2 shows coupled forest plots for patient-level analysis of PSMA-PET versus mpMRI (19 studies, 1190 patients). A visual representation of the relationship between the sensitivities and specificities of mpMRI and PSMA-PET at the intrastudy level is provided in Figure 3 as a linked SROC

Table 1 – Characteristics of the studies included

Study	Study period	Type	Country	PSMA radioligand	PET scanner	CIM	MRI sequences	Ref.	TI (d)	Patients (*n*)	D'Amico risk class[a]	PSA (ng/ml)
Tumour staging: EPE detection												
Arslan 2020 [21]	2015–2020	R, SC	Turkey	^{68}Ga-PSMA-11	PET/CT	mpMRI	TSE, DWI	RP	NR	39	IR-HR	9.53 (2.38–59)[b]
Çelen 2020 [22]	–	P, SC	Turkey	^{68}Ga-PSMA-I/T	PET/CT	mpMRI	TSE, DWI	RP	Range: ≤42	30	LR-HR (2/30)	9.49 (1.3–27)[b]
Chen 2020 [23]	–	R, SC	China	^{68}Ga-PSMA-11	PET/CT PET/MRI	mpMRI	TSE, DWI, DCE	RP	NR	54	LR-HR (4/54)	13.3 (4.04–110)[b]
Koseoglu 2020 [24]	2015–2020	R, SC	Turkey	^{68}Ga-PSMA-11	PET/CT PET/MRI	mpMRI	–	RP	NR	81	LR-HR (5/81)	7 (2–8)[c]
Muehlematter 2019 [25]	2016–2018	R, SC	Switzerland	^{68}Ga-PSMA-11	PET/MRI	mpMRI	TSE, DWI	RP	90 ± 60[d]	40	IR-HR	8.12 ± 7.56[d]
Skawran 2022 [26]	2016–2019	R, SC	Switzerland	^{68}Ga-PSMA-11	PET/MRI	mpMRI	DWI	RP	120 (60–180)[e]	35	IR-HR	18.3 (7.1–18.8)[c]
Yilmaz 2019 [27]	2016– 2018	R, SC	Turkey	^{68}Ga-PSMA-11	PET/CT	mpMRI	TSE, DWI	RP	Range: ≤45	24	LR-HR (2/24)	12 (2.4–32) [b]
Tumour staging: SVI detection												
Berger 2018 [28]	2015–2017	R, SC	Australia	^{68}Ga-PSMA-11	PET/CT	mpMRI	–	RP	84 (49–105)[e]	48	IR-HR	10.6 ± 8.1[d]
Çelen 2020 [22]	–	P, SC	Turkey	^{68}Ga-PSMA-I/T	PET/CT	mpMRI	TSE, DWI	RP	Range: ≤42	30	LR-HR (2/30)	9.49 (1.3–27)[b]
Chen 2020 [23]	–	R, SC	China	^{68}Ga-PSMA-11	PET/CT PET/MRI	mpMRI	TSE, DWI, DCE	RP	NR	54	LR-HR (4/54)	13.3 (4.04–110)[b]
Koseoglu 2020 [24]	2015–2020	R, SC	Turkey	^{68}Ga-PSMA-11	PET/CT PET/MRI	mpMRI	–	RP	NR	81	LR-HR (5/81)	7 (2–8)[c]
Muehlematter 2019 [25]	2016–2018	R, SC	Switzerland	^{68}Ga-PSMA-11	PET/MRI	mpMRI	TSE, DWI	RP	90 ± 60[d]	40	IR-HR	8.12 ± 7.56[d]
Nandurkar 2018 [29]	2015–2016	R, SC	Australia	^{68}Ga-PSMA-11	PET/CT	mpMRI	–	RP	NR	112	IR-HR	–
Pallavi 2020 [30]	2016–2018	P, SC, NRT	India	^{68}Ga-PSMA-11	PET/CT	mpMRI	3D VISTA SPIR, BTFE, DWI	RP	Range: ≤10	29	IR-HR	Median: 12.4
van Leeuwen 2019 [31]	2015–2017	R, MC	Netherlands	^{68}Ga-PSMA-11	PET/CT	mpMRI	DWI, DCE	RP	NR	140	IR-HR	Median: 9.4
Yilmaz 2019 [27]	2016–2018	R, SC	Turkey	^{68}Ga-PSMA-11	PET/CT	mpMRI	TSE, DWI	RP	Range: ≤45	24	LR-HR (2/24)	12 (2.4–32)[b]
Nodal staging												
Hofman 2020 [32]	2017–2018	P, MC, RCT	Australia	^{68}Ga-PSMA-11	PET/CT	CT	–	PLND or CRS	Range: ≤14	295	HR	10.2 (6.6–17.1)[b]
Pienta 2021 [9]	2016–2018	P, MC, RCT	America, Canada	^{18}F-DCFPyL	PET/CT	CT	–	ePLND	Range: 28–42	252	HR	9.7 (1.2–125.3)[b]
Malaspina 2021 [33]	–	P, SC	Finland	^{18}F-PSMA-1007	PET/CT	CT, mpMRI	–	PLND or CRS	8 (1–44)[e]	79	IR-HR	12 (7–23) [c]
Park 2018 [34]	–	P, SC	America	^{68}Ga-PSMA-11	PET/MRI	CT, mpMRI	–	PLND Left: 5.5 ± 3.6[d] Right: 6 ± 3.8[d]	28 ± 3.8[d]	33	IR-HR	9.6 (3.7–34.5)[b]
Kroenke 2019 [35]	2017–2018	R, SC	Germany	^{18}F-rhPSMA-17	PET/CT PET/MRI	CT, mpMRI	–	ePLND 18 (8–53)[e]	NR	58	HR	12.2 (7.3–22.4)[c]
Maurer 2016 [36]	2012–2014	R, SC	Germany	^{68}Ga-PSMA-11	PETCT PET/MRI	CT, mpMRI	–	PLND	21 (11–39)[c]	140	IR-HR	11.55 (6.85–24.50)[c]
Berger 2018 [28]	2015–2017	R, SC	Australia	^{68}Ga-PSMA-11	PET/CT	mpMRI	–	PLND 12 (3–22)[e]	84 (49–105)[c]	48	IR-HR	10.6 ± 8.1
Çelen 2020 [22]	–	P, SC	Turkey	^{68}Ga-PSMA-I/T	PET/CT	mpMRI	TSE, DWI	PLND	Range: ≤42	30	LR-HR (2/30)	9.49 (1.3–27)[b]
Franklin 2021 [37]	2014–2019	P & R, SC	Australia	^{68}Ga-PSMA-11	PET/CT	mpMRI	DWI	PLND 16 (1–53)[e]	28 (0–650)[c]	233	IR-HR	7.4 (1.5–72)[b]
Frumer 2020 [38]	2016–2019	R, MC	Israel	^{68}Ga-PSMA-11	PET/CT	mpMRI	TSE, DWI	PLND 9 (6–14)[e]	PSMA-PET to PLND: 72.5 (42–95)[c] mpMRI to PLND: 112 (40–198)[c]	89	IR-HR	8.5 (5–15)[c]

Table 1 (*continued*)

Study	Study period	Type	Country	PSMA radioligand	PET scanner	CIM	MRI sequences	Ref.	TI (d)	Patients (*n*)	D'Amico risk class[a]	PSA (ng/ml)
Gupta 2017 [39]	2014–2015	R, SC	India	^{68}Ga-PSMA-11	PET/CT	mpMRI	SE, TSE, SPIR, DWI	ePLND Median 20	NR	12	HR	–
Kulkarni 2020 [40]	2016–2018	R, SC	India	^{68}Ga-PSMA-11	PET/CT	mpMRI	TSE, STIR, DWI	ePLND Mean 19	Range: ≤10	35	IR-HR	39.4 (4–90)[b]
Maurer 2016 [36]	2012–2014	R, SC	Germany	^{68}Ga-PSMA-11	PET/CT PET/MRI	mpMRI	–	PLND	21 (11–39)[c]	140	IR-HR	11.55 (6.85–24.50)[c]
Öbek 2017 [41]	2014–2015	R, MC	Turkey	^{68}Ga-PSMA-11	PET/CT	mpMRI	–	ePLND 18.5 (10–47)[e]	Mean: 26.8±16.7	51	IR-HR	26.5 ± 21.4[d]
Pallavi 2020 [30]	2016–2018	P, SC, NRT	India	^{68}Ga-PSMA-11	PET/CT	mpMRI	3D VISTA SPIR, BTFE, DWI, m-Dixon	PLND	Range: ≤10	29	IR-HR	Median: 12.4
Petersen 2019 [42]	2015–2016	P, SC	Germany	^{68}Ga-PSMA-11	PET/CT	mpMRI	DWI, STIR	ePLND (mean 28)	Range: ≤5	20	IR-HR	12.5 (2.8–66)[b]
Skawran 2022 [26]	2016–2019	R, SC	Switzerland	^{68}Ga-PSMA-11	PET/MRI	mpMRI	DWI	PLND	120 (60–180)[e]	35	LR-HR (2/24)	18.3 (7.1–18.8)[c]
Szigeti 2021 [43]	2017–2020	P, SC, NRT	Austria	^{68}Ga-PSMA-11	PET/CT	mpMRI	DWI	ePLND Mean 15	2 (0–16)[e]	81	IR-HR	15.4 (4.1–94)[b]
Van Damme 2021 [44]	2016–2019	R, SC	Belgium	^{68}Ga-PSMA-11	–	mpMRI	3D TSE, STIR, DWI	PLND or CRS	8 (15)[c]	81	HR	12.29 (7.93–29)[c]
van Leeuwen 2019 [31]	2015–2017	R, MC	Netherlands	^{68}Ga-PSMA-11	PET/CT	mpMRI	DWI, DCE	ePLND 16 (12–21)[c]	NR	140	IR-HR	Median: 9.4
Yilmaz 2019 [27]	2016–2018	R, SC	Turkey	^{68}Ga-PSMA-11	PET/CT	mpMRI	TSE, DWI	PLND	NR	24	LR-HR (2/24)	12 (2.4–32)[b]
Zhang 2017 [45]	2017	R, SC	China	^{68}Ga-PSMA-11	PET/CT	mpMRI	TSE, DWI	PLND Mean 15	Range: ≤120	42	IR-HR	52.31 (7.2–348)[b]
Bone metastasis staging												
Hofman 2020 [32]	2017–2018	P, MC, RCT	Australia	^{68}Ga-PSMA-11	PET/CT	BS + SPECT	–	CRS: Hx, CLx, BCx	Range: ≤14	295	HR	10.2 (6.6–17.1)[b]
Janssen 2018 [46]	2013–2017	R, SC	Germany	^{68}Ga-PSMA-11	PET/CT	BS + SPECT or SPECT/CT	–	CRS: CLx, BCx, RDx	23.5 (1–77)[e]	54	NR	38.4 ± 77.9[d]
Lengana 2018 [47]	–	P, SC	South Africa	^{68}Ga-PSMA-11	PET/CT	BS + SPECT	–	CRS: Hx, CLx, BCx, RDx	NR	25	LR-HR (2/25)	<10: 13.3% 10–20: 11.5% >20: 75.2%
Pyka 2016 [48]	2012–2015	R, SC	Germany	^{68}Ga-PSMA-11	PET/CT PET/MRI	BS + SPECT	–	CRS: CLx, BCx, RDx	20 (0–90)[e]	37	NR	43.5 (2.7–500)[b]
Simsek 2020 [49]	2015–2019	R, SC	Turkey	^{68}Ga-PSMA-11	PET/CT	BS + SPECT/CT	–	CRS: CLx, BCx, RDx	Range: ≤28	77	LR-HR (14/138)	18.3 (0.3–853)[b]
Zacho 2020 [50]	2015–2018	R, SC	Denmark	^{68}Ga-PSMA-11	PET/CT	BS	–	CRS: RDx	22 (6–80)[e]	105	IR-HR	34.5 (1.7–276)[b]

CIM = conventional imaging modality; Ref. = reference standard (numbers indicate the number of pelvic lymph nodes removed for PLND/ePLND); RP = radical prostatectomy; CRS = composite reference standard; CLx = clinical; BCx = biochemical; Hx = histopathology; RDx = radiological; TI = time interval between PSMA-PET and CIM; R = Retrospective; P = Prospective; SC = single-centre; MC = multicentre; RCT = randomised controlled trial; NRT = nonrandomised trial; PET = positron emission tomography; CT = computed tomography; mpMRI: multiparametric magnetic resonance imaging; DWI = diffusion-weighted Imaging; DCE = dynamic contrast enhancement; HASTE = half-Fourier single-shot turbo-spin Echo; STIR = short-tau inversion recovery; VIBE = volumetric interpolated breath-hold examination; TSE = turbo spin echo; VISTA = volume isotropic turbo spin echo acquisition; SPIR = spectral presaturation with inversion recovery; BTFE = balanced turbo field echo; SE = spin echo; FSE = fast spin echo; PLND = pelvic lymph node dissection; ePLND = extended PLND; IQR = Interquartile range; SD = Standard Deviation, BS = Bone Scan; SPECT = Single-photon emission computed tomography; PSA = prostate-specific antigen; NR = not reported; LR = low risk; IR = intermediate risk; HR = high risk; EPE = extraprostatic extension; SVI = seminal vesicle invasion.

[a] Numbers in parentheses denote the number of LR patients over the total number of patients if the cohort includes LR patients.

[b] Mean (range).

[c] Median (interquartile range).

[d] Mean ± standard deviation.

[e] Median (range).

Table 2 – PSMA-PET/MRI versus MRI and PSMA-PET/CT versus MRI for detection of ECE and SVI

	PSMA-PET/MRI versus mpMRI		PSMA-PET/CT versus mpMRI	
	PSMA-PET/MRI	mpMRI	PSMA-PET/CT	mpMRI
EPE detection				
Sensitivity, % (95%CI)	78.7 (69.3–85.8)	52.9 (43.3–62.3)	51.5 (32.7–69.9)	61.0 (47.1–73.3)
Absolute difference (95% CI)	25.8 (13.2–38.5); $p < 0.001$[a]		−9.6 (−32.1 to 12.9); $p = 0.2$[a]	
Specificity, % (95% CI)	82.2 (71.3–89.5)	86.2 (76.2, 92.4)	81.1 (62.9–91.6)	85.8 (75.0–92.4)
Absolute difference (95% CI)	−4.0 (−13.7 to 5.7); $p = 0.4$[a]		−4.7 (−21.5 to 12.1); $p = 0.2$[a]	
SVI detection				
Sensitivity, % (95%CI)	66.7 (48.4–88.0)	51.0 (33.2–68.8)	44.9 (26.4–65.0)	61.8 (43.8–77.0)
Absolute difference (95% CI)	15.7 (7.6–23.8); $p = 0.02$[a]		−16.9 (−33.5 to −0.3); $p = 0.1$[a]	
Specificity, % (95% CI)	92.4 (86.8–95.7)	96.6 (92.0–98.6)	93.1 (87.4–96.3)	95.9 (92.4–97.8)
Absolute difference (95% CI)	−4.3 (−9.6 to 11.1); $p = 0.1$[a]		−2.8 (−7.8 to 2.2); $p = 0.09$[a]	

CI = confidence interval; CT = computed tomography; EPE = extraprostatic extension; mpMRI = multiparametric magnetic resonance imaging; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; SVI = seminal vesicle invasion.
[a] Likelihood ratio test.

plot, with lines connecting paired results from the same study and summary estimates of sensitivity and specificity of PSMA-PET and mpMRI derived from meta-analyses. Bivariate meta-regression revealed that PSMA-PET was significantly more sensitive and specific than mpMRI by absolute differences of 34.8 percentage points (95% CI 16.4–53.3; $p < 0.001$) and 15.0 percentage points (95% CI 6.7–23.2; $p < 0.001$), respectively (Table 3). Substantial heterogeneity was observed, as evidenced by the extent of the 95% prediction region around the summary points on the SROC plot (Fig. 4).

PSMA-PET was also significantly more sensitive and specific than CT (six studies, 687 patients) by larger absolute differences of 34.7 percentage points (95% CI 21.1–48.3; $p < 0.001$) and 14.1 percentage points (95% CI 5.4–22.8; $p < 0.001$), respectively (Table 3, Supplementary Figures 6 and 7).

PSMA-PET was also significantly more sensitive than mpMRI (Table 3) in lesion-level analyses (seven studies, 329 patients) comparing PSMA-PET and mpMRI (Supplementary Figures 8 and 9).

3.6. Bone staging

The sensitivities and specificities of PSMA-PET versus BS in the patient analysis (six studies, 541 patients) were 98.0% (95% CI 88.0–99.7) versus 73.0% (95% CI 63.6–80.7), and 96.2% (95% CI 90.9–98.5) versus 79.1% (95% CI 72.3–84.4), respectively. Meta-regression revealed that PSMA-PET was significantly more sensitive and specific than BS by absolute differences of 24.8 percentage points (95% CI 15.3–34.2; $p < 0.001$) and 17.1 percentage points (95% CI 9.7–22.2; $p < 0.001$), respectively (Supplementary Figures 10 and 11).

3.7. Heterogeneity and sensitivity analyses

Across all analyses, significant heterogeneity was observed, as evidenced by the extent of the 95% prediction regions in Figure 4 and Supplementary Figures 7, 9, and 11. PET scanner was a source of heterogeneity for the tumour staging analyses and formal comparisons were thus undertaken separately for PSMA-PET/CT and PSMA-PET/MRI (Supplementary Table 4.3). Time interval was a significant source of heterogeneity for PSMA-PET and CIM sensitivity and specificity across the nodal staging analyses: the absolute differences between PSMA-PET and mpMRI sensitivities and specificities were larger and smaller respectively in studies with an interval of $\leq$1 mo between the different imaging modalities (Supplementary Table 4.1). Heterogeneity decreased for both PSMA-PET and mpMRI sensitivities and specificities after exclusion of studies with large time intervals. This is illustrated by the difference in sizes of the 95% prediction regions in Figure 4 and Supplementary Table 4.1.

Supplementary Table 5 summarises the sensitivity analyses undertaken: The direction and statistical significance of differences in sensitivity and specificity, as well as estimates of PSMA-PET and CIM sensitivities and specificities, remained consistent with those from the primary analyses.

3.8. Discussion

The excellent diagnostic capabilities of PSMA-PET are well established. However, whether PSMA-PET should be offered to all patients with intermediate- to high-risk PCa for primary staging and replace CIM as the new standard of care is a question of whether there is a significant difference between the diagnostic capabilities of PSMA-PET and CIM. While we await longitudinal data on patient outcomes, this SRMA has employed direct comparison to provide definitive evidence on the relative diagnostic abilities of PSMA-PET and all CIMs (mpMRI, CT, and BS) across tumour nodal and bone metastasis staging in PCa.

Previous indirect comparisons between PSMA-PET and CIM primarily examined retrospective studies that report the diagnostic accuracy of each imaging modality separately [13,51]. Guidelines on diagnostic test accuracy (DTA) reviews have recommended that conclusions from indirect comparisons should be interpreted with caution owing to the potential for bias from confounding [18,52]. Comparing studies on CIM alone to those on PSMA-PET alone, for which patient selection is unspecified, or in the context of inconclusive CIM findings, may result in unfair comparison. Following the emergence of studies performing PSMA-PET and CIM in the same patient cohorts, using either

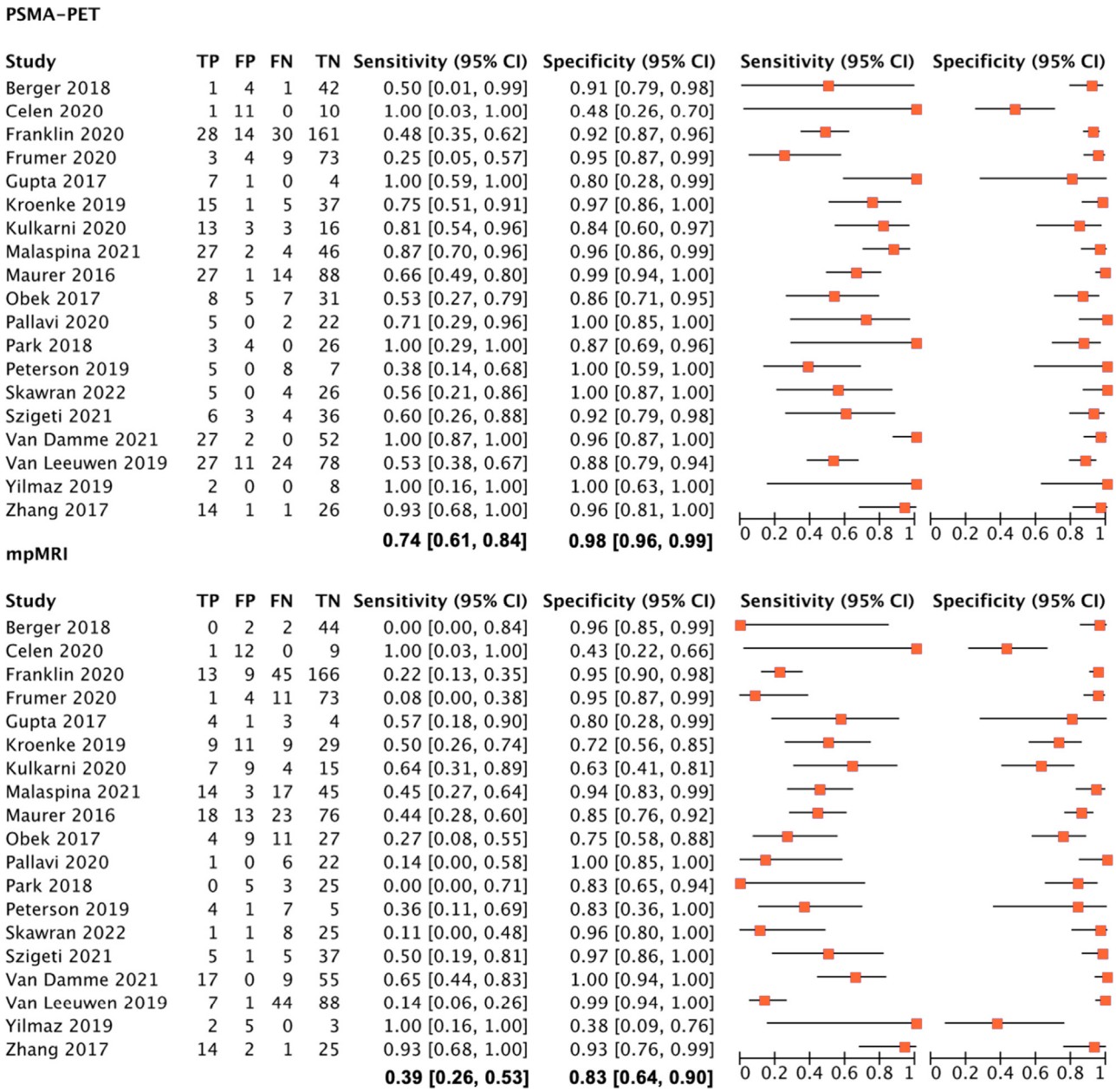

Fig. 2 – Forest plot of estimates of the sensitivity and specificity of prostate-specific membrane antigen positron emission tomography (PSMA-PET) and multiparametric magnetic resonance imaging (mpMRI) for detection of pelvic lymph node metastasis (patient-level analysis).CI = confidence interval; FN = false negative; FP = false positive; TN = true negative; TP = true positive.

histopathology or a CRS as the reference, this SRMA presents a head-to-head comparison of PSMA-PET and CIM.

For local staging of PCa, we found that PSMA-PET/MRI was more sensitive than mpMRI in EPE and SVI detection, while PSMA-PET/CT was less sensitive than mpMRI in SVI detection. While Woo et al. [53] observed that PSMA-PET/MRI was more sensitive than PSMA-PET/CT in EPE detection (87% vs 60%), how PSMA-PET performed with respect to the current standard of mpMRI remained unanswered. The inferiority of PSMA-PET/CT could be attributed to poorer tracer uptake by primary tumours [54] and variations in bladder volume, which can confound accurate detection of SVI [27]. This implies that in tumour staging where accurate definition of local tumour extent is highly dependent on visualisation of anatomic detail, the spatial resolution from mpMRI cannot be replaced, but can be enhanced by the avidity for small lesions accorded by PSMA-PET.

Summary findings suggest that PSMA-PET outperforms both CT and mpMRI in nodal staging. This comparison of PSMA-PET and mpMRI from 13 retrospective and six prospective studies is the largest yet and crucially confirms that PSMA-PET is more specific than mpMRI. While previous reviews had observed limited differences (Wu et al. [13]: 94% vs 92%; Wang et al. [66]: 92% vs 92%), our direct comparison showed that PSMA-PET was significantly more specific by 15.0 percentage points (95% CI 6.7–23.2; $p < 0.001$). The superiority of PSMA-PET to CIM can be attributed to differences in defining lymph node invasion

Table 3 – Patient-level and lesion-level comparison of PSMA-PET/MRI versus mpMRI and CT for nodal staging

	PSMA-PET versus mpMRI		PSMA-PET versus CT	
	PSMA-PET	mpMRI	PSMA-PET	CT
Patient-level analysis				
Sensitivity, % (95%CI)	73.7 (60.6–83.7)	38.9 (26.3–53.0)	73.2 (56.4–85.2)	38.5 (31.9–45.5)
Absolute difference (95% CI)	34.8 (16.4–53.3); $p < 0.001$[a]		34.7 (21.1–48.3); $p < 0.001$	
Specificity, % (95% CI)	97.5 (95.7–98.9)	82.6 (63.8–90.3)	97.8 (96.0–98.8)	83.6 (73.3–90.4)
Absolute difference (95% CI)	15.0 (6.7–23.2); $p < 0.001$[a]		14.1 (5.4–22.8); $p < 0.001$[a]	
Lesion-level analysis				
Sensitivity, % (95%CI)	74.8 (49.2–90.1)	32.2 (11.2–64.2)	–	–
Absolute difference (95% CI)	42.6 (69.0–78.3); $p < 0.001$[a]		–	
Specificity, % (95% CI)	99.2 (98.5–99.6)	98.6 (97.4–99.3)	–	–
Absolute difference (95% CI)	0.6 (−0.05 to 1.4); $p = 0.08$[a]		–	

CI = confidence interval; mpMRI = multiparametric magnetic resonance imaging; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.
[a] Likelihood ratio test.

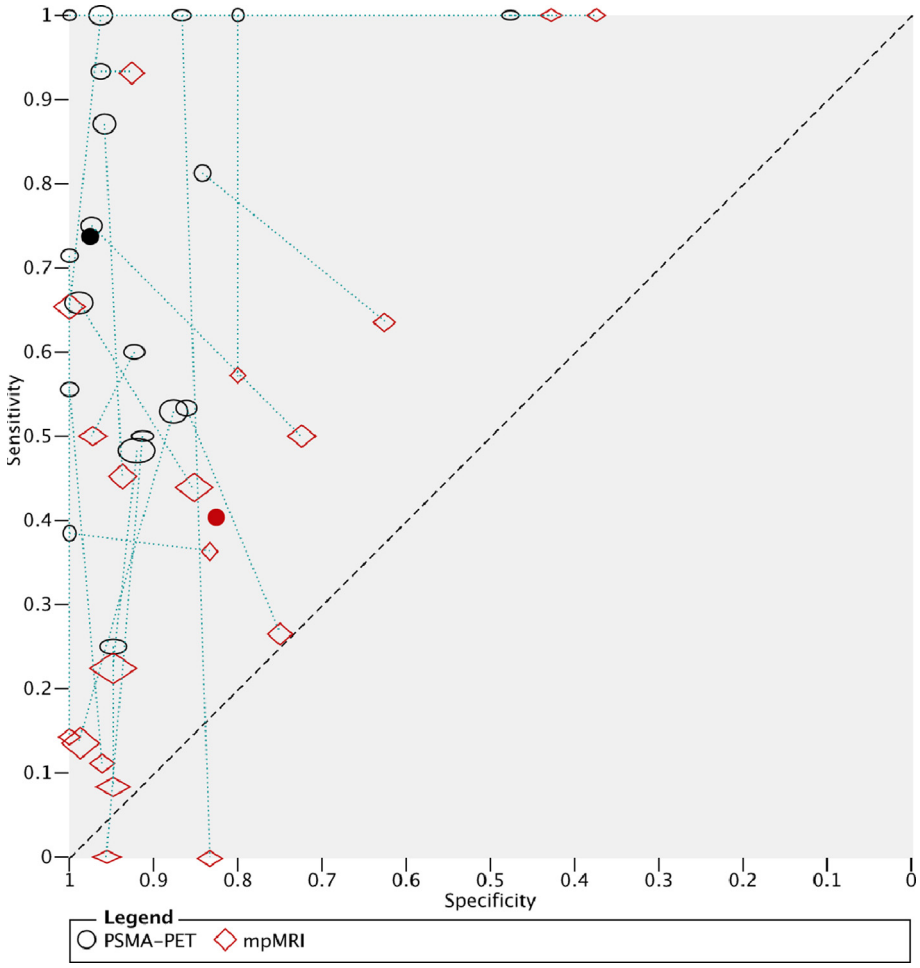

Fig. 3 – Linked summary receiver operating characteristic plot of prostate-specific membrane antigen positron emission tomography (PSMA-PET) versus multiparametric magnetic resonance imaging (mpMRI) for detection of pelvic lymph node metastasis (patient-level analysis) with pairwise analyses. Hollow symbols (circles and diamonds) represent study estimates for each test and are scaled by the sample size for the group with and without the target condition to reflect the precision of the sensitivity and specificity estimates. Solid symbols represent the summary estimates of sensitivity and specificity (summary point) for each test. The green dotted lines connect the pair of PSMA-PET and mpMRI estimates obtained from the same studies and is a visual representation of the pairwise analysis undertaken.

(LNI). While LNI on CIM depends on size (≥10 mm) or the presence of suspicious features such as fatty hilum invasion [31], radiotracer uptake on PSMA-PET relative to the background signal identifies LNI regardless of node size. This difference translated to higher detection rates for micronodal metastases [42,45,55] and lower rates of equivocal findings [32]. Higher rates of inter-reader agreement were also observed for PSMA-PET (0.78–0.92) than for CIM (0.40–

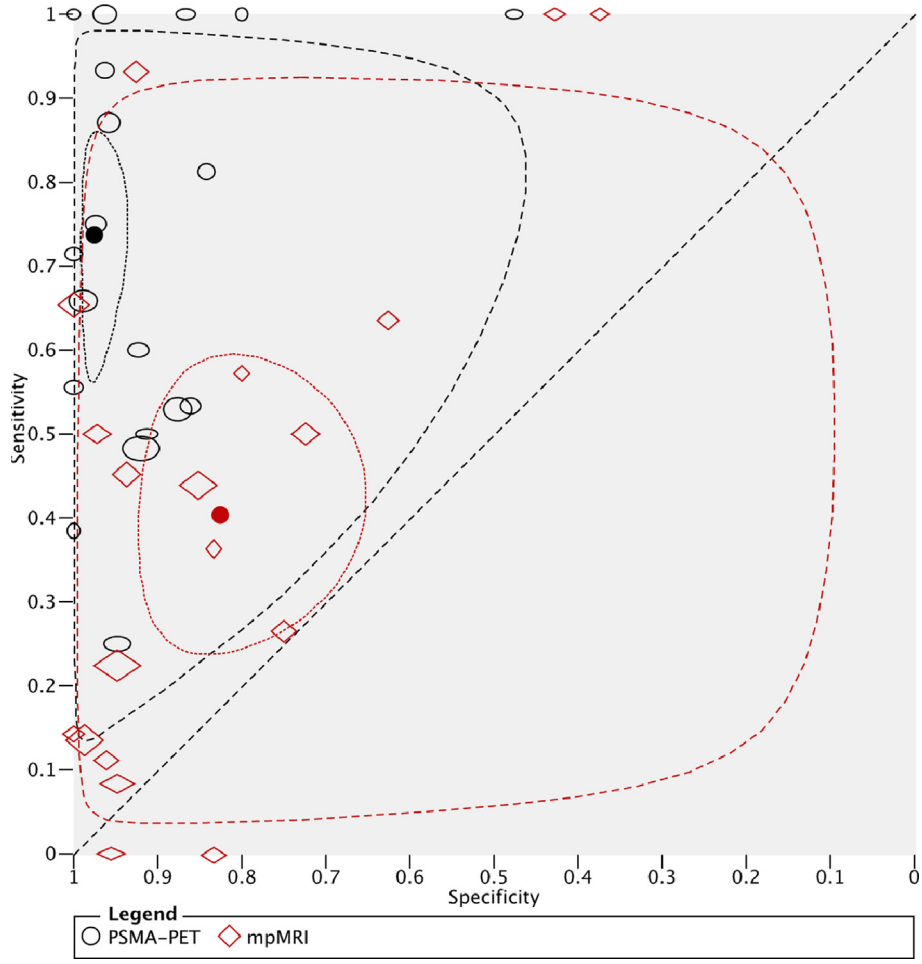

Fig. 4 – Summary receiver operating characteristic plot of prostate-specific membrane antigen positron emission tomography (PSMA-PET) versus multiparametric magnetic resonance imaging (mpMRI) for detection of pelvic lymph node metastasis (patient-level analysis) with 95% confidence regions and 95% prediction regions. Hollow symbols (circles and diamonds) represent study estimates for each test and are scaled by the sample size for the group with and without the target condition to reflect the precision of the sensitivity and specificity estimates. Solid symbols represent the summary estimates of sensitivity and specificity (summary point) for each test. The red/black dotted lines around each summary point represent the 95% confidence region, and the red/black dashed lines represent the 95% prediction region. The 95% confidence regions illustrate the uncertainty in the summary estimates. The 95% prediction regions are regions for which there is 95% certainty that the results of a future study will lie within the region, and illustrate the extent of heterogeneity.

0.55) across four studies [9,25,26,33], among which three based PSMA-PET reporting on the Molecular Imaging Reporting and Data Systems (MI-RADS) 5-point scale. The high interobserver agreement observed for PSMA-PET is concordant with a recent SRMA by Chavoshi et al. [56], highlighting the importance of standardised structured reporting guidelines for PCa metastases that are otherwise not established for morphological imaging. The ability to rely on target expression for quantitative imaging and for subselection of lesions by target definitions [57,58] contributes to minimisation of potential bias, decreases inter-reader variability, and enhances communication.

For bone metastasis staging, PSMA-PET had significantly higher sensitivity and specificity in comparison to BS with and without single-photon emission CT enhancement. Our results confirm the ability of PSMA-PET to overcome the intrinsic limitation of BS in identifying marrow-based or lytic skeletal metastases [59], thereby increasing sensitivity[47,50]. The resultant stage migration between localised, low- and high-volume metastatic disease has been shown to subsequently affect management [60,61]. Regarding concerns about the risk of overtreating FP lesions detected via PSMA-PET [62], our head-to-head comparison observed lower FP rates for PSMA-PET as compared to BS (0-11.8% vs 16.0-34.8%). This suggests that PSMA-PET can potentially lower over-treatment risks when performed in place of BS. However, it must be said that all comparative studies on bone metastasis staging in this review used PSMA-PET with ^{68}Ga-PSMA-11, while higher FP rates have been observed with the ^{18}F-PSMA tracers.

The strength of our study lies in more representative and reliable head-to-head comparisons of PSMA-PET and CIM, bolstered by the inclusion of many high-quality prospective studies. Empirical evidence [63] suggests that because of methodological differences, direct comparisons often yield significantly different summary estimates from indirect comparisons, and thus remain the preferred gold-standard methodology for DTA reviews. Besides differences in pooled values observed in our study in comparison to previous indirect reviews, the time interval between imaging modal-

ities was identified as be a significant source of heterogeneity. This confirms the need for evaluation of different imaging modalities within the same patient cohort given that disease status can change with time. The reliability of our conclusions is further strengthened by the use of likelihood ratio tests to statistically assess for true differences in pooled sensitivity and specificity values, as opposed to observatory comparisons of pooled values undertaken in previous reviews. This accounts for different variances in random effects known to exist when comparing different index tests [18]. In addition, our SRMA is the first to draw conclusions about the relative diagnostic accuracies of PSMA-PET/MRI in comparison to mpMRI for tumour staging, and to CT for nodal staging.

Although we can reliably conclude that PSMA-PET has superior diagnostic capability over CIM, whether this translates to an improvement in clinical outcomes is unknown. While Hofman et al. [32] found that PSMA-PET leads to significant rates of change in management in comparison to CIM, ongoing prospective trials [64] investigating the differential clinical impact of PSMA-PET and CIM, and further studies on consequent longitudinal oncological outcomes are necessary. Particularly of note would be the clinical impact of PSMA-PET in detection of micro-metastasis: although there is evidence suggesting that micrometastasis predicts BCR in patients with otherwise localised PCa, clinical outcome data for patients with CIM-occult metastasis and for those who start early intensified therapy [65] are still lacking and would be of great interest.

Our study has several limitations. First, our conclusions can only be applied to patients with intermediate to high risk PCa, as patients with low risk PCa constituted <2.2% of the study cohort. Second, preplanned subgroup analyses by risk group and PSA level could not be performed owing to the paucity of data stratified by these clinical parameters. Future studies reporting stratified data would allow for more comprehensive comparisons and thus better selection of patients likely to experience the maximal benefit from PSMA-PET. Third, some nodal staging studies did not report the number of pelvic lymph nodes removed during PLND or specify if a fixed template was used, which precludes more precise standardisation across studies. Fourth, differences existed in standards used for the interpretation of PSMA-PET which understandably exists given its relative novelty. We recommend that future studies report findings according to the European Association of Nuclear Medicine standardised reporting guidelines [57,58], to allow for greater clinical reproducibility. Finally, there was considerable heterogeneity between studies. Future comparative accuracy studies should recruit a consecutive or random sample of patients and ensure complete reporting, including the time interval between PSMA-PET and CIM.

4. Conclusions

This SRMA synthesising evidence from head-to-head comparisons of PSMA-PET and CIM in the same patient cohorts has shown PSMA-PET to be significantly more sensitive and specific than CT, mpMRI, and BS for staging of nodal and bone metastases, and more sensitive than mpMRI for local tumour staging when PSMA-PET/MRI was used. These results derived from direct comparisons provide definitive evidence on the relative diagnostic abilities of PSMA-PET and CIM, and suggest that replacing CIM with PSMA-PET as first-line imaging for primary PCa would result in significant improvements in diagnostic accuracy.

Author contributions: Kenneth Chen 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.

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Acquisition of data: Chow K.M., So W.Z., Yap D.W.T.
Analysis and interpretation of data: Chow K.M., Takwoingi. Y.
Drafting of the manuscript: Chow K.M., So W.Z., Lee H.J., Chen K.
Critical revision of the manuscript for important intellectual content: Lee H. J., Lee A. Yap D.W.T., Yakwoingi Y., Tay K.J., Tuan J., Thang S.P., Lam W., Yuen J., Lawrentschuk N., Hofman M.S., Murphy D.G., Chen K.
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