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Head-to-head comparison of the Diagnostic Accuracy of Prostate-specific Membrane Antigen Positron Emission Tomography (PSMA-PET) and Conventional Imaging Modalities for the Initial Staging of Intermediate-to-High Risk Prostate Cancer: A Systematic Review and Meta-Analysis

Chow Kit Mun[1], So Wei Zheng[1], Lee Han Jie[2], Alvin Lee[2], Dominic Wei Ting Yap[1], Yemisi Takwoingi[3], Tay Kae Jack[2], Jeffrey Tuan[4], Thang Sue Ping[5], Winnie Lam[5], John Yuen[2], Nathan Lawrentschuk[6,7], Michael S. Hofman[8], Declan Murphy[9], Kenneth Chen[2]

[1] YLL School of Medicine, National University of Singapore, Singapore
[2] Department of Urology, Singapore General Hospital, Singapore
[3] Institute of Applied Health Research, University of Birmingham, Birmingham, UK
[4] Division of Radiation Oncology, National Cancer Centre Singapore, Singapore
[5] Department of Nuclear Medicine, Singapore General Hospital, Singapore
[6] Department of Urology and Department of Surgery, Royal Melbourne Hospital, University of Melbourne, Australia.
[7] EJ Whitten Prostate Cancer Research Centre at Epworth, Melbourne, Australia.
[8] Prostate Cancer Theranostics and Imaging Centre of Excellence, Molecular Imaging and Therapeutic Nuclear Medicine, Peter MacCallum Cancer Centre, and Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia
[9] Department of Urology, Peter MacCallum Cancer Centre, Melbourne, Australia; Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia.

Corresponding author: Kenneth Chen
MBBS (S'pore), MRCS (Edin), MCI, DFD (CAW), FRCS (Glas), FAMS (Urol)
Department of Urology
31 Third Hospital Ave, Singapore 168753
Email: Kenneth.chen@singhealth.com.sg

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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 tumour, nodal and bone metastasis staging.

Evidence Acquisition: A search of PubMed, Embase, Central and Scopus databases, from inception to December 2021, was conducted. Only studies where patients underwent both PSMA-PET and CIM, and referenced imaging 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 between sensitivities and specificities of PSMA-PET and CIM were performed by adding imaging modality as a covariate to bivariate mixed-effects meta-regression models and whether statistically significant differences existed was assessed by likelihood ratio tests.

Evidence Synthesis: 32 studies (2431 patients) were included. PSMA-PET/MRI was more sensitive than mpMRI for extra-prostatic extension (78.7% versus 52.9%) and seminal vesicle invasion (66.7% versus 55.2%) detection. For nodal staging, PSMA-PET was more sensitive and specific than mpMRI (73.7% versus 38.9%, 93.6% versus 89.4%) and CT (73.2% versus 38.5%, 97.8% versus 83.6%). For bone metastasis staging, PSMA-PET was more sensitive and specific than bone scan with or without SPECT/CT (98.0% versus 73.0%, 93.6% versus 89.4%). Time interval between imaging modalities >1 month was found to be a source of heterogeneity across all nodal staging analyses.

Conclusion: Direct comparisons found PSMA-PET to significantly outperform CIM which suggests PSMA-PET should be used as first-line for the initial staging of PCa.

Patient summary: In this systematic-review and meta-analysis, we performed a direct comparison of the diagnostic abilities of prostate-specific membrane antigen positron emission tomography (PSMA-PET), an emerging radiological diagnostic tool, to current standard-of-care conventional imaging modalities (CIM) by synthesising evidence from studies where patients have undergone both PSMA-PET and CIM. We have demonstrated that compared to CIM, PSMA-PET can more accurately detect the spread of prostate cancer outside the prostate to adjacent tissue, nearby lymph nodes and to bony sites.

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 years [2-4]. This is attributed in part to limitations of current conventional imaging modalities (CIM) 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 crucially can alter a PCa patient's oncological outcomes, shift the cost-benefit analysis of definitive therapy and potentially spare patients the morbidity of unnecessary treatments. The high target-to-background expression levels on PSMA-PET which allows for greater delineation of whole-body tumour burden [5], suggests that it has the potential to overcome inherent limitations of CIM. PSMA-PET however remains second line to CIM as it is not without limitations: Though multiple studies[6-9] have demonstrated high specificity, reported sensitivity is variable. Additionally, there are concerns about tracer uptake by non-prostatic malignancies and benign lesions [10] potentially resulting in overtreatment of patients with localised or oligometastatic disease [11]. Moreover, though data on cost savings is available[12], its widespread use can be a resource-intensive endeavour. Thus, before it can be introduced into the primary staging pathway, definitive evidence on the relative diagnostic accuracy of PSMA-PET 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 both modalities, thus resulting in weaker conclusions due to the possibility of bias due to confounding. This systematic review and meta-analysis (SRMA) therefore aims to assess all current literature for direct head-to-head comparisons between both imaging modalities for primary staging of local invasion, lymph node involvement and bone metastasis of PCa.

EVIDENCE ACQUISITION

This SRMA was reported in accordance with the Cochrane and Preferred Reporting Items for SRMA (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)

SEARCH STRATEGY & SELECTION CRITERIA

A systematic review of the literature was conducted using the Pubmed, EMBASE, Cochrane's library CENTRAL and Scopus databases for articles published from inception to 21 December 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'). (see Supplementary Table 1) Bibliographies of retrieved studies 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 study methodological quality could not be assessed.

Studies were included if (1) primary staging was performed in patients with biopsy-proven PCa prior to 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, and (4) the number of true positive (TP), false positive (FP), false negative (FN) and true negatives (TN) were reported or could be calculated for the construction of 2x2 tables.

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) which consists 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. In the patient selection domain, studies that did not specify consecutive or randomised patient recruitment were deemed high RoB. For the index test domain, studies where readers of PSMA-PET or CIM were not blinded to the corresponding results of the other imaging modality were deemed high RoB. For the reference standard domain, since our inclusion criteria requires imaging findings to be verified against histopathology or CRS, all studies were deemed low RoB. Studies that did not report the time interval between PSMA-PET and CIM were deemed high RoB in 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 resolved by a third author (L.H.J)

OUTCOMES

The primary outcome of this analysis was a 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 and multiparametric MRI (mpMRI) for local tumour staging, (2) PSMA-PET and mpMRI for nodal staging, (3) PSMA-PET and abdominopelvic CT for nodal staging, and (4) PSMA-PET and BS for bone metastasis staging. Secondarily, a lesion-level analysis comparing PSMA-PET and mpMRI for nodal staging was conducted.

DATA EXTRACTION & ANALYSIS

From the included studies, the following information were extracted: (1) study population characteristics; (2) PSMA-PET and CIM parameters; (3) study design details including blinding of PSMA-PET readers to the results of CIM, 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 was used [16] for meta-analysis to estimate summary sensitivities and specificities with their 95% confidence intervals (CI). 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 were also investigated and 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, where 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, PBC, Boston, MA). Bivariate meta-regression was carried out by fitting the generalised linear mixed model (GLMM) 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 and CIM were plotted using 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 (≤1 months vs. >1 months). We used a cut-off of 1 month based on the spread of time intervals reported by included studies since no previous comparative study had established a significant threshold for 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 FDA approved PSMA-PET radioligands (^{68}Ga-PSMA-11 and ^{18}FCDPyL); (2) studies that only used histopathology as reference standards; and (3) studies that only included intermediate-high risk patients.

Assessment of publication bias by the Deeks test [20] was not undertaken due to observed heterogeneity beacuse the approach has low power for detecting funnel plot asymmetry when there is heterogeneity [21]

RESULTS

STUDY SELECTION

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

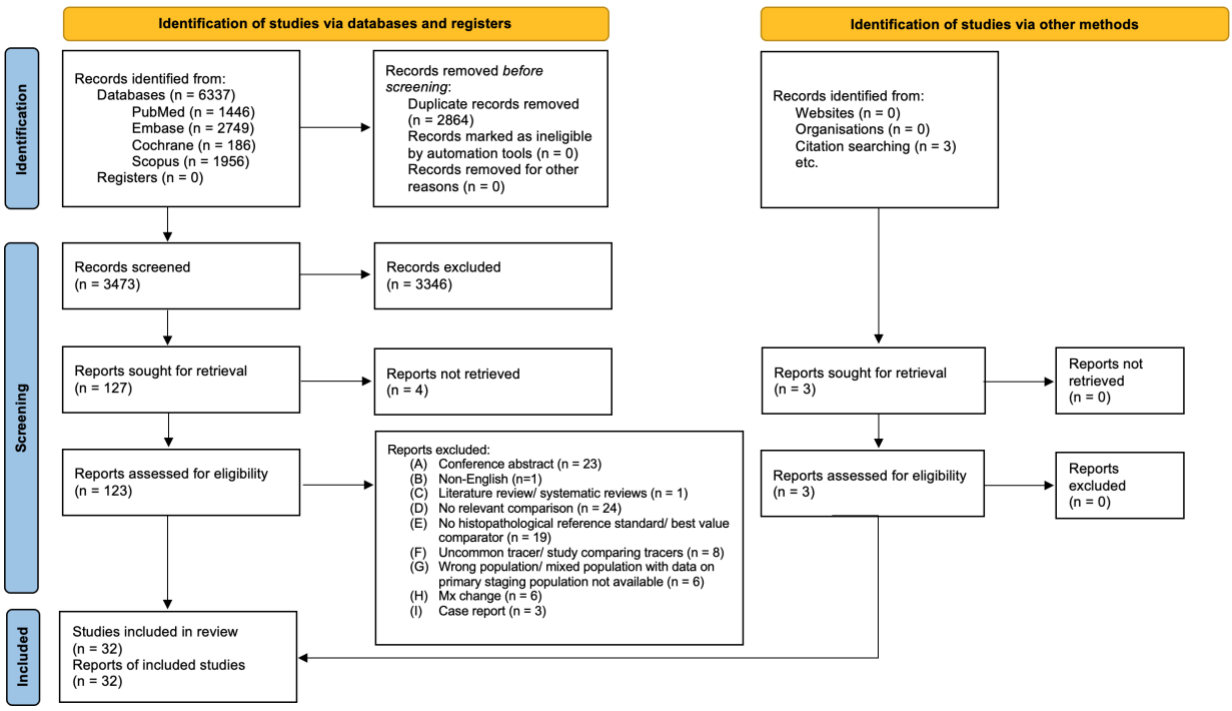


Figure 1. PRISMA flow diagram of study selection

CHARACTERISTICS OF INCLUDED STUDIES

In total 32 studies were included. In 23 tumour and nodal staging studies, patients underwent RP and/or PLND while in 3 studies a combination of histopathology and predefined CRS was used for reference. All 6 bone metastasis staging studies used CRS to define reference standards, of which 2 included histopathology, 5 used a combination of clinical, biochemical and radiological findings, and 1 used only follow-up radiological findings to define the CRS. In 25, 5 and 2 studies, patients underwent PSMA-PET/CT, PSMA-PET/MRI and both respectively. Majority of studies used FDA approved PSMA-PET radioligands ^{68}Ga-PSMA-11 (n=27) and ^{18}F-DCFPyL (n=2) while 3 used ^{18}F-PSMA-1007 (n=1), ^{18}F-rhPSMA-17 (n=1) and ^{68}Ga-PSMA-I/T (n=1). Most studies included only intermediate to high risk PCa patients with low risk patients constituting only 2.2% (14/632) and 0.4% (8/1877) of patients in the tumour and nodal staging analyses respectively. Table 1 summarises study and patient characteristics. Technical features of PSMA-PET are summarised in Supplementary Table 2

RISK OF BIAS & APPLICABILITY CONCERNS

Supplementary Table 3 and Supplementary Figures 1.1-1.6 summarises findings of the QUADAS-2 and QUADAS-C assessments. Methodological quality varied: 38%, 17% and 50% of studies comparing PSMA-PET to mpMRI, CT and BS were deemed low RoB in all four QUADAS-2 domains respectively. 21%, 17% and 50% of studies comparing PSMA-PET to mpMRI, CT and BS were deemed low RoB in all four QUADAS-C domains respectively. 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 7 (22%) studies did not report the time intervals between PSMA-PET and CIM. Applicability was generally considered as low concern across all studies for both index tests and reference standard, owing to well-defined patient cohorts and clear methodological interpretation of the imaging tests.

Author, year	Study Period	Study Type	Country	PSMA Radioligand	PSMA PET scanner	CIM	Sequence	Reference Standard*	Time Interval between PSMA-PET and CIM (days)	Total no. of patients	D'Amico Risk Classification**	Prostate Specific Antigen (PSA) values (ng/ml)
Tumour staging: EPE detection												
Arslan 2020 [22]	2015-2020	R, SC	Turkey	68Ga-PSMA-11	PET/CT	mpMRI	TSE, DWI	RP	Unreported	39	intermediate-high	Mean: 9.53 Range: 2.38-59
Celen 2020 [23]	-	P, SC	Turkey	68Ga-PSMA-I/T	PET/CT	mpMRI	TSE, DWI	RP	Range: ≤ 42	30	Low-high (2/30)	Mean: 9.49 Range: 1.3-27
Chen 2020 [24]	-	R, SC	China	68Ga-PSMA-11	PET/CT PET/MRI	mpMRI	TSE, DWI, DCE	RP	Unreported	54	Low-high (4/54)	Mean: 13.3 Range: 4.04-110
Koseoglu 2020 [25]	2015-2020	R, SC	Turkey	68Ga-PSMA-11	PET/CT PET/MRI	mpMRI	-	RP	Unreported	81	Low-high (5/81)	Median 7 IQR: 2-8
Muehlematter 2019 [26]	2016-2018	R, SC	Switzerland	68Ga-PSMA-11	PET/MRI	mpMRI	TSE, DWI	RP	Mean: 90±60	40	intermediate-high	8.12 ± 7.56
Skawran 2022 [27]	2016-2019	R, SC	Switzerland	68Ga-PSMA-11	PET/MRI	mpMRI	DWI	RP	Median: 120 Range: 60-180	35	intermediate-high	Median: 18.3 IQR: 7.1-18.8
Yilmaz 2019 [28]	2016-2018	R, SC	Turkey	68Ga-PSMA-11	PET/CT	mpMRI	TSE, DWI	RP	Range: ≤45	24	Low-high (2/24)	Mean: 12 Range: 2.4-32
Tumour staging: SVI detection												
Berger 2018 [29]	2015-2017	R, SC	Australia	68Ga-PSMA-11	PET/CT	mpMRI	-	RP	Median: 84 Range: 49-105	48	intermediate-high	10.6 ± 8.1
Celen 2020 [23]	-	P, SC	Turkey	68Ga-PSMA-I/T	PET/CT	mpMRI	TSE, DWI	RP	Range: ≤42	30	Low-high (2/30)	Mean: 9.49 Range: 1.3-27
Chen 2020 [24]	-	R, SC	China	68Ga-PSMA-11	PET/CT	mpMRI	TSE, DWI, DCE	RP	Unreported	54	Low-high (4/54)-	Mean: 13.3 Range: 4.04-110
Koseoglu 2020 [25]	2015-2020	R, SC	Turkey	68Ga-PSMA-11	PET/CT	mpMRI	-	RP	Unreported	81	Low-high (5/81)	Median 7 IQR: 2-8
Muehlematter 2019 [26]	2016-2018	R, SC	Switzerland	68Ga-PSMA-11	PET/MRI	mpMRI	TSE, DWI	RP	Mean: 90±60	40	intermediate-high	8.12 ± 7.56
Nandurkar 2018 [30]	2015-2016	R, SC	Australia	68Ga-PSMA-11	PET/CT	mpMRI	-	RP	Unreported	112	intermediate-high	-
Pallavi 2020 [31]	2016-2018	P, SC, NR	India	68Ga-PSMA-11	PET/CT	mpMRI	3D VISTA SPIR, BTFE, DWI	RP	Range: ≤10	29	intermediate-high	Median: 12.4
Van Leeuwen 2019 [32]	2015-2017	R, MC	Netherlands	68Ga-PSMA-11	PET/CT	mpMRI	DWI, DCE	RP	Unreported	140	intermediate-high	Median: 9.4
Yilmaz 2019 [28]	2016-2018	R, SC	Turkey	68Ga-PSMA-11	PET/CT	mpMRI	TSE, DWI	RP	Range: ≤45	24	low-high (2/24)	Mean: 12 Range: 2.4-32
Nodal staging												

Hofman 2020 [33]	2017-2018	P, MC, RCT	Australia	68Ga-PSMA-11	PET/CT	CT	-	PLND or CRS	Range: ≤14	295	high	Mean: 10.2 Range: 6.6-17.1
Pienta 2021 [9]	2016-2018	P, MC, RCT	America, Canada	18F-DCFPyL	PET/CT	CT	-	ePLND	Range: 28-42	252	high	Mean: 9.7 Range: 1.2-125.3
Malaspina 2021 [34]	-	P, SC	Finland	18F-PSMA-1007	PET/CT	CT, mpMRI	-	PLND or CRS	Median: 8 Range: 1-44	79	intermediate-high	Median: 12 IQR: 7-23
Park 2018 [35]	-	P, SC	America	68Ga-PSMA-11	PET/MRI	CT, mpMRI	-	PLND (Left: mean 5.5, SD ± 3.6 Right: mean 6, SD ± 3.8)	Mean: 28±3.8	33	intermediate-high	Mean: 9.6 Range: 3.7-34.5
Kroenke 2019 [36]	2017-2018	R, SC	Germany	18F-rhPSMA-17	PET/CT PET/MRI	CT, mpMRI	-	ePLND (Median 18, Range 8-53)	Unreported	58	high	Median: 12.2 IQR: 7.3-22.4
Maurer 2016 [37]	2012-2014	R, SC	Germany	68Ga-PSMA-11	PETCT PET/MRI	CT, mpMRI	-	PLND	Median: 21 IQR: 11-39	140	intermediate-high	Median: 11.55 IQR: 6.85-24.50
Berger 2018 [29]	2015-2017	R, SC	Australia	68Ga-PSMA-11	PET/CT	mpMRI	-	PLND (Median 12, Range 3-22)	Median: 84 IQR: 49-105	48	intermediate-high	10.6 ± 8.1
Celen 2020 [23]	-	P, SC	Turkey	68Ga-PSMA-I/T	PET/CT	mpMRI	TSE, DWI	PLND	Range: ≤42	30	Low-high (2/30)	Mean: 9.49 Range: 1.3-27
Franklin 2021 [38]	2014-2019	P & R, SC	Australia	68Ga-PSMA-11	PET/CT	mpMRI	DWI	PLND (Median 16, Range 1-53)	Median: 28 Range: 0-650	233	intermediate-high	Mean: 7.4 Range: 1.5-72
Frumer 2020 [39]	2016-2019	R, MC	Israel	68Ga-PSMA-11	PET/CT	mpMRI	TSE, DWI	PLND (Median 9, IQR 6-14)	PSMA-PET to PLND: Median: 72.5 IQR: 42-95 mpMRI to PLND: Median: 112 IQR: 40-198	89	intermediate-high	Median: 8.5 IQR: 5-15
Gupta 2017 [40]	2014-2015	R, SC	India	68Ga-PSMA-11	PET/CT	mpMRI	SE, TSE, SPIR, DWI	ePLND (Median 20)	Unreported	12	high	-
Kulkarni 2020 [41]	2016-2018	R, SC	India	68Ga-PSMA-11	PET/CT	mpMRI	TSE, STIR, DWI	ePLND (Mean 19)	Range: ≤10	35	intermediate-high	Mean: 39.4 Range: 4-90
Maurer 2016 [37]	2012-2014	R, SC	Germany	68Ga-PSMA-11	PETCT PET/MRI	mpMRI	-	PLND	Median: 21 IQR: 11-39	140	intermediate-high	Median: 11.55 IQR: 6.85-24.50
Obek 2017 [42]	2014-2015	R, MC	Turkey	68Ga-PSMA-11	PET/CT	mpMRI	-	ePLND (Median 18.5, Range 10-47)	Mean: 26.8±16.7	51	intermediate-high	26.5 ± 21.4

Pallavi 2020 [31]	2016-2018	P, SC, NR	India	68Ga-PSMA-11	PET/CT	mpMRI	3D VISTA SPIR, BTFE, DWI, m-Dixon	PLND	Range: ≤10	29	intermediate-high	Median: 12.4
Petersen 2019 [43]	2015-2016	P, SC	Germany	68Ga-PSMA-11	PET/CT	mpMRI	DWI, STIR,	ePLND (mean 28)	Range: ≤5	20	intermediate-high	Mean: 12.5 Range: 2.8-66
Skawran 2022 [27]	2016-2019	R, SC	Switzerland	68Ga-PSMA-11	PET/MRI	mpMRI	DWI	PLND	Median: 120 Range: 60-180	35	Low-high (2/24)	Median: 18.3 IQR: 7.1-18.8
Szigeti 2021 [44]	2017-2020	P, SC, NR	Austria	68Ga-PSMA-11	PET/CT	mpMRI	DWI	ePLND (Mean 15)	Median: 2 Range: 0-16	81	intermediate-high	Mean: 15.4 Range: 4.1-94
Van Damme 2021 [45]	2016-2019	R, SC	Belgium	68Ga-PSMA-11	-	mpMRI	3D TSE, STIR, DWI	PLND or CRS	Median: 8 IQR: 15	81	high	Median: 12.29 IQR: 7.93-29
Van Leeuwen 2019 [32]	2015-2017	R, MC	Netherlands	68Ga-PSMA-11	PET/CT	mpMRI	DWI, DCE	ePLND (Median 16, IQR 12-21)	Unreported	140	intermediate-high	Median: 9.4
Yilmaz 2019 [28]	2016-2018	R, SC	Turkey	68Ga-PSMA-11	PET/CT	mpMRI	TSE, DWI	PLND	Unreported	24	low-high (2/24)	Mean: 12 Range: 2.4-32
Zhang 2017 [46]	2017	R, SC	China	68Ga-PSMA-11	PET/CT	mpMRI	TSE, DWI	PLND (Mean 15)	Range: ≤120	42	intermediate-high	Mean: 52.31 Range: 7.2-348
Bone metastasis staging												
Hofman 2020 [33]	2017-2018	P, MC, RCT	Australia	68Ga-PSMA-11	PET/CT	BS + SPECT	-	CRS: Histopathology, Clinical, Biochemical	Range: ≤14	295	high	Mean: 10.2 Range: 6.6-17.1
Janssen 2018 [47]	2013-2017	R, SC	Germany	68Ga-PSMA-11	PET/CT	BS + SPECT or BS + SPECT/CT	-	CRS: Clinical, Biochemical, Radiological	Median: 23.5 Range: 1-77	54	unspecified	38.4 ± 77.9
Lengana 2018 [48]	-	P, SC	South Africa	68Ga-PSMA-11	PET/CT	BS + SPECT	-	CRS: Histopathology, Clinical, Biochemical, Radiological	Unreported	25	Low-high (2/25)	<10: 13.3% 10-20: 11.5% >20: 75.2%
Pyka 2016 [49]	2012-2015	R, SC	Germany	68Ga-PSMA-11	PET/CT PET/MRI	BS + SPECT	-	CRS: Clinical, Biochemical, Radiological	Median: 20 Range: 0-90	37	unspecified	Mean: 43.5 Range: 2.7-500
Simsek 2020 [50]	2015-2019	R, SC	Turkey	68Ga-PSMA-11	PET/CT	BS + SPECT/CT	-	CRS: Clinical Biochemical, Radiological	Range: ≤28	77	Low-high (14/138)	Mean: 18.3 Range: 0.3-853
Zacho 2020 [51]	2015-2018	R, SC	Denmark	68Ga-PSMA-11	PET/CT	BS	-	CRS: Radiological	Median: 22 Range: 6-80	105	intermediate-high	Mean: 34.5 Range: 1.7-276

Table 1. Characteristics of Included Studies

*number in brackets refer to reported number of pelvic lymph nodes removed for PLND/ePLND
**numbers in brackets refer to number of low risk patients over total number of patients, if patient cohort consists of low risk patients
R = Retrospective; P = Prospective; SC = single-centre; MC = multi-centre; RCT = Randomised Controlled Trial; NR = Non-Randomised; PET = Positron emission tomography; CT = Computed tomography; mpMRI: multiparametric magnetic resonance imaging; DWI = Diffusion-weighted Imaging; DWI = Diffusion-weighted Imaging; 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 Pelvic Lymph Node Dissection; IQR = Inter-quartile Range; SD = Standard Deviation, BS = Bone Scan; SPECT = Single-photon emission computed tomograph

LOCAL TUMOUR STAGING

Supplementary Figures 2-5 shows the coupled forest plots of the patient level analysis of PSMA-PET/MRI versus mpMRI for extra-prostatic extension (EPE) (4 studies, 210 patients) and seminal vesicle invasion (SVI) (3 studies, 175 patients), and that of PSMA-PET/CT versus mpMRI for EPE (5 studies, 228 patients) and SVI (8 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 to 38.5, p<0.001) for EPE detection and 15.7 percentage points (95% CI 7.6 to 23.8, p=0.02) for SVI detection. In 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)

	PSMA-PET/MRI versus mpMRI		PSMA-PET/CT versus mpMRI	
	PSMA-PET/MRI	mpMRI	PSMA-PET/CT	mpMRI
Extraprostatic Extension (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), P value*	25.8 (13.2, 38.5), p<0.001		-9.6 (-32.1, 12.9), p=0.2	
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), P value*	-4.0 (-13.7, 5.7), p=0.4		-4.7 (-21.5, 12.1), p=0.2	
Seminal Vesicle Invasion (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), P value*	15.7 (7.6, 23.8), p=0.02		-16.9 (-33.5, -0.3), p=0.1	
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), P value*	-4.3 (-9.6, 11.1), p=0.1		-2.8 (-7.8, 2.2), p=0.09	

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

*P values were obtained from likelihood ratio tests

NODAL STAGING

Figure 2 shows the coupled forest plots of the patient level analysis of PSMA-PET versus mpMRI (19 studies, 1190 patients). A visual representation of the relationship between sensitivities and specificities of mpMRI and PSMA-PET at the intra-study level is provided in Figure 3 as a linked SROC 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 found PSMA-PET to be significantly more sensitive and specific than mpMRI by absolute differences of 34.8 percentage points (95%CI 16.4 to 53.3, p<0.001) and 15.0 percentage points (95%CI 6.7 to 23.2, p<0.001) respectively (Table 3). Substantial heterogeneity was observed as shown by the extent of the 95% prediction region around the summary points on the SROC plot (Figure 4).

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

PSMA-PET was additionally significantly more sensitive than mpMRI (Table 3) in a lesion-level analyses (7 studies, 329 patients) comparing PSMA-PET and mpMRI (Supplementary Figures 8 and 9).

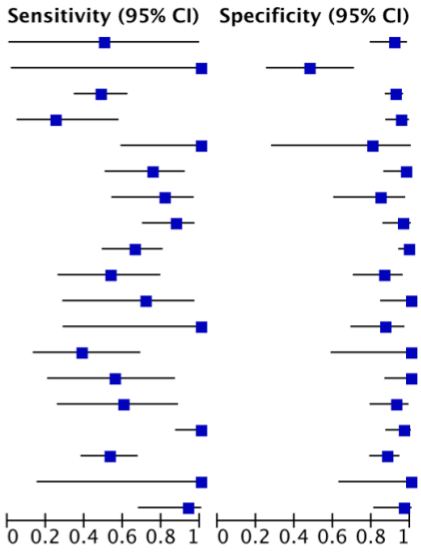
	PSMA-PET versus mpMRI		PSMA-PET versus CT	
	PSMA-PET	mpMRI	PSMA-PET	CT
Patient-level analysis				
Sensitivity,% (95%CI)	73.7 (60.6, 83.7)	38.9 (26.3, 53.0)	73.2 (56.4, 85.2)	38.5 (31.9, 45.5)
Absolute difference (95% CI), P value	34.8 (16.4, 53.3), p<0.001		34.7 (21.1, 48.3), p<0.001	
Specificity,% (95% 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), P value	15.0 (6.7, 23.2), p<0.001		14.1 (5.4, 22.8), p<0.001	
Lesion-level analysis				
Sensitivity,% (95%CI)	74.8 (49.2, 90.1)	32.2 (11.2, 64.2)	-	-
Absolute difference (95% CI), P value	42.6 (69.0, 78.3), p<0.001		-	
Specificity,% (95% CI)	99.2 (98.5, 99.6)	98.6 (97.4, 99.3)	-	-
Absolute difference (95% CI), P value	0.6 (-0.05, 1.4), p=0.08		-	

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

*P values were obtained from likelihood ratio tests

PSMA-PET

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Berger 2018	1	4	1	42	0.50 [0.01, 0.99]	0.91 [0.79, 0.98]
Celen 2020	1	11	0	10	1.00 [0.03, 1.00]	0.48 [0.26, 0.70]
Franklin 2020	28	14	30	161	0.48 [0.35, 0.62]	0.92 [0.87, 0.96]
Frumer 2020	3	4	9	73	0.25 [0.05, 0.57]	0.95 [0.87, 0.99]
Gupta 2017	7	1	0	4	1.00 [0.59, 1.00]	0.80 [0.28, 0.99]
Kroenke 2019	15	1	5	37	0.75 [0.51, 0.91]	0.97 [0.86, 1.00]
Kulkarni 2020	13	3	3	16	0.81 [0.54, 0.96]	0.84 [0.60, 0.97]
Malaspina 2021	27	2	4	46	0.87 [0.70, 0.96]	0.96 [0.86, 0.99]
Maurer 2016	27	1	14	88	0.66 [0.49, 0.80]	0.99 [0.94, 1.00]
Obek 2017	8	5	7	31	0.53 [0.27, 0.79]	0.86 [0.71, 0.95]
Pallavi 2020	5	0	2	22	0.71 [0.29, 0.96]	1.00 [0.85, 1.00]
Park 2018	3	4	0	26	1.00 [0.29, 1.00]	0.87 [0.69, 0.96]
Peterson 2019	5	0	8	7	0.38 [0.14, 0.68]	1.00 [0.59, 1.00]
Skawran 2022	5	0	4	26	0.56 [0.21, 0.86]	1.00 [0.87, 1.00]
Szigeti 2021	6	3	4	36	0.60 [0.26, 0.88]	0.92 [0.79, 0.98]
Van Damme 2021	27	2	0	52	1.00 [0.87, 1.00]	0.96 [0.87, 1.00]
Van Leeuwen 2019	27	11	24	78	0.53 [0.38, 0.67]	0.88 [0.79, 0.94]
Yilmaz 2019	2	0	0	8	1.00 [0.16, 1.00]	1.00 [0.63, 1.00]
Zhang 2017	14	1	1	26	0.93 [0.68, 1.00]	0.96 [0.81, 1.00]
					0.74 [0.61, 0.84]	**0.98 [0.96, 0.99]**



mpMRI

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Berger 2018	0	2	2	44	0.00 [0.00, 0.84]	0.96 [0.85, 0.99]
Celen 2020	1	12	0	9	1.00 [0.03, 1.00]	0.43 [0.22, 0.66]
Franklin 2020	13	9	45	166	0.22 [0.13, 0.35]	0.95 [0.90, 0.98]
Frumer 2020	1	4	11	73	0.08 [0.00, 0.38]	0.95 [0.87, 0.99]
Gupta 2017	4	1	3	4	0.57 [0.18, 0.90]	0.80 [0.28, 0.99]
Kroenke 2019	9	11	9	29	0.50 [0.26, 0.74]	0.72 [0.56, 0.85]
Kulkarni 2020	7	9	4	15	0.64 [0.31, 0.89]	0.63 [0.41, 0.81]
Malaspina 2021	14	3	17	45	0.45 [0.27, 0.64]	0.94 [0.83, 0.99]
Maurer 2016	18	13	23	76	0.44 [0.28, 0.60]	0.85 [0.76, 0.92]
Obek 2017	4	9	11	27	0.27 [0.08, 0.55]	0.75 [0.58, 0.88]
Pallavi 2020	1	0	6	22	0.14 [0.00, 0.58]	1.00 [0.85, 1.00]
Park 2018	0	5	3	25	0.00 [0.00, 0.71]	0.83 [0.65, 0.94]
Peterson 2019	4	1	7	5	0.36 [0.11, 0.69]	0.83 [0.36, 1.00]
Skawran 2022	1	1	8	25	0.11 [0.00, 0.48]	0.96 [0.80, 1.00]
Szigeti 2021	5	1	5	37	0.50 [0.19, 0.81]	0.97 [0.86, 1.00]
Van Damme 2021	17	0	9	55	0.65 [0.44, 0.83]	1.00 [0.94, 1.00]
Van Leeuwen 2019	7	1	44	88	0.14 [0.06, 0.26]	0.99 [0.94, 1.00]
Yilmaz 2019	2	5	0	3	1.00 [0.16, 1.00]	0.38 [0.09, 0.76]
Zhang 2017	14	2	1	25	0.93 [0.68, 1.00]	0.93 [0.76, 0.99]
					0.39 [0.26, 0.53]	**0.83 [0.64, 0.90]**

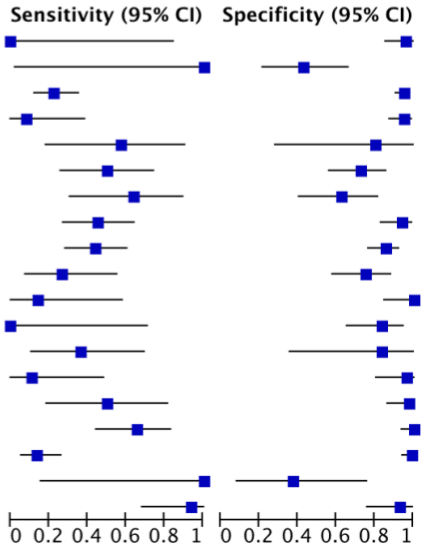


Figure 2. Forest plot of estimates of sensitivity and specificity of PSMA-PET and mpMRI for the detection of pelvic lymph node metastasis (patient level analysis)

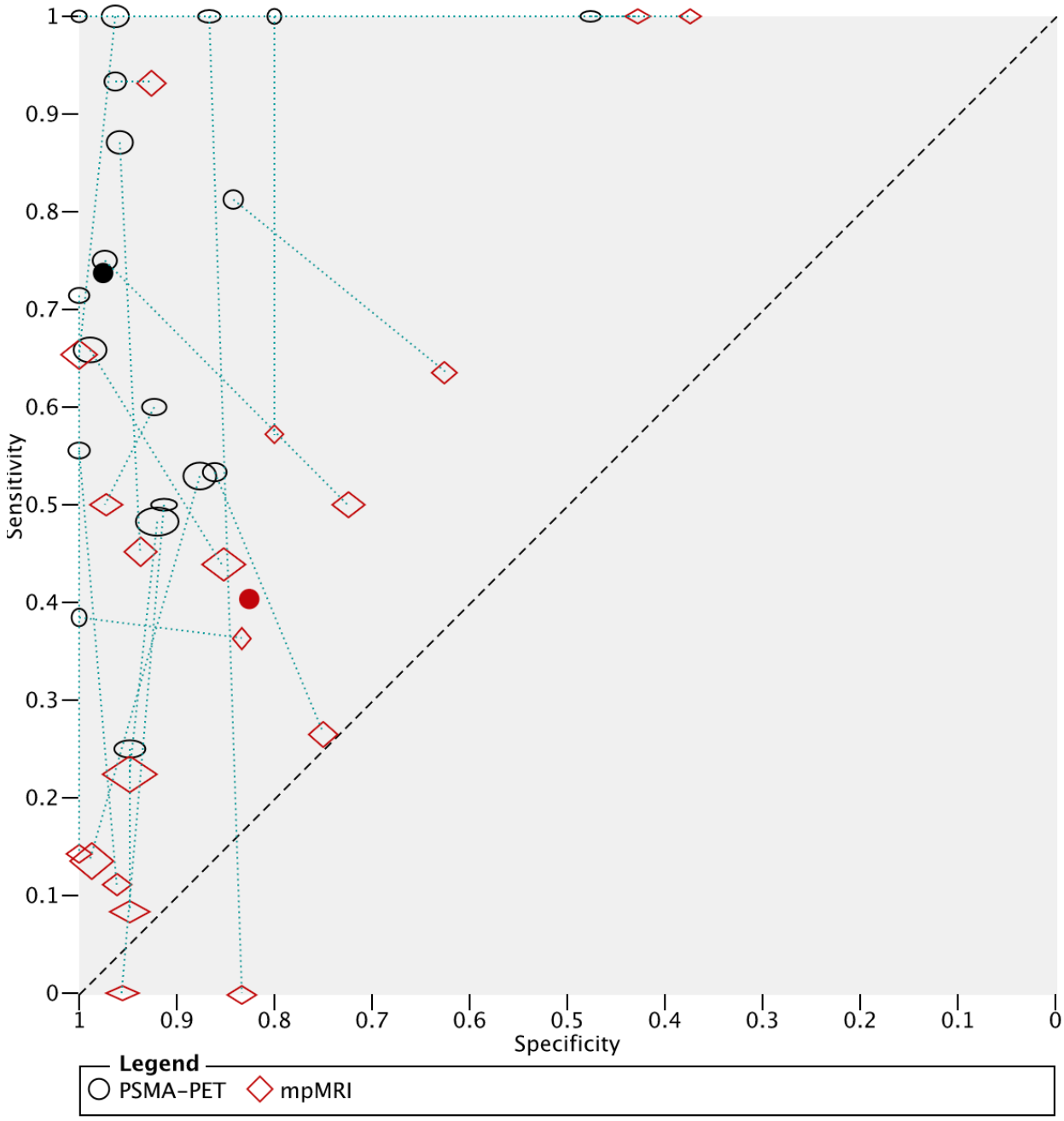


Figure 3. Linked SROC plot of PSMA-PET versus mpMRI for the detection of pelvic lymph node metastasis (patient level analysis) with pairwise analyses

*The hollow symbols (circle/ diamond) represent study estimates for each test and are scaled by the sample sizes for the group with and without the target condition to reflect the precision of the sensitivity and specificity estimates. The 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

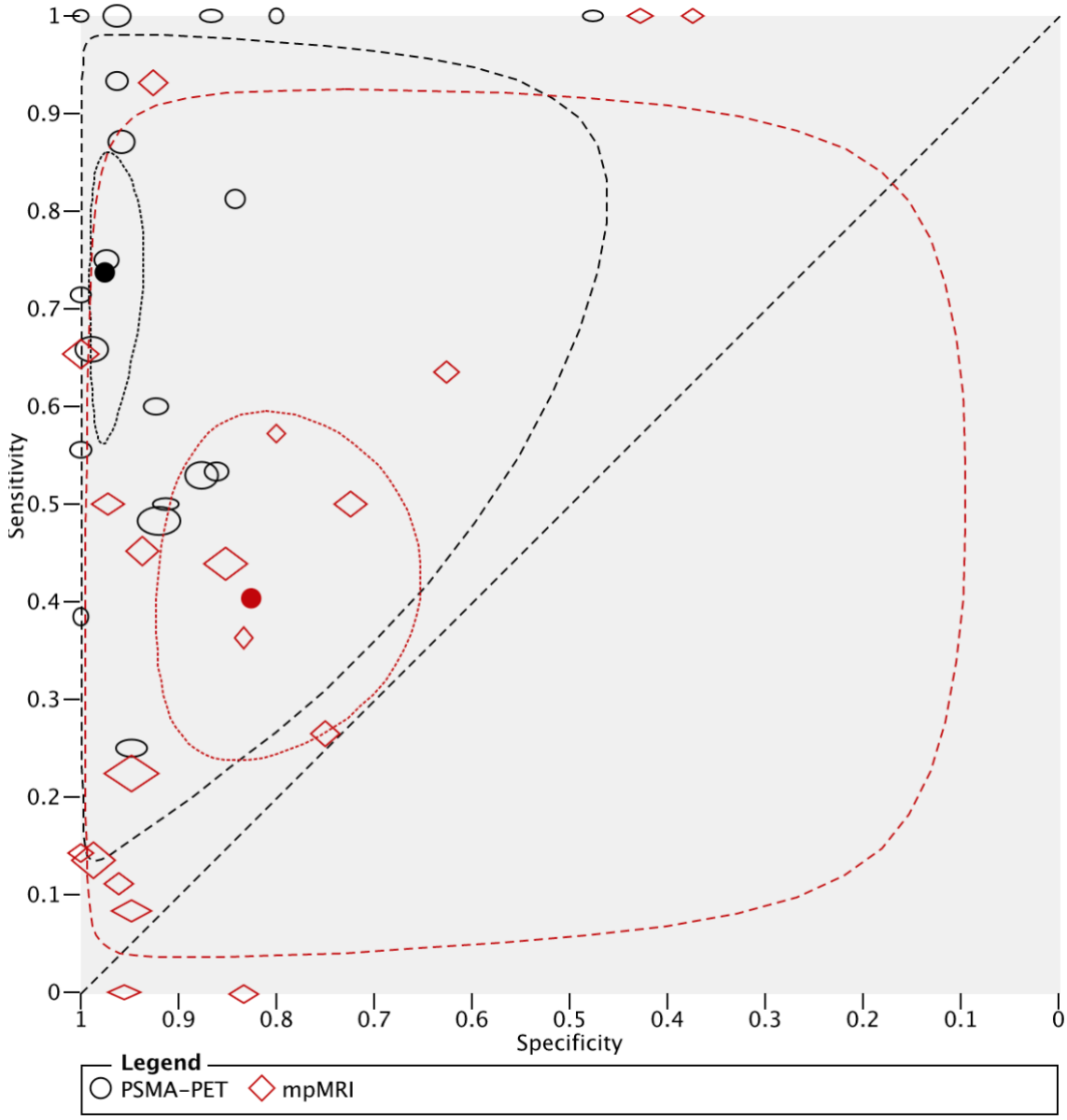


Figure 4. SROC plot of PSMA-PET versus mpMRI for the detection of pelvic lymph node metastasis (patient level analysis) with 95% confidence regions and 95% prediction regions

* The hollow symbols (circle/ diamond) represent study estimates for each test and are scaled by the sample sizes for the group with and without the target condition to reflect the precision of the sensitivity and specificity estimates. The solid symbols represent the summary estimates of sensitivity and specificity (summary point) for each test. The red/ black **dotted** lines around each summary point represents the 95% confidence region and the red/ black **dashed** line represents the 95% prediction region. The 95% confidence regions illustrate the uncertainty in the summary estimates. The 95% prediction regions are the regions within which one is 95% certain the results of a future study will lie and illustrate the extent of heterogeneity.

BONE STAGING

Sensitivities and specificities of PSMA-PET and BS in the patient analysis (6 studies, 541 patients) were 98.0% (95%CI 88.0 to 99.7) versus 73.0% (95%CI 63.6 to 80.7), and 96.2% (95%CI 90.9 to 98.5) versus 79.1% (95%CI 72.3 to 84.4). Meta-regression found PSMA-PET to be significantly more sensitive and specific than BS by absolute differences of 24.8 percentage points (95%CI 15.3 to 34.2, p<0.001) and 15.9 percentage points (95%CI 9.7 to 22.2, p< 0.001) respectively (Supplementary Figures 10 and 11).

HETEROGENEITY & SENSITIVITY ANALYSES

Across all analyses, significant heterogeneity was observed as shown by the extent of the 95% prediction regions in Figure 4 and Supplementary Figures 7,9,11. 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. 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 smaller in studies with a ≤1 month interval between imaging modalities. (Supplementary tables 4.1-4.3). Heterogeneity was observed to decrease for both PSMA-PET and mpMRI sensitivities and specificities after exclusion of studies with large time intervals. This is illustrated by the difference in the sizes of the 95% prediction regions in Figure 4 and Supplementary Figure 12.

Supplementary table 5.1-5.3 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 the primary analyses.

DISCUSSION

The excellent diagnostic capabilities of PSMA-PET are well established. Whether it should be offered to all patients with intermediate-high risk PCa for primary staging and replace CIM as the new standard-of-care, is however a question of whether it significantly outperforms CIM and thereby potentially improves patient outcomes. 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 CIM (mpMRI, CT and BS) across tumour nodal and bone metastasis staging of PCa.

Previous indirect comparisons between PSMA-PET and CIM have primarily included retrospective studies which report the diagnostic accuracy of each modality separately [13, 52]. Guidelines on Diagnostic test accuracy (DTA) reviews have recommended that conclusions from indirect comparisons should be interpreted with caution due to the potential for bias from confounding [18, 53]: 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 an unfair comparison. Following emergence of studies performing PSMA-PET and CIM in the same patient cohorts, using either histopathology or CRS as reference standards, this SRMA presents a head-to-head comparison of PSMA-PET and CIM.

In the 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 [54] had previously observed PSMA-PET/MRI to be more sensitive than PSMA-PET/CT in EPE detection (87% versus 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[55] and variations in bladder volume which can confound accurate detection of SVI[28]. This implies that the spatial resolution of mpMRI cannot be replaced, possibly because the accurate definition of local tumour extent is highly dependent on visualisation of anatomical detail. PSMA-PET/MRI however outperforms mpMRI, suggesting that mpMRI can be enhanced by small lesion avidity accorded by PSMA-PET.

Summary findings suggest PSMA-PET outperforms both CT and mpMRI in nodal staging. This comparison of PSMA-PET and mpMRI with 13 retrospective and 6 prospective studies is the largest yet and crucially confirms PSMA-PET to be more specific than mpMRI. While previous reviews had observed limited differences (Woo et al [54]: 94% versus 92%, Wang et al[59]: 92% versus 92%), our direct comparison showed PSMA-PET to be significantly more specific by 15.0 percentage points (95%CI 6.7 to 23.2, $p<0.001$). The superiority of PSMA-PET to CIM can be attributed to differences in defining lymph node invasion (LNI). While LNI on CIM depends on size (≥10mm) or the presence of suspicious features such as fatty hilum invasion[32], on PSMA-PET, radiotracer uptake relative to background signal identifies LNI regardless of node size. This difference translated to higher rates of micro-nodal metastases detection[43, 46, 56] and lower rates of equivocal findings [33]. Higher rates of inter-reader agreement was observed for PSMA-PET (0.78-0.92) than CIM (0.40-0.55) across 4 studies[9, 26, 27, 34], among which, 3 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 are concordant to a recent SRMA by Chavoshi et al. [57], signalling the importance of standardised structured reporting guidelines for prostate cancer 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 [58, 59] contributes to minimising potential bias, decreasing inter-reader variability and enhances communication.

For bone metastasis staging, PSMA-PET had significantly higher sensitivity and specificity compared to BS with and without SPECT-CT enhancement. Our results affirm PSMA-PET's ability to overcome the intrinsic limitation of BS in identifying marrow-based or lytic skeletal metastases [60], thereby increasing sensitivity [48, 51]. The resultant stage migration between localised, low- and high-volume metastatic disease has been shown to subsequently affect management [61, 62]. With regards to concerns about the risk of overtreating false positive lesions detected by PSMA-PET [63], this head-to-head comparison has observed that PSMA-PET in fact has a relatively lower rate of false positivity as compared to BS (0 to 11.8% versus 16.0 to 34.8%), and can thus potentially lower such a risk. It must however be said that all comparative studies on bone metastasis staging in this review utilised PSMA-PET with 68Ga-PSMA-11, while higher rates of false positivity has been observed with the 18F-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 [64] suggests that due to 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 as compared to previous indirect reviews, time interval between imaging modalities was found to be a significant source of heterogeneity. This affirms the need for evaluation of different imaging modalities to be done within the same patient cohort, given that disease status changes 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 [20]. Additionally, our SRMA is the first to draw conclusions about the relative diagnostic accuracies of PSMA-PET/MRI to mpMRI for tumour staging, and to CT for nodal staging.

Though we can reliably conclude that PSMA-PET has superior diagnostic capabilities to CIM, whether this translates to improvement in clinical outcomes is unknown. While Hofman et al [33] has found that PSMA-PET leads to significant rates of management changes when compared to CIM, ongoing prospective trials [65] 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 micro-metastasis predicts BCR in patients with otherwise

localised PCa, clinical outcome data on patients with CIM occult metastasis and on those that start early intensified therapy [66] is still unknown and of great interest.

Our study has several limitations – firstly, our conclusions can only be applied to intermediate-high risk patients as low-risk patients constituted <2.2% of the study cohort. Secondly, pre-planned subgroup analysis by risk group and PSA level could not be performed due to paucity of data stratified by these clinical parameters. Future studies reporting stratified data would allow for more comprehensive comparisons to better select patients for maximal benefit from PSMA-PET. Thirdly, 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 a more precise standardisation across studies. Finally, differences existed in standards used for the interpretation of PSMA-PET which understandably exists given its relative novelty. We recommend future studies to report findings according to the European Association of Nuclear Medicine (EANM) standardised reporting guidelines [58, 59], 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.

CONCLUSIONS

This SRMA synthesizing 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 in nodal and bone metastases staging, and more sensitive than mpMRI in 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 of primary PCa would result in significant improvements in diagnostic accuracy.

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SUPPLEMENTARY MATERIALS

Table of Contents

Supplementary Table 1: Search strategy

Pubmed	1446 articles
#1 ((prostate cancer[Title/Abstract]) OR (prostatic cancer[Title/Abstract]) OR (prostate carcinoma[Title/Abstract]) OR (prostatic carcinoma[Title/Abstract]) OR (prostate neoplasm[Title/Abstract]) OR (prostatic neoplasm[Title/Abstract]))	
#2 ((psma[Title/Abstract]) OR (prostate specific membrane antigen[Title/Abstract]) OR (prostate-specific membrane antigen[Title/Abstract]))	
#3 ((positron emission tomography[Title/Abstract]) OR (PET[Title/Abstract]) OR (PET-CT[Title/Abstract]) OR (PET-MRI[Title/Abstract]))	
#4 ((stage[Title/Abstract]) OR (staging[Title/Abstract]) OR (lymph nod*[Title/Abstract]) OR (metas*[Title/Abstract]))	
#1 AND #2 AND #3 AND #4	
Embase	2749 articles
Prostate cancer concept	
1	'prostate cancer':ti,ab,kw OR 'prostatic cancer':ti,ab,kw OR 'prostate carcinoma':ti,ab,kw OR 'prostatic carcinoma':ti,ab,kw OR 'prostate neoplasm':ti,ab,kw OR 'prostatic neoplasm':ti,ab,kw
PSMA-PET concept	
2	'prostate specific membrane antigen':ti,ab,kw OR 'prostate-specific membrane antigen':ti,ab,kw OR 'psma':ti,ab,kw
3	'pet':ti,ab,kw OR 'positron emission tomography':ti,ab,kw OR 'pet-ct':ti,ab,kw OR 'pet-mri':ti,ab,kw
4	#2 AND #3
Staging concept	
5	'staging':ti,ab,kw OR 'stage':ti,ab,kw
6	OR 'lymph':ti,ab,kw OR 'bone':ti,ab,kw OR 'metastasis':ti,ab,kw
7	#5 OR #6
COMBINE #1 AND #4 AND #7	
Cochrane Controlled Register of Trials (CENTRAL)	186 articles
Prostate cancer concept	
1	MeSH descriptor: [Prostatic Neoplasms] explode all trees
2	('prostate cancer' OR 'prostatic cancer' OR 'prostate carcinoma' OR 'prostatic carcinoma' OR 'prostate neoplasm' OR 'prostatic neoplasm'):ti,ab,kw (Word variations have been searched)

3	#1 AND #2
PSMA-PET concept	
4	('psma' OR 'prostate specific membrane antigen' OR 'prostate-specific membrane antigen'):ti,ab,kw
5	MeSH descriptor: [Positron-Emission Tomography] explode all trees
6	("positron emission tomograph*" OR 'positron emission computed tomograph*' OR 'PET' OR 'PET-CT' OR 'PET-MRI'):ti,ab,kw
7	#4 AND #5 OR #6
Staging concept	
8	('staging' OR 'stage' OR 'lymph' OR 'bone' OR metastas*'):ti,ab,kw
COMBINE #3 AND #7 AND #8	
SCOPUS	1956 articles
Prostate cancer Concept	
1	TITLE-ABS-KEY ((prostate AND cancer) OR (prostatic AND cancer) OR (prostate AND carcinoma) OR (prostatic AND carcinoma) OR (prostate AND neoplasm) OR (prostatic AND neoplasm))
PSMA-PET Concept	
2	TITLE-ABS-KEY ((psma) OR (prostate AND specific AND membrane AND antigen) OR (prostate-specific AND membrane AND antigen))
3	TITLE-ABS-KEY ((stage) OR (staging) OR (bone) OR (lymph) OR (metastas*))
Reconstruction Concept	
4	TITLE-ABS-KEY ((positron AND emission AND tomograph*) OR (positron AND emission AND computed AND tomograph*) OR (pet) OR (pet-ct) OR (pet-mri))
COMBINE #1 AND #2 AND #3 AND #4	

Date searched: 11 December 2021

Total articles: 6337

After endnote + Rayyan deduplication: 3473

Supplementary Table 2. PSMA-PET characteristics

Author	PSMA Radioligand	PET Vendor	Scanner (PET/CT or PET/MRI)	Uptake Time (min)	Uptake Time (min) (SD/Range)	Dose (MBq)	Dose (MBq) (SD/Range)
Arslan 2020 [1]	68Ga-PSMA-11	Siemens, GE	PET/CT	60	-	-	-
Berger 2018 [2]	68Ga PSMA-11	Philips	PET/CT	-	-	-	-
Celen 2020 [3]	68Ga-PSMA-I/T	Philips	PET/CT	60	-	185	Range: 125-317
Chen 2020 [4]	68Ga-PSMA-11	United Imaging Healthcare	PET/CT	60	-	136	Range: 126-178
Franklin 2020 [5]	68Ga-PSMA-11	Philips, GE	PET/CT	45-60	-	200	-
Frumer 2020 [6]	68Ga-PSMA-11	Philips	PET/CT	50-60	-	-	Range: 111-185
Gupta 2017 [7]	68Ga-PSMA-11	Siemens	PET/CT	-	-	2 (per kg)	-
Hofman 2020 [8]	68Ga-PSMA-11	GE, Philips, Siemens	PET/CT	63.2	SD: 17.7	164	SD: 38.6
Janssen 2018 [9]	68Ga-PSMA-11	Philips	PET/CT	61.7	SD: 32.2	120	SD: 20.4
Koseoglu 2020 [10]	68Ga-PSMA-11	-	-	-	-	-	-
Kulkarni 2020 [11]	68Ga-PSMA-11	GE	PET/CT	60	-	111-166	-
Kroenke 2019 [12]	18F-rhPSMA-17	Siemens	PET/CT PET/MRI	79.5	Range: 60-153	327	Range: 132-410
Lengana 2018 [13]	68Ga-PSMA-11	Siemens	PET/CT	60	-	137	Range: 45.9-305
Malaspina 2021 [14]	18F-PSMA-1007	GE	PET/CT	60	-	250	Range: 206-279
Maurer 2016 [15]	68Ga-PSMA-11	Siemens	PETCT PET/MRI	59.8	Range: 36-165	1.76 (per kg)	IQR: 1.47/kg - 2.03/kg
Muehlematter 2019 [16]	68Ga-PSMA-11	GE	PET/MRI	60	-	131	SD: 18.8
Nandurkar 2018 [17]	68Ga-PSMA-11	Philips	PET/CT	60	-	2/kg	
Obek 2017 [18]	68Ga-PSMA-11	Siemens	PET/CT	45-60	-	166	SD: 83
Van Damme 2021 [19]	68Ga-PSMA-11	Philips	PET/CT	79	SD: 17	123	SD: 33
Van Leeuwen 2019 [20]	68Ga-PSMA-11	Philips	PET/CT	60	-	2 (per kg)	-
Pallavi 2020 [21]	68Ga-PSMA-11	Phillips	PET/CT	60	-	1.76 (per kg)	-
Petersen 2019 [22]	68Ga-PSMA-11	GE	PET/CT	60	SD: 9	2 (per kg)	-
Pienta 2021 [23]	18F-DCFPyL	-	PET/CT	60-120	-	333	
Pyka 2016 [24]	68Ga-PSMA-11	Siemens	PET/CT PET/MRI	60	-	151	SD: 26
Simsek 2020 [25]	68Ga-PSMA-11	Siemens	PET/CT	45-60	-	185	-
Skawran 2022 [26]	68Ga-PSMA-11	GE	PET/MRI	60	-	134	SD: 18.8
Park 2018 [27]	68Ga-PSMA-11	GE	PET/MRI	41-61	SD: 5.4	152	SD: 25.9
Szigeti 2021 [28]	68Ga-PSMA-11	Philips, Siemens	PET/CT	60	Range: 59-63	2 (per kg)	-
Yilmaz 2019 [29]	68Ga-PSMA-11	Ans-Belgium	PET/CT	-	-	-	-
Zacho 2020 [30]	68Ga-PSMA-11	GE, Siemens	PET/CT	60	-	2 (per kg)	Range: 100-200
Zhang 2017 [31]	68Ga-PSMA-11	United Imaging Healthcare	PET/CT	60	-	132	Range: 131-178

Supplementary Appendix 1. The modified Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) checklist used for risk of bias assessment and applicability concern

Domain 1: Participant Selection

A. RISK OF BIAS: Could selection of patients have introduced bias?

Describe the methods of patient selection briefly:	
Signalling Question (SQ)1: Was a consecutive or random sample of patients enrolled?	Yes / No / Unclear
SQ2: Was a case-control/matched cohort design avoided? Yes: If the study is a paired study (each patient undergoes both tests) or an RCT, please answer "Yes". No: If it was clear that a case-control design was adopted (ie. selection for PSMA-PET or conventional imaging was not determined by the study team) but rather subjects are observed and followed up, please answer "No". Unclear: If the patient selection procedure was unclear or not reported.	Yes / No / Unclear
SQ3: Did the study avoid inappropriate exclusions? Inappropriate exclusions would be exclusion of patients who are more or less likely to have disease which may influence the diagnostic accuracy of the test. Examples of inappropriate exclusions include 1) excluding patients with intermediate to high-risk prostate cancer, 2) patients that underwent radical prostatectomy and pelvic lymph node dissection with histopathological confirmation of cancer, 3) both PSMA-PET and conventional imaging were performed within the same patient population. Yes: If a high proportion of eligible patients was included without clear selection. No: If a significant proportion of eligible patients was excluded with clear exclusion criteria or providing a reason. Unclear: If the inclusion/exclusion criteria was not clearly defined.	Yes/No/Unclear
SUMMARY: **Risk of bias for participant selection:** High risk if 'No' for at least one SQ Low risk if 'Yes' for all SQs. Unclear risk if "Unclear" for at least one SQ	Low risk / High risk / Unclear risk

B. CONCERNS FOR APPLICABILITY OF PATIENT SELECTION DOMAIN

Are there concerns that the included patients and setting do not match the review question? This is a pragmatic review hence the inclusion criteria are wide. If the study includes patients that fulfil the criteria above, this is “Low concern”. If it does not, this is “High concern”. If insufficient data are reported to make a decision then this is “Unclear concern”.	Low concern / High concern / Unclear concern

Domain 2: Index Test

A. RISK OF BIAS: Could the conduct or interpretation of the index test have introduced bias?

Describe briefly the nature of the PSMA-PET scan/conventional imaging modality (CIM: MRI/CT/Bone Scan), how it was conducted and results interpreted:	
SQ1: Was the PSMA-PET scan/CIM performed without knowledge of the results of 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? If both scans were done in the same setting (within 6 months’ interval) and interpreted within a pre-determined time period from the operation, the results from the reference standard are usually masked from the interpreter. In which case, the answer is “Yes”.	Yes / No / Unclear
SQ2: Was the PSMA-PET scan conducted independently of the conduct of histopathological diagnosis? To answer this question consider both of the following: 1. For example, did all patients undergo both PSMA-PET/CIM and histopathological confirmation or CRS, regardless of the circumstances surrounding the performance of the index test? If so, then the answer “Yes”. Otherwise, the answer is “No”. 2. Was the PSMA-PET scan interpreter blinded to the results of the reference standard (histopathological diagnosis/CRS)? If not, answer “No”. If not stated, say “Unclear” If 1) or 2) is “No”, this overrules “Unclear”.	Yes / No / Unclear

B. CONCERNS FOR APPLICABILITY

SUMMARY: **Risk of bias for index test:** Could the conduct or interpretation of the index test have introduced bias? High risk if ‘No’ for at least one applicable SQ Low risk if ‘Yes’ for all applicable SQs. Unclear risk if “Unclear” for at least one applicable SQ.	Low risk / High risk / Unclear risk

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern /

Given the varying components of CIM (MRI/CT/Bone Scan), each has its own unique acquisition technique and sequence as specified by the authors. If not stated, this is “High Concern”. If all imaging results were interpreted by board-certified radiological expertise in a randomized, blinded fashion with standardized protocol, this is “Low Concern”. If the evaluation setting, equipment technicalities and personnel were not detailed, this is “Unclear Concern”. All PSMA-PET scan acquisition and readings were obtained with clear delineation of type and dosage of PSMA radiotracer, as well as time elapsed post-radiotracer administration. Board-certified radiological expertise for interpretation with randomized and blinding is also part of the standardized protocol. If this was not detailed, the answer is “High Concern”. If this is stated, the answer is “Low Concern”. If there was no information regarding PSMA-PET scan interpretation, this answer is “Unclear Concern”.	High concern / Unclear concern

Domain 3: Reference Standard

A. RISK OF BIAS: Could the conduct or interpretation of the reference standard have introduced bias?

Describe briefly the nature of the reference standard (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), how it was conducted and results interpreted:	
SQ1: Was histopathological results or CRS interpreted without knowledge of the results of the PSMA-PET/CIM findings? If either index tests were done in the same setting (within 6 months’ interval) and interpreted within a pre-determined time period from the operation, the results from the reference standard are usually masked from the interpreter. In which case, the answer is “Yes”.	Yes / No / Unclear
SQ2: Was histopathological confirmation/CRS conducted independently of the conduct of the PSMA-PET scan? For example, did all patients undergo both index and reference modalities regardless of the circumstances surrounding the performance of the index test? If so, then the answer “Yes”.	Yes / No / Unclear
SUMMARY: **Risk of bias for reference test:** High risk if ‘No’ for at least one applicable SQ Low risk if ‘Yes’ for all applicable SQs. Unclear risk if “Unclear” for at least one applicable SQ. (Though “No” for one SQ supersedes “Unclear” if both results present).	Low risk / High risk / Unclear risk

B. CONCERNS FOR APPLICABILITY

Are there concerns that the comparator test, its conduct, or interpretation differ from the review question?	Low concern / High concern / Unclear concern

Domain 4: Flow and Timing

A. RISK OF BIAS: - Could the patient flow have introduced bias?

Describe any patients who did not receive the index or reference test, or who were excluded from the analysis. Describe the interval and any interventions between the index and reference tests.	
SQ1: Was the time interval between any of the following combinations of tests less than 6 months? 1. PSMA-PET and CT 2. PSMA-PET and mpMRI 3. PSMA-PET and Bone Scan 4. PSMA-PET and Bone Scan + SPECT	Yes / No / Unclear
SQ2: Did all patients receive the same reference test? Yes: if all participants received at least one of the relevant reference standard (CIM). No: if only (part of) the index test positives or index test negatives received the complete reference standard. Unclear: if it was not reported	Yes / No / Unclear
SQ3: Were all patients who underwent testing included in the analysis? Studies with patients lost to follow-up or patient withdrawal within each, the answer is “No”.	Yes / No / Unclear
SUMMARY: **Risk of bias for flow and timing:** **Could the participant flow have introduced bias?** High risk if ‘No’ for at least one SQ Low risk if ‘Yes’ for all SQs. Unclear risk if “Unclear” for at least one SQ. (Though “No” for one SQ supersedes “Unclear” if both results present).	Low risk / High risk / Unclear risk

Supplementary Table 3. QUADAS 2 and QUADAS-C individual study results

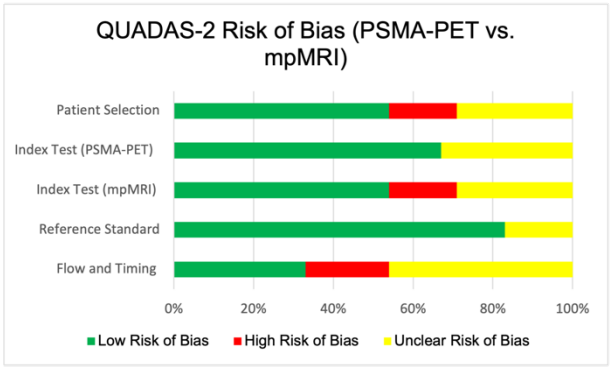
	Risk of Bias (QUADAS-2)					Applicability Concerns (QUADAS-2)				Risk of Bias (QUADAS-C)			
	P	I		R	FT	P	I		R	P	I	R	FT
		PSMA-PET	mpMRI/CT/BS				PSMA-PET	mpMRI/CT/BS					
Studies of PSMA-PET versus mpMRI for tumour and nodal staging													
Arslan 2020 [1]													
Celen 2020 [3]													
Chen 2020 [4]													
Koseoglu 2020 [10]													
Muehlematter 2019 [16]													
Skawran 2022 [26]													
Yilmaz 2019 [29]													
Berger 2018 [2]													
Nandurkar 2018 [17]													
Pallavi 2020 [21]													
Van Leeuwen 2019 [20]													
Park 2018 [27]													
Malaspina 2021 [14]													
Kroenke 2019 [12]													
Szigeti 2021 [28]													
Petersen 2019 [22]													
Gupta 2017 [7]													
Van Damme 2021 [19]													
Frumer 2020 [6]													
Kulkarni 2020 [11]													
Zhang 2017 [32]													
Maurer 2016 [15]													
Öbek 2017 [18]													
Franklin 2021 [5]													
Studies of PSMA-PET versus CT for nodal staging													
Hofman 2020 [8]													
Pienta 2021 [23]													
Malaspina 2021 [14]													
Park 2018 [27]													
Kroenke 2019 [12]													

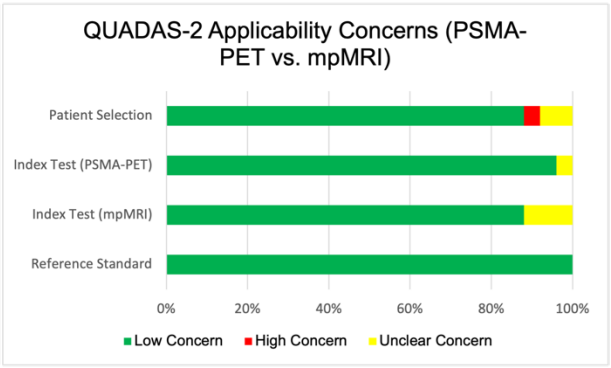
Maurer 2016 [15]													
Studies of PSMA-PET versus BS for nodal staging													
Hofman 2020 [8]													
Zacho 2020 [30]													
Simsek 2020 [25]													
Lengana 2018 [13]													
Janssen 2018 [9]													
Pyka 2016 [24]													

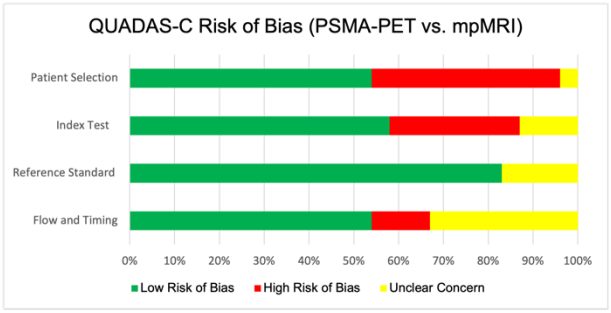
P = patient selection, **I** = index test, **R** = reference standard, **FT** = flow and timing

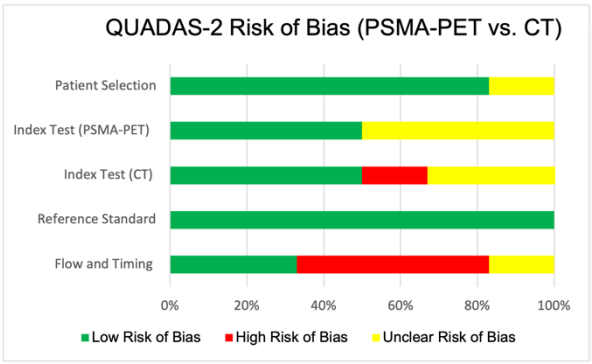
	Low risk of bias/ low concern
	High risk of bias/ high concern
	Unclear risk of bias/ unclear concern

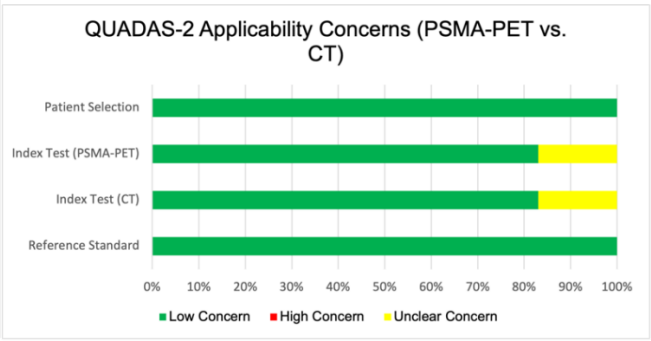
Supplementary Figures 1.1-1.6 Overall summary bar graphs of risk of bias and applicability concerns across studies using the Modified Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) and Quality Assessment of Diagnostic Accuracy Studies-Comparative (QUADAS-C) Checklist.

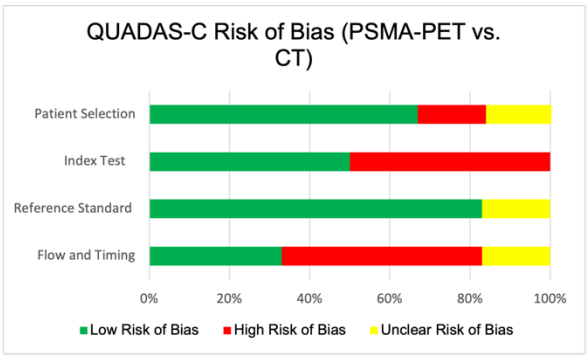


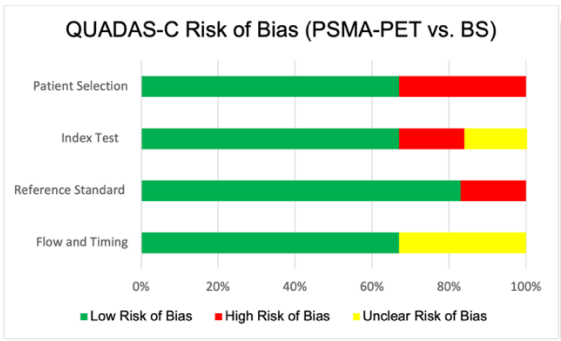


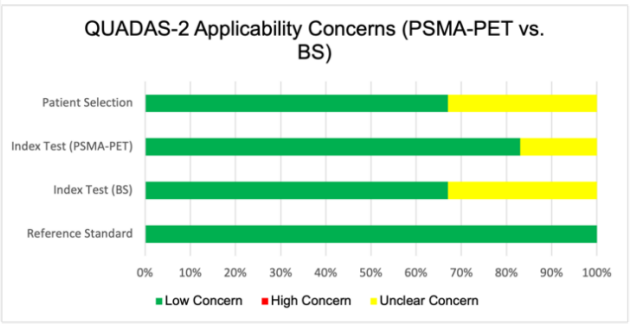


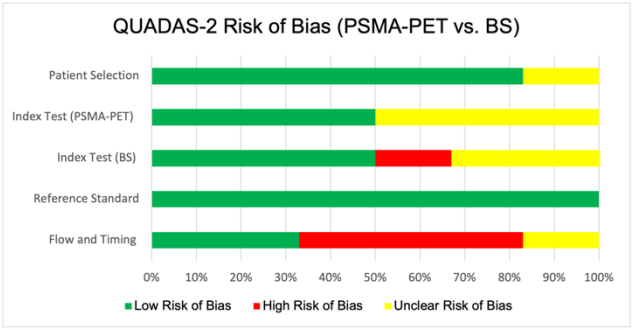




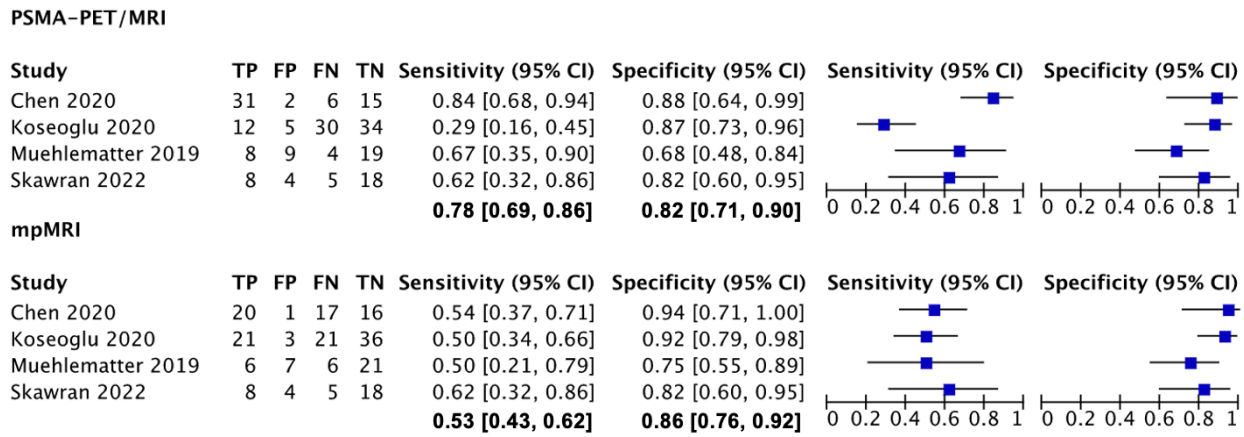



QUADAS-C Risk of Bias (PSMA-PET vs. BS)
Patient Selection
Index Test
Reference Standard
Flow and Timing
0%
20%
40%
60%
80%
100%
Low Risk of Bias
High Risk of Bias
Unclear Risk of Bias

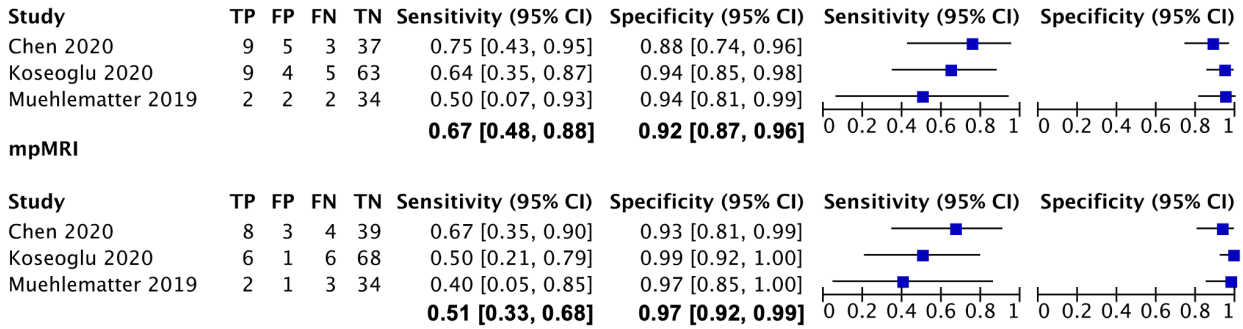

QUADAS-2 Applicability Concerns (PSMA-PET vs. BS)
Patient Selection
Index Test (PSMA-PET)
Index Test (BS)
Reference Standard
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Low Concern
High Concern
Unclear Concern


QUADAS-2 Risk of Bias (PSMA-PET vs. BS)
Patient Selection
Index Test (PSMA-PET)
Index Test (BS)
Reference Standard
Flow and Timing
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Low Risk of Bias
High Risk of Bias
Unclear Risk of Bias

Supplementary Figure 2. Forest plot of sensitivity and specificity of PSMA-PET/MRI and mpMRI for the detection of EPE (patient level analysis)



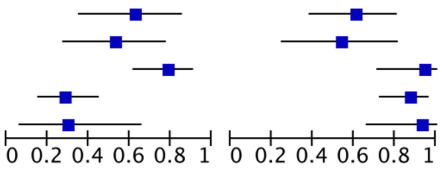
Supplementary Figure 3. Forest plot of sensitivity and specificity of PSMA-PET/MRI and mpMRI for the detection of SVI (patient level analysis)



Supplementary Figure 4. Forest plot of sensitivity and specificity of PSMA-PET/CT and mpMRI for the detection of EPE (patient level analysis)

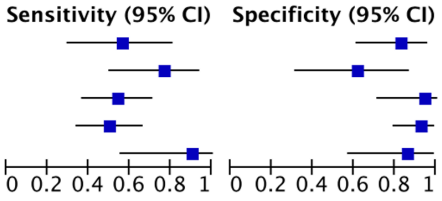
PSMA-PET/CT

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Arslan 2020	10	9	6	14	0.63 [0.35, 0.85]	0.61 [0.39, 0.80]
Celen 2020	9	6	8	7	0.53 [0.28, 0.77]	0.54 [0.25, 0.81]
Chen 2020	29	1	8	16	0.78 [0.62, 0.90]	0.94 [0.71, 1.00]
Koseoglu 2020	12	5	30	34	0.29 [0.16, 0.45]	0.87 [0.73, 0.96]
Yilmaz 2019	3	1	7	13	0.30 [0.07, 0.65]	0.93 [0.66, 1.00]
					0.52 [0.33, 0.70]	**0.81 [0.63, 0.92]**



mpMRI

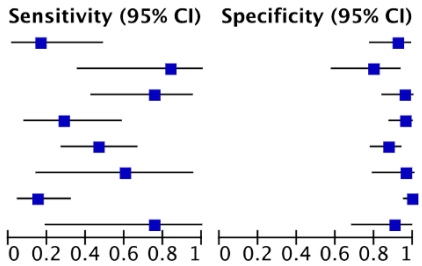
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Arslan 2020	9	4	7	19	0.56 [0.30, 0.80]	0.83 [0.61, 0.95]
Celen 2020	13	5	4	8	0.76 [0.50, 0.93]	0.62 [0.32, 0.86]
Chen 2020	20	1	17	16	0.54 [0.37, 0.71]	0.94 [0.71, 1.00]
Koseoglu 2020	21	3	21	36	0.50 [0.34, 0.66]	0.92 [0.79, 0.98]
Yilmaz 2019	9	2	1	12	0.90 [0.55, 1.00]	0.86 [0.57, 0.98]
					0.61 [0.47, 0.73]	**0.86 [0.75, 0.92]**



Supplementary Figure 5. Forest plot of sensitivity and specificity of PSMA-PET/CT and mpMRI for the detection of SVI (patient level analysis)

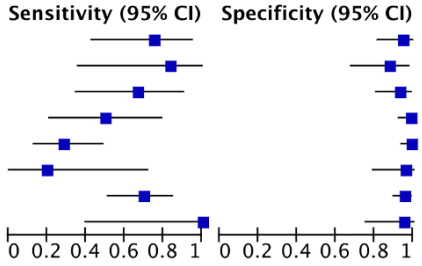
PSMA-PET/CT

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Berger 2018	2	3	10	33	0.17 [0.02, 0.48]	0.92 [0.78, 0.98]
Celen 2020	5	5	1	19	0.83 [0.36, 1.00]	0.79 [0.58, 0.93]
Chen 2020	9	2	3	40	0.75 [0.43, 0.95]	0.95 [0.84, 0.99]
Koseoglu 2020	4	3	10	64	0.29 [0.08, 0.58]	0.96 [0.87, 0.99]
Nandurkar 2018	13	11	15	73	0.46 [0.28, 0.66]	0.87 [0.78, 0.93]
Pallavi 2020	3	1	2	23	0.60 [0.15, 0.95]	0.96 [0.79, 1.00]
Van Leeuwen 2019	5	1	28	106	0.15 [0.05, 0.32]	0.99 [0.95, 1.00]
Yilmaz 2019	3	2	1	18	0.75 [0.19, 0.99]	0.90 [0.68, 0.99]
					0.45 [0.26, 0.65]	**0.93 [0.87, 0.96]**

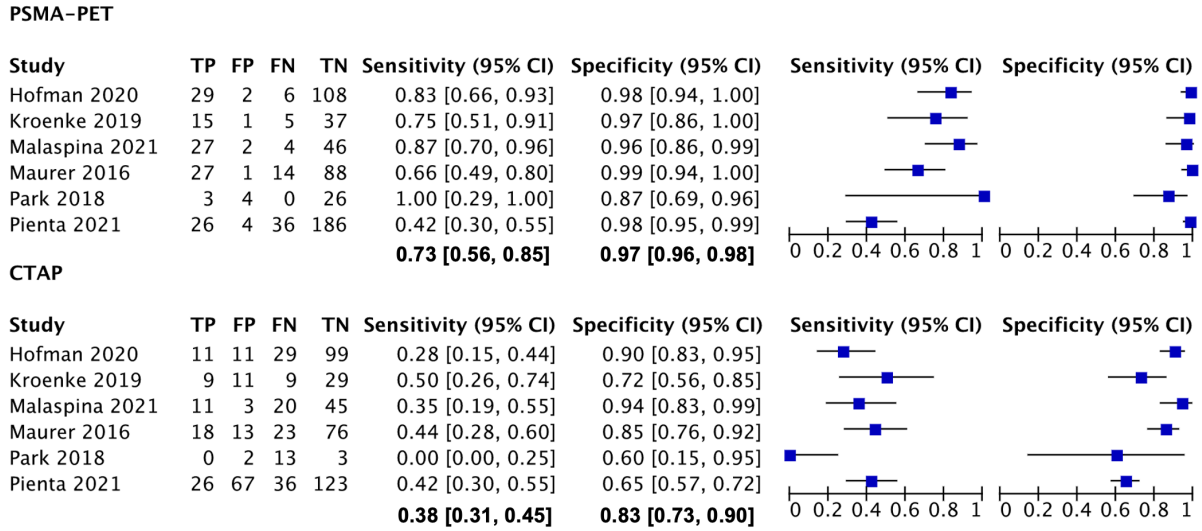


mpMRI

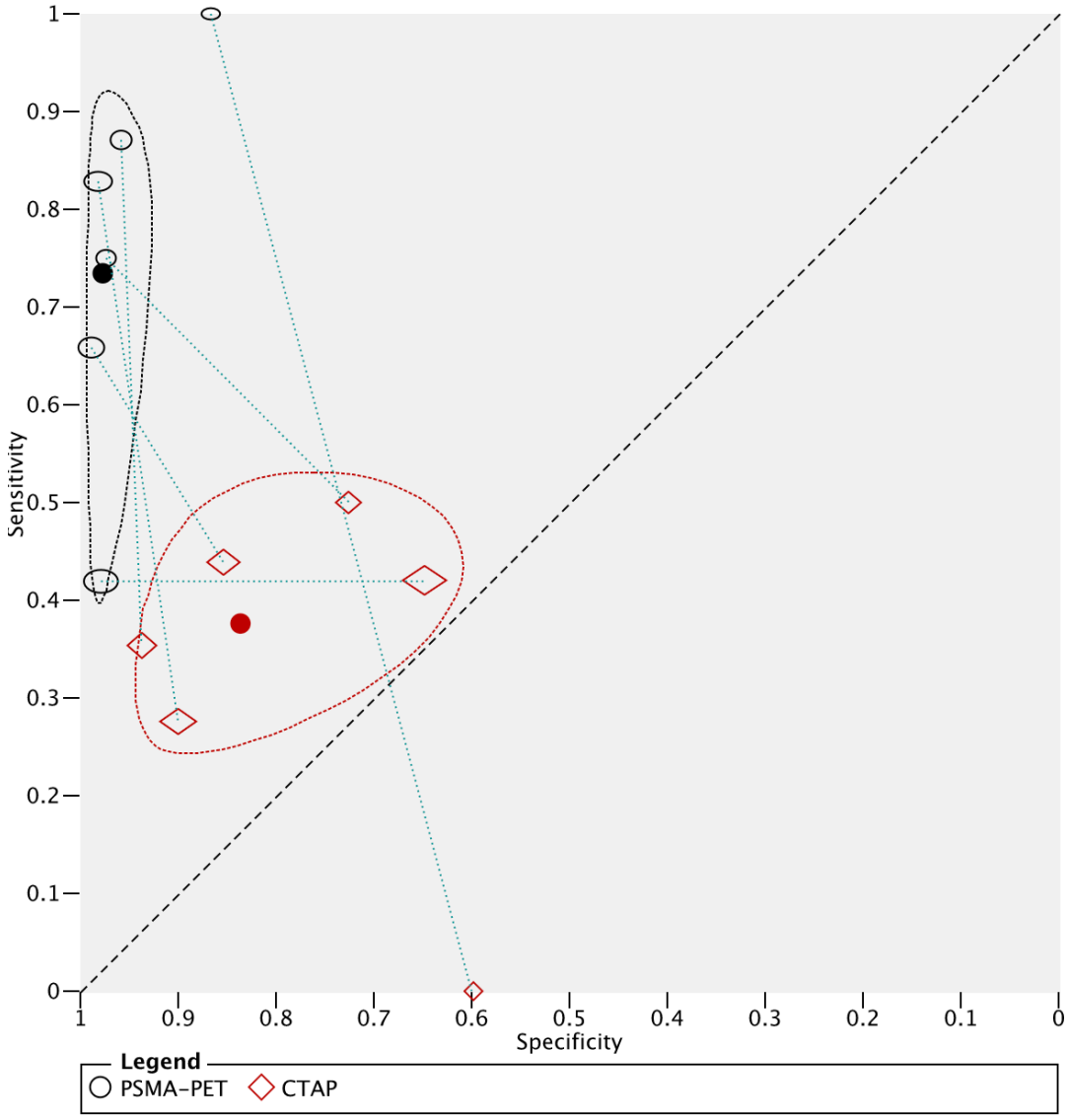
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Berger 2018	9	2	3	34	0.75 [0.43, 0.95]	0.94 [0.81, 0.99]
Celen 2020	5	3	1	21	0.83 [0.36, 1.00]	0.88 [0.68, 0.97]
Chen 2020	8	3	4	39	0.67 [0.35, 0.90]	0.93 [0.81, 0.99]
Koseoglu 2020	6	1	6	68	0.50 [0.21, 0.79]	0.99 [0.92, 1.00]
Nandurkar 2018	8	1	20	83	0.29 [0.13, 0.49]	0.99 [0.94, 1.00]
Pallavi 2020	1	1	4	23	0.20 [0.01, 0.72]	0.96 [0.79, 1.00]
Van Leeuwen 2019	23	5	10	102	0.70 [0.51, 0.84]	0.95 [0.89, 0.98]
Yilmaz 2019	4	1	0	19	1.00 [0.40, 1.00]	0.95 [0.75, 1.00]
					0.62 [0.44, 0.77]	**0.96 [0.92, 0.98]**



Supplementary Figure 6. Forest plot of sensitivity and specificity of PSMA-PET and CT for the detection of pelvic lymph node metastasis (patient level analysis)

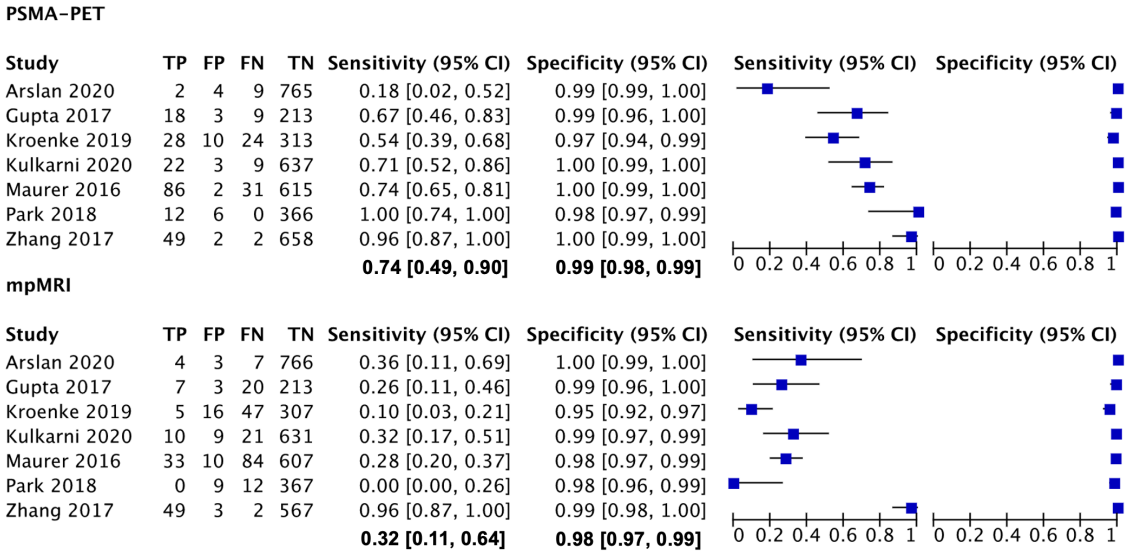


Supplementary Figure 7. SROC plot of PSMA-PET versus CTAP for the detection of pelvic lymph node metastasis (patient level analysis)

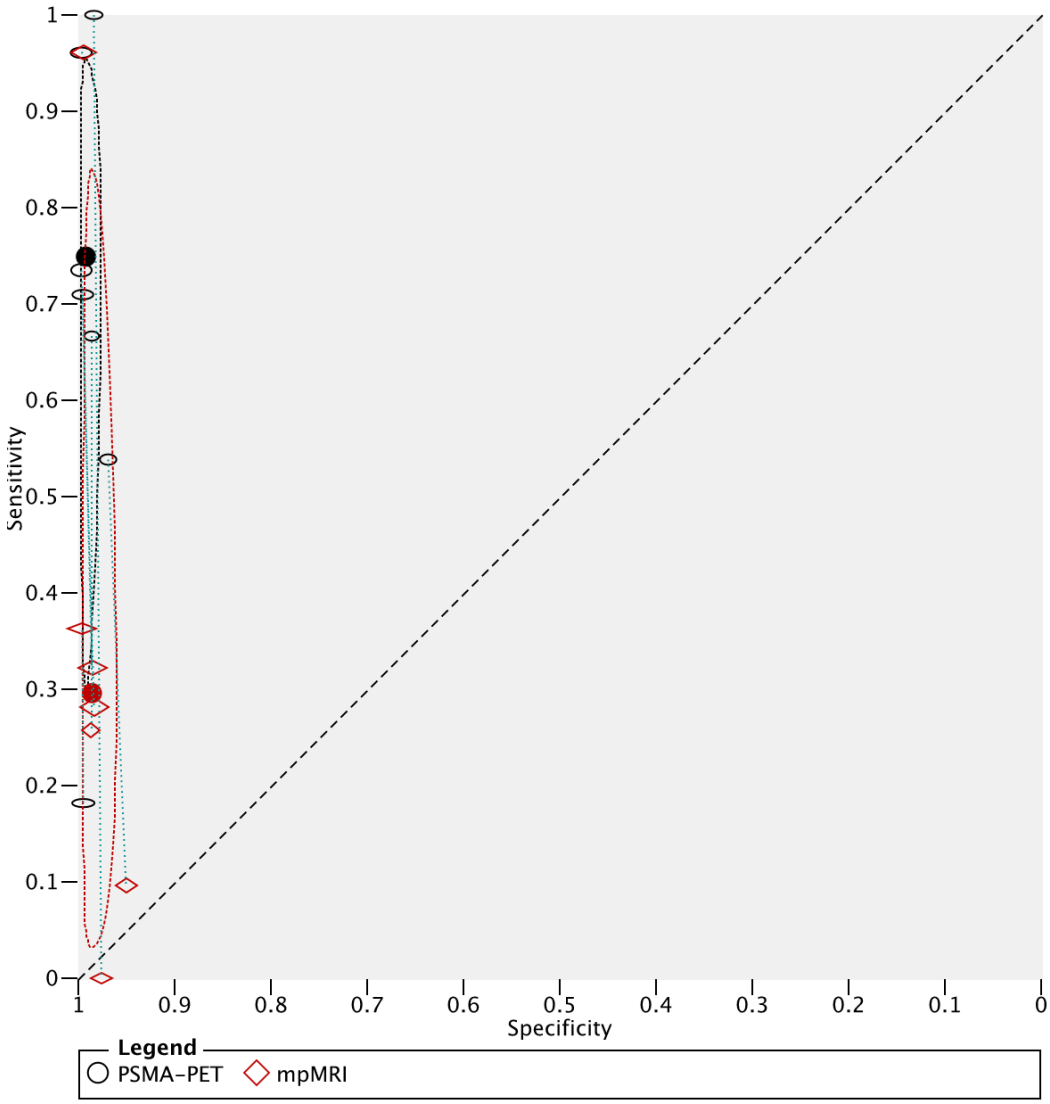


*The hollow symbols (circle/ diamond) represent study estimates for each test and are scaled by the sample sizes for the group with and without the target condition to reflect the precision of the sensitivity and specificity estimates. The solid symbols represent the summary estimates of sensitivity and specificity (summary point) for each test. The dotted line around each summary point represents the 95% confidence region and the dashed line represents the 95% prediction region. The 95% confidence regions illustrate the uncertainty in the summary estimates. The 95% prediction regions are the regions within which one is 95% certain the results of a future study will lie and illustrate the extent of heterogeneity.

Supplementary Figure 8. Forest plot of sensitivity and specificity of PSMA-PET and mpMRI for the detection of pelvic lymph node metastasis (lesion level analysis)

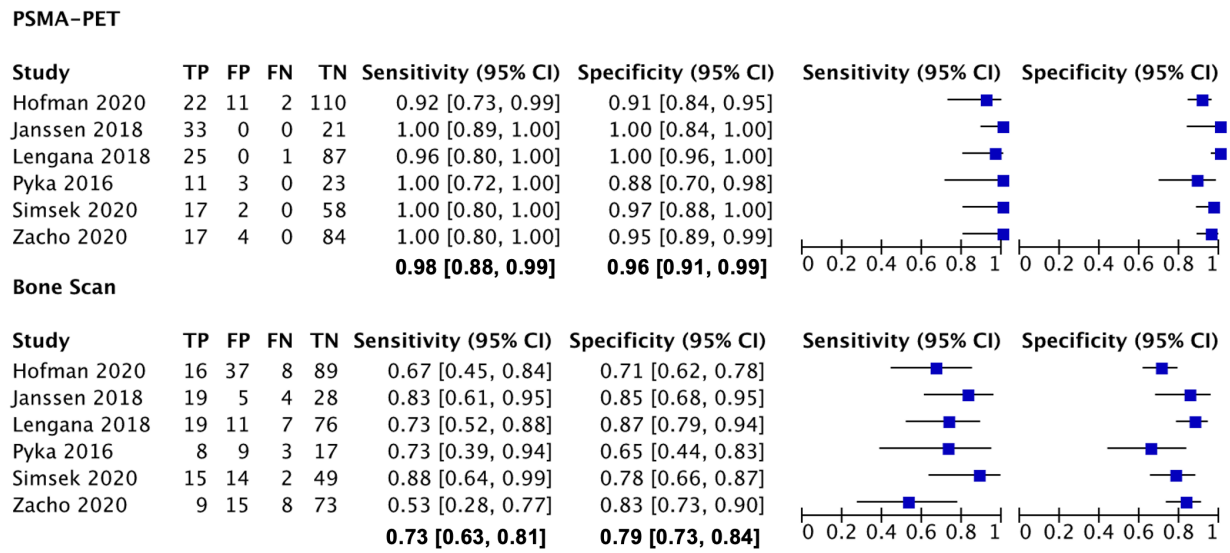


Supplementary Figure 9. SROC plot of PSMA-PET versus mpMRI for the detection of pelvic lymph node metastasis (lesion level analysis)

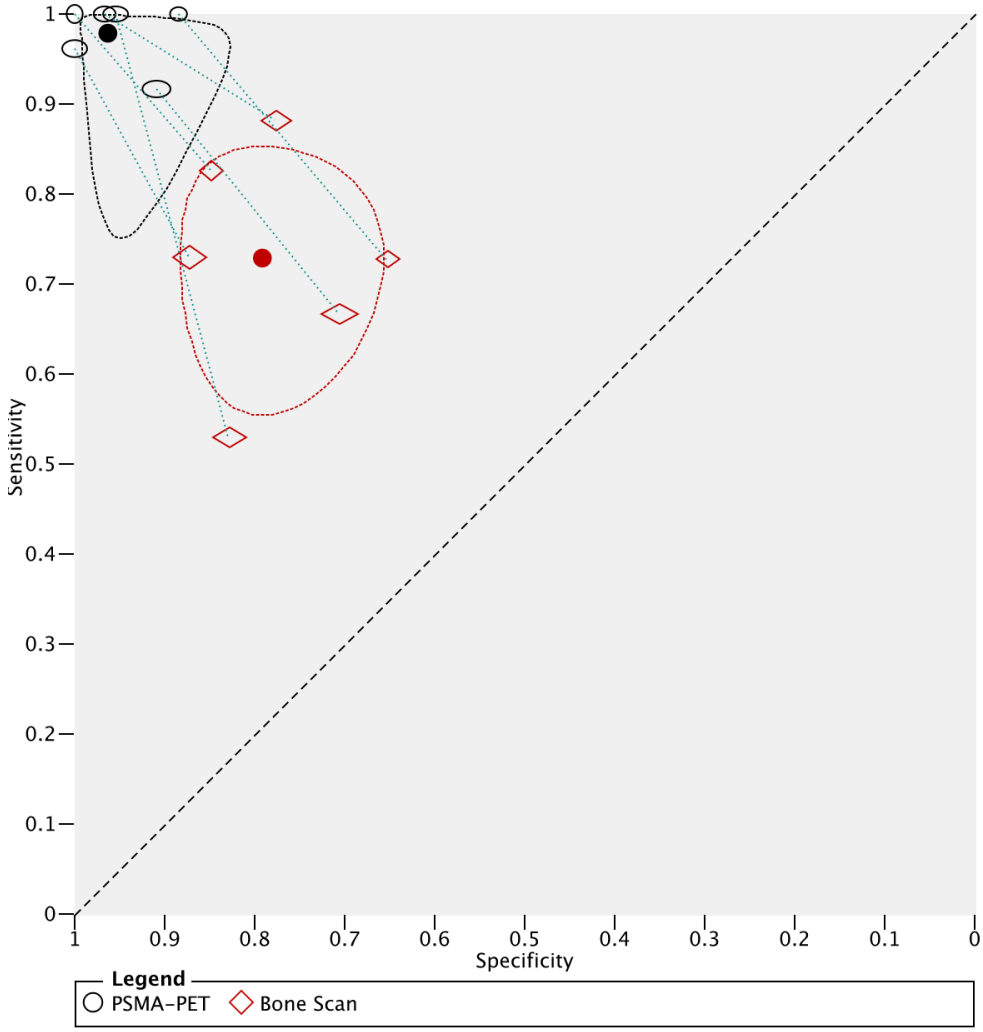


*The hollow symbols (circle/ diamond) represent study estimates for each test and are scaled by the sample sizes for the group with and without the target condition to reflect the precision of the sensitivity and specificity estimates. The solid symbols represent the summary estimates of sensitivity and specificity (summary point) for each test. The dotted line around each summary point represents the 95% confidence region and the dashed line represents the 95% prediction region. The 95% confidence regions illustrate the uncertainty in the summary estimates. The 95% prediction regions are the regions within which one is 95% certain the results of a future study will lie and illustrate the extent of heterogeneity.

Supplementary Figure 10. Forest plot of sensitivity and specificity of PSMA-PET and BS for the detection of bone metastasis (patient level analysis)



Supplementary Figure 11. SROC plot of PSMA-PET versus BS for the detection of bone metastasis (patient level analysis)



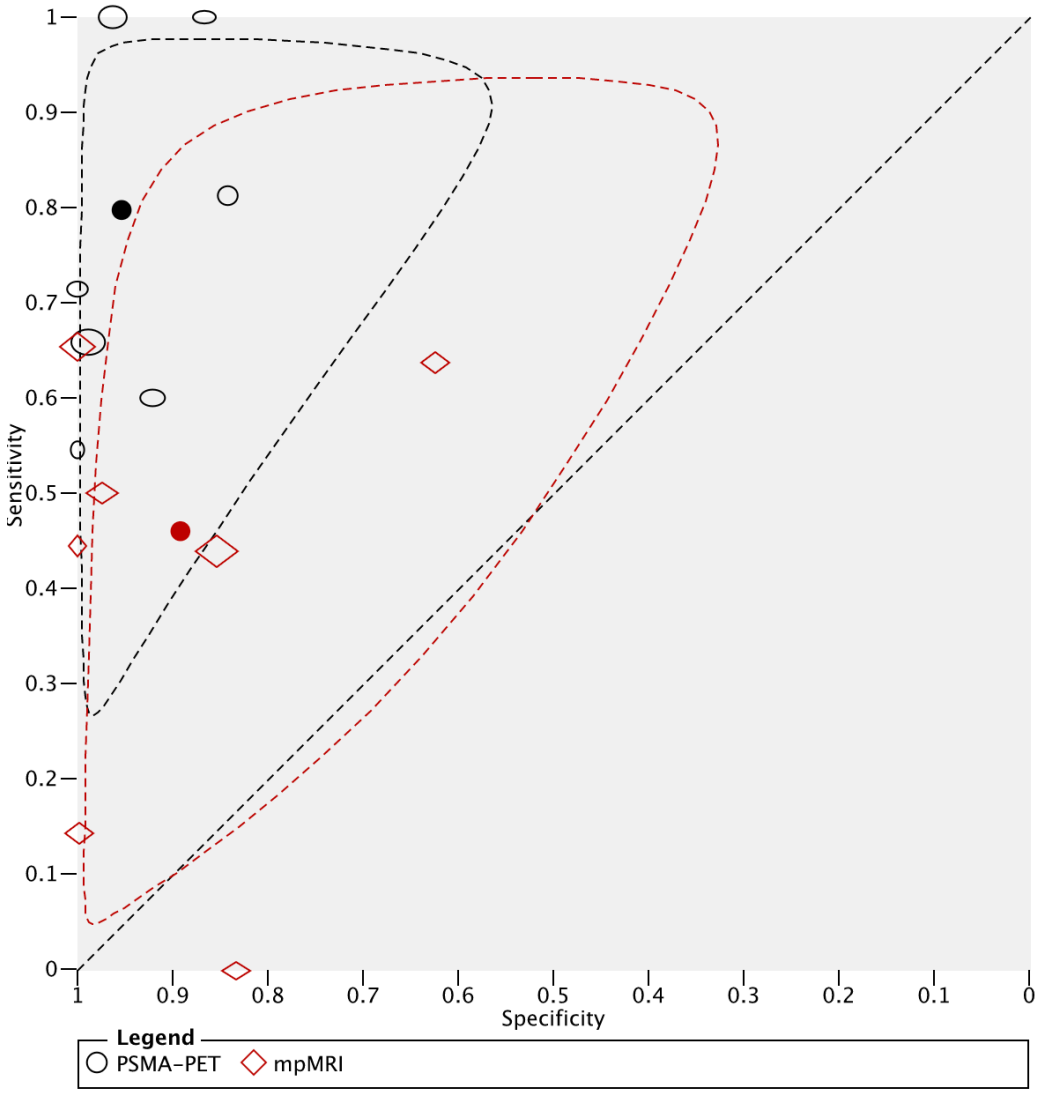
*The hollow symbols (circle/ diamond) represent study estimates for each test and are scaled by the sample sizes for the group with and without the target condition to reflect the precision of the sensitivity and specificity estimates. The solid symbols represent the summary estimates of sensitivity and specificity (summary point) for each test. The dotted line around each summary point represents the 95% confidence region and the dashed line represents the 95% prediction region. The 95% confidence regions illustrate the uncertainty in the summary estimates. The 95% prediction regions are the regions within which one is 95% certain the results of a future study will lie and illustrate the extent of heterogeneity.

Supplementary Table 4.1 Investigation of heterogeneity – effect of time interval between imaging modalities on the sensitivity and specificity of PSMA-PET and mpMRI

Covariate	No. studies	PSMA-PET sensitivity,% (95% CI)	mpMRI sensitivity,% (95% CI)	PSMA-PET specificity,% (95% CI)	mpMRI specificity,% (95% CI)
Nodal staging: patient-level comparison of PSMA-PET v. mpMRI					
Time interval ≤ 1 month	7	79.2 (59.5, 90.8)	46.9 (35.9, 58.2)	94.5 (89.0, 99.0)	87.1 (85.0, 89.2)
Absolute difference (95% CI), P value *		32.3 (14.7, 49.9), p<0.001		7.4 (2.3, 12.5) p=0.02	
Time interval > 1 month	9	67.1 (45.7, 83.1)	38.4 (15.2, 68.5)	98.2 (96.6, 99.8)	79.4 (48.9, 94.0)
Absolute difference (95% CI), P value *		27.8 (9.6, 47.1), p<0.001		18.8 (5.4, 32.2), p<0.001	
Test for difference by time interval		p=0.02	p=0.01	p<0.001	p=0.01

* P values were obtained from likelihood ratio tests

Supplementary Figure 12. Linked SROC plot of PSMA-PET versus mpMRI for the detection of pelvic lymph node metastasis (patient level analysis), excluding studies with time interval between imaging exceeding 1month or unknown time intervals, with 95% prediction regions.



* The hollow symbols (circle/ diamond) represent study estimates for each test and are scaled by the sample sizes for the group with and without the target condition to reflect the precision of the sensitivity and specificity estimates. The solid symbols represent the summary estimates of sensitivity and specificity (summary point) for each test. The red/ black **dashed** line represents the 95% prediction region. The 95% prediction regions are the regions within which one is 95% certain the results of a future study will lie and illustrate the extent of heterogeneity.

Supplementary Table 4.2 Investigation of heterogeneity – effect of study design on the diagnostic accuracies of PSMA-PET and CIM

Covariate	No. studies	PSMA-PET sensitivity,% (95% CI)	CIM sensitivity,% (95% CI)	PSMA-PET specificity,% (95% CI)	CIM specificity,% (95% CI)
Nodal staging: patient-level comparison of PSMA-PET v. mpMRI					
Prospective study	6	75.4 (59.1, 86.7)	41.0 (29.4, 53.6)	92.1 (73.9, 97.9)	83.3 (62.2, 88.7)
Absolute difference (95% CI), P value *		35.9 (12.7, 59.1), p<0.001		8.8 (0.4, 17.2), p=0.01	
Retrospective study	13	73.5 (55.4, 86.1)	39.9 (23.6, 58.8)	98.1 (97.0, 99.2)	79.4 (54.1, 89.0)
Absolute difference (95% CI), P value *		33.5 (9.4, 57.6), p<0.001		18.7 (8.0, 29.5), p<0.001	
Test for difference by study design		p=0.8	p=0.9	p=0.3	p=0.4

* P values were obtained from likelihood ratio tests

Supplementary Table 4.3 Investigation of heterogeneity – effect of PSMA-PET scanner on the sensitivity and specificity of PSMA-PET

Covariate	No. studies	PSMA-PET sensitivity,% (95% CI)	PSMA-PET specificity,% (95% CI)
Tumour staging: patient-level comparison of PSMA-PET v. mpMRI for ECE detection			
PSMA-PET/CT	5	51.5 (32.7, 69.9)	81.1 (62.9, 91.6)
PSMA-PET/MRI	4	78.7 (69.3, 85.8)	82.2 (71.3, 89.5)
Test for difference by PSMA-PET scanner		p<0.001	p=0.8
Tumour staging: patient-level comparison of PSMA-PET v. mpMRI for SVI detection			
PSMA-PET/CT	8	45.4 (26.2, 66.1)	93.6 (88.3, 96.6)
PSMA-PET/MRI	6	66.7 (48.4, 81.0)	92.4 (86.8, 95.7)
Test for difference by PSMA-PET scanner		p=0.01	P=0.6
Nodal staging: patient-level comparison of PSMA-PET v. CT/mpMRI			
PSMA-PET/CT	15	76.5 (59.7, 87.2)	97.6 (95.7, 99.0)
PSMA-PET/MRI	4	76.7 (47.6, 86.9)	95.4 (60.5, 99.7)
Test for difference by PSMA-PET scanner		p=0.9	p=0.7

* P values were obtained from likelihood ratio tests

Supplementary Table 5.1 Sensitivity Analyses – diagnostic accuracy of PSMA-PET and CIM from studies using FDA approved radioligands only

	Imaging modality	Studies **	Sensitivity,% (95%CI)	Absolute difference in sensitivity (95% CI), P value *	Specificity,% (95%CI)	Absolute difference in specificity (95% CI), P value *
Tumour staging: patient-level comparison of PSMA-PET/CT v. mpMRI for EPE detection						
All studies	PSMA-PET/CT	5	51.5 (32.7,69.9)	-10.9 (-17.3, 25.5) p=0.2	81.1 (62.9, 91.6)	-4.4 (-21.5, 12.7) p=0.2
	mpMRI		61.0 (47.1, 73.3)		85.8 (75.0, 92.4)	
FDA approved Radioligand	PSMA-PET/CT	4	51.0 (28.3, 73.3)	-5.1 (-31.3, 21.1) p=0.4	85.4 (85.2, 85.6)	-4.1 (-18.0, 9.9) p=0.2
	mpMRI		56.2 (46.6, 65.3)		89.2 (81.2, 94.1)	
Tumour staging: patient-level comparison of PSMA-PET/CT v. mpMRI for SVI detection						
All studies	PSMA-PET/CT	8	44.9 (26.4, 65.0)	-16.9 (-33.5, -0.3) p=0.1	93.1 (87.4, 96.3)	-2.8 (-7.8, 2.2), p=0.09
	mpMRI		61.8 (43.8, 77.0)		95.9 (92.4, 97.8)	
FDA approved Radioligand	PSMA-PET/CT	7	40.1 (22.8, 60.3)	-18.7 (-19.1, -18.3) P=0.02	94.6 (90.0, 97.2)	-2.17 (-2.2, -0.2) P=0.1
	mpMRI		57.8 (39.9, 73.9)		96.3 (93.9, 97.8)	
Nodal staging: patient-level comparison of PSMA-PET v. CT						
All studies	PSMA-PET	6	73.2 (56.4, 85.2)	34.7 (21.1, 48.3) p<0.001	97.8 (96.0, 98.8)	14.1 (5.4, 22.8) p<0.001
	CT		38.5 (31.9, 45.5)		83.6 (73.3, 90.4)	
FDA approved Radioligand	PSMA-PET	4	70.2 (48.0, 86.7)	32.5 (14.2, 50.8) P<0.001	98.0 (96.1, 99.0)	15.4 (6.2, 21.6) P<0.001
	CT		37.7 (30.2, 45.8)		82.6 (69.9, 90.6)	
Nodal staging: patient-level comparison of PSMA-PET v. mpMRI						
All studies	PSMA-PET	19	73.7 (60.6, 83.7)	34.8 (16.4, 53.3) p<0.001	97.5 (95.7, 98.9)	15.0 (6.7, 23.2), p<0.001
	mpMRI		38.9 (26.3, 53.0)		82.6 (63.8, 90.3)	
FDA approved Radioligand	PSMA-PET	17	71.5 (57.0, 82.6)	40.7 (21.2, 60.2) P<0.001	95.6 (91.2, 100)	15.1 (5.6, 24.6), p<0.001
	mpMRI		30.8 (15.1, 52.7)		80.4 (65.3, 95.5)	

Nodal staging: lesion-level comparison of PSMA-PET v. mpMRI						
All studies	PSMA-PET	7	74.8 (49.2, 90.1)	45.4 (36.8, 53.9) p<0.001	99.2 (98.5, 99.6)	0.63 (-6.12, 7.37) p=0.1
	mpMRI		32.2 (11.2, 64.2)		98.6 (97.4, 99.3)	
FDA approved Radioligand	PSMA-PET	6	78.6 (48.2, 93.5)	43.5 (31.1, 55.9) P<0.001	97.4 (95.0, 99.6)	0.51 (-3.1, 3.63) P=0.2
	mpMRI		35.1 (9.4, 73.7)		96.9 (95.2, 99.3)	

* P values obtained from likelihood ratio tests

** Refers to number of (a) studies utilising FDA approved radioligands

Supplementary Table 5.2 Sensitivity Analyses – diagnostic accuracy of PSMA-PET and CIM from studies including only intermediate-high risk patients

	Imaging modality	Studies **	Sensitivity, % (95%CI)	Absolute difference in sensitivity (95% CI), P value *	Specificity, % (95%CI)	Absolute difference in specificity (95% CI), P value *
Tumour staging: patient-level comparison of PSMA-PET/CT v. mpMRI for SVI detection						
All studies	PSMA-PET	8	45.4 (26.2, 66.1)	-16.9 (-43.5, 9.8) p=0.1	93.6 (88.3, 96.6)	-2.79 (-7.8, 2.2) p=0.09
	mpMRI		60.7 (43.1, 75.9)		95.8 (93.4, 97.4)	
Intermediate-high risk only	PSMA-PET	4	29.6 (15.1, 49.9)	-22.1 (-22.6, -21.7) p=0.1	95.0 (86.4, 98.2)	-2.0 (-2.1, -1.9) p=0.1
	mpMRI		50.8 (27.4, 73.8)		96.4 (93.3, 98.1)	
Nodal staging: patient-level comparison of PSMA-PET v. mpMRI						
All studies	PSMA-PET	19	73.7 (60.6, 83.7)	34.8 (16.4, 53.3) p<0.001	97.5 (95.7, 98.9)	15.0 (6.7, 23.2), p<0.001
	mpMRI		38.9 (26.3, 53.0)		82.6 (63.8, 90.3)	
Intermediate-high risk only	PSMA-PET	15	75.6 (61.1, 86.0)	37.9 (17.1, 58.8) P<0.01	95.7 (92.5, 97.8)	15.7 (7.2. 24.2) p=0.02
	mpMRI		37.7 (24.2, 53.0)		80.0 (73.2, 83.5)	
Bone metastasis staging: patient-level comparison of PSMA-PET v. BS						
All studies	PSMA-PET	6	98.0 (88.0, 99.7)	24.8 (15.3, 34.2) p<0.001	96.2 (90.9, 98.5)	27.3 (7.2, 47.3) p<0.001
	BS		73.0 (63.6, 80.7)		69.1 (47.0, 85.0)	
Intermediate-high risk only	PSMA-PET	3	95.1 (82.5, 98.8)	24.4 (16.2, 32.6) P=0.01	92.8 (88.4, 95.6)	22.5 (6.3, 38.7) p<0.01
	BS		70.7 (53.3, 83.6)		70.3 (63.1, 75.9)	

Supplementary Table 5.3 Sensitivity Analyses – diagnostic accuracy of PSMA-PET and CIM from studies including only studies that utilised only histopathology as reference standard

Nodal staging: patient-level comparison of PSMA-PET v. CT						
All studies	PSMA-PET	6	73.2 (56.4, 85.2)	34.7 (21.1, 48.3) p<0.001	97.8 (96.0, 98.8)	14.1 (5.4, 22.8) p<0.001
	CT		38.5 (31.9, 45.5)		83.6 (73.3, 90.4)	
Histo-pathology reference standard only	PSMA-PET	4	71.9 (53.4, 87.4)	29.2 (-5.7, 64.1) P=0.01	97.9 (95.7, 99.0)	21.3 (-11.1, 53.8) P<0.0001
	CT		42.7 (34.3, 51.6)		76.6 (65.0, 85.2)	
Nodal staging: patient-level comparison of PSMA-PET v. mpMRI						
All studies	PSMA-PET	19	73.7 (60.6, 83.7)	34.8 (16.4, 53.3) p<0.001	97.5 (95.7, 98.9)	15.0 (6.7, 23.2), p<0.001
	mpMRI		38.9 (26.3, 53.0)		82.6 (63.8, 90.3)	
Histo-pathology reference standard only	PSMA-PET	17	66.1 (54.9, 75.7)	34.1 (-32.2, 96. 5) P<0.0001	97.3 (95.1, 98.8)	17.8 (1.02, 34.6) P<0.001
	mpMRI		32.2 (18.8, 48.1)		79.5 (58.8, 88.8)	

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