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Review – Prostate Cancer – Editor's choice

A Comprehensive Systematic Review and Meta-analysis of the Role of Prostate-specific Membrane Antigen Positron Emission Tomography for Prostate Cancer Diagnosis and Primary Staging before Definitive Treatment

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Abstract

Background and objective: Positron emission tomography (PET) with prostate-specific membrane antigen (PSMA) in the diagnosis and primary staging of patients with prostate cancer (PCa) has an established role, but recent summative evidence on its actual diagnostic and staging value is still missing. We aimed to collect and analyze published studies reporting the accuracy of PSMA PET for the diagnosis of clinically significant prostate cancer (csPCa) and detection of distant metastases at primary staging before definitive treatment.

Methods: We performed a systematic review of the literature, by searching the PubMed/MEDLINE, Cochrane library's CENTRAL, EMBASE, and Scopus databases, from inception to April 2024. Two coprimary outcomes were assessed: first, to evaluate the sensitivity, specificity, positive (PPV) and negative (NPV) predictive values of PSMA PET in detecting intraprostatic csPCa on a per-patient level, and second, to assess the positivity rates of metastatic disease in the primary staging, prior to definitive therapy. As a secondary outcome, the diagnostic accuracy of PET PSMA for the detection of lymph nodal invasion (LNI) was tested in a per-patient–level analysis of studies where pelvic lymph node dissection (PLND) was available as the reference standard. Positivity and detection rates were pooled using random-effect models. Preplanned subgroup analyses tested the

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diagnostic accuracy of PET PSMA across different study cohorts. Variation in PPV and NPV over csPCa and LNI prevalence was evaluated.

Key findings and limitations: In total, 12 and 99 studies, with a total of 1533 and 18 649 participants, respectively, were included in the quantitative synthesis for intraprostatic diagnosis and staging. For intraprostatic disease, the sensitivity, specificity, PPV, and NPV of PSMA PET for csPCa were 82% (95% confidence interval [CI] 73–90%), 67% (95% CI 46–85%), 77% (95% CI 63–88%), and 73% (95% CI 56–87%), respectively. At a bivariate analysis, the diagnostic accuracy of PSMA PET estimated through a summary receiver operating characteristic curve–derived area under the curve was 84%, increasing up to 88% when combined with magnetic resonance imaging (MRI). On staging level, PSMA PET results were positive outside the prostate in 23% of the patients, with substantial variation in positivity rates between high-risk (31%) and intermediate-risk (12%) subcohorts. When using PLND as the reference standard (51 studies, 7713 patients), the sensitivity, specificity, PPV, and NPV of PSMA PET were, respectively, 54%, 94%, 77%, and 86%. With higher csPCa and LNI prevalence, a similar increase in PPV and a decrease in NPV were observed.

Conclusions and clinical implications: The current updated systematic review and meta-analysis provides updated evidence on the diagnostic and staging accuracy of PSMA PET in PCa. We reported good accuracy of PSMA PET to discriminate csPCa, particularly when added to MRI, but NPV alone is insufficient to omit a biopsy. Regarding staging, PSMA PET cannot be used alone to determine the need for lymph node dissection (LND) and should be combined with additional clinical information within predictive tools. As such, further research should develop and validate models that incorporate PSMA PET to reliably inform biopsy or LND.

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ADVANCING PRACTICE

What does this study add?

Over the past decade, prostate-specific membrane antigen (PSMA) positron emission tomography (PET) has revolutionized prostate cancer (PCa) staging, significantly enhancing the precision of a disease burden assessment. While guidelines now recommend its use when available, its actual clinical value, particularly for staging and diagnosis, remains a topic of ongoing debate. Based on this premise, our study aimed to provide comprehensive evidence supporting PSMA PET as a diagnostic and staging tool for PCa, especially effective in identifying clinically significant PCa (csPCa) and metastatic spread.

Clinical Relevance

This updated systematic review and meta-analysis reinforces existing evidence on the diagnostic and staging accuracy of PSMA PET in men with suspected or confirmed prostate cancer. However, it is crucial to highlight that the collated findings suggest PSMA PET alone is insufficient to rule out the need for biopsy in men with elevated PSA, to determine the necessity of pelvic lymph node dissection in those with high-risk disease, or guide any other escalation or de-escalation strategies across the disease spectrum. This underscores the importance of integrating clinical and other relevant data for informed decision-making and implementation of personalized care pathways. Associate Editor: Gianluca Giannarini, MD.

Patient Summary

In this systematic review and meta-analysis, we demonstrated that PSMA PET can assist in the detection of csPCa and optimize primary staging, guiding the management of PCa patients who are candidates for definitive treatment.

1. Introduction

During the past decade, positron emission tomography (PET) with prostate-specific membrane antigen (PSMA) has played a pivotal role in the context of diagnosis and staging of prostate cancer (PCa). This was possible thanks to the specificity of PSMA for PCa: as extensively reported in literature, PSMA is a transmembrane protein that is significantly overexpressed in PCa cells compared with normal prostate tissue, making it an ideal molecular target for

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imaging [1,2]. PSMA PET imaging involves the use of radiolabeled ligands, such as 68Ga-PSMA-11 or 18F-DCFPyL, that bind to PSMA allowing for accurate detection of PCa cells [3]. By harnessing the specificity of PSMA expression in PCa, PSMA PET offers superior accuracy in identifying both primary and metastatic lesions to conventional imaging methods such as computed tomography (CT), magnetic resonance imaging (MRI), and bone scans [4,5].

For the diagnosis of intraprostatic PCa, the added value of PSMA PET is still debated given its relatively new introduction in this early disease stage. Prospective data showed high sensitivity for the detection of suspicious lesions that may otherwise be missed by traditional imaging techniques [6]. Furthermore, PSMA PET can reliably identify the intraprostatic location and extent of cancer, thus enhancing guidance for biopsies and overall diagnostic accuracy. Given these characteristics, it could potentially be implemented as a viable alternative option to MRI or to improve overall accuracy when combined with MRI [6,7], but strong summative evidence is still missing.

In the context of metastatic primary staging, PSMA PET significantly improves the detection of both local and distant disease: unlike conventional imaging, which may not detect micrometastases accurately, PSMA PET has a high potential in identifying small lymph node involvement and bone metastases, thus providing a more comprehensive assessment of cancer spread [4,8]. This is crucial in the determination of the appropriate therapeutic strategy, particularly in the context of patients who are candidates for definitive treatment [9]. Given the increasing amount of evidence supporting the role of PSMA PET, it is now incorporated into clinical practice guidelines for PCa staging [10].

Despite previous meta-analyses having already provided a comprehensive overview of the role of PSMA in various disease stages [11–14], recent novel evidence has further enriched the clinical scenario in this field over the past few years. However, an updated summative review addressing the value of PSMA PET in diagnosis and staging is still missing. In this review, we will discuss the current applications of PSMA PET in the diagnosis and primary staging of PCa, highlighting the benefits and added value of this imaging modality. Furthermore, we aimed at exploring the variation of PSMA PET accuracy according to different risk groups and disease prevalence.

2. Methods

2.1. Study identification and evaluation

A systematic review of the literature was conducted using the Web of Science/MEDLINE, Cochrane library's CENTRAL, and EMBASE databases (Supplementary material). We searched the databases from inception to April 25, 2024. All the references of key reviews on PET PSMA were also screened. The research terms used for the research were as follows: "(prostate cancer OR prostate neoplasms OR prostate malignancy) AND (positron emission tomography OR PET) AND (prostate specific membrane antigen OR PSMA)". This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) guidelines [15], and it was registered with the International Prospective Registry of Systematic Reviews (PROSPERO registration number CRD42024557079).

2.2. Initial screening, eligibility/inclusion criteria, and risk of bias assessment

After the identification of all eligible studies, four independent reviewers in pairs (D.C., L.Q., D.C.C., and A.T.) screened all the titles and abstracts (or full text, for further clarification) for inclusion in the study. The extracted data were collected in Excel (Microsoft Corporation, Redmond, CA, USA). Reports were considered relevant if these provided extractable data on the PET PSMA scan in the diagnostic or staging process before primary treatment settings. Case reports, editorials, letters, review articles, and meeting abstracts were excluded at the initial screening (Fig. 1). Only original studies that responded to the study question were included for a full-text evaluation and potential inclusion in the final quantitative synthesis.

Regarding the assessment of intraprostatic diagnostic performance of PSMA PET, we included studies evaluating the utility of PSMA PET in the detection of csPCa in patients with a suspicion of PCa (prior to a biopsy). For this purpose, the mandatory inclusion criteria were as follows: (1) available overall number of patients receiving a preoperative PSMA PET scan (with any tracer), (2) available detection rates of PSMA PET guided biopsies, and (3) available systematic biopsy or prostatectomy pathological report as the reference standard.

Regarding the metastatic staging performance of PSMA PET, we included studies evaluating the utility of PSMA PET in the detection of local or metastatic disease in intermediate- or high-risk and advanced PCa for primary staging (prior to definitive therapy). For this purpose, the mandatory inclusion criteria were the following: (1) available overall number of patients receiving a preoperative PSMA PET scan and (2) available detection rates for PSMA PET scans. Additionally, at least one of the following two criteria should have been fulfilled: (1) series including distribution of positivity sites at PSMA PET and (2) series assessing diagnostic accuracy of PSMA using histopathology as reference (available overall number of patients receiving pelvic lymph node dissection [PLND] at the time of radical prostatectomy). A detailed report of the inclusion and exclusion criteria is summarized in the Supplementary material. Disagreements regarding eligibility were resolved by discussion with an experienced investigator (E.M.) until consensus was reached.

The methodological quality of the included studies was graded using the modified Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) checklist [16]. Four investigators (D.C., L.Q., D.C.C., and A.T.) in pairs independently assessed the risk of bias for all studies. In case of disagreements, a discussion with an additional experienced investigator (E.M.) was carried out.

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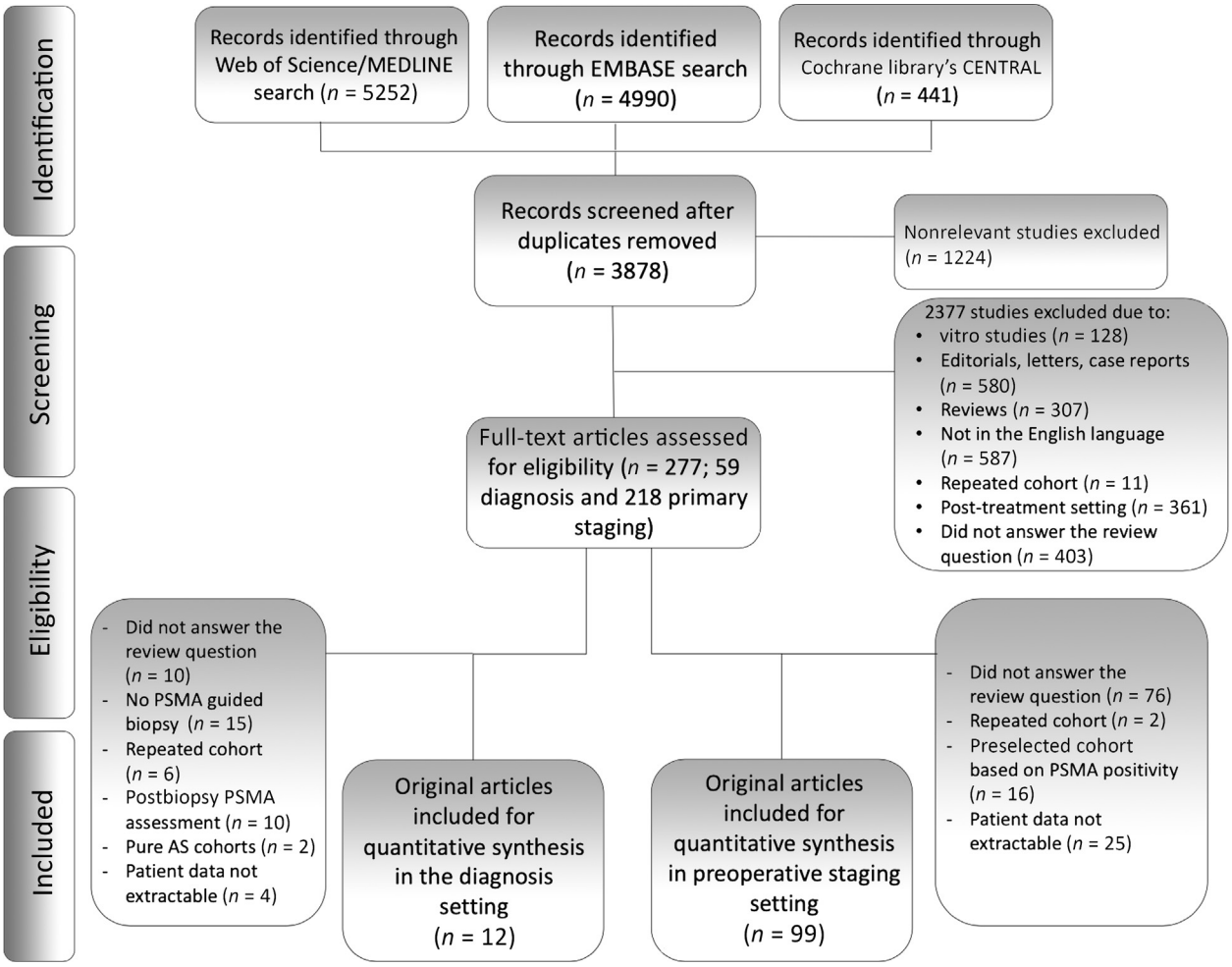

Fig. 1 – Flowchart of the screening process based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses criteria. AS = active surveillance; PSMA = prostate-specific membrane antigen.

2.3. Outcome definition

Regarding the intraprostatic diagnostic performance of PSMA PET in the prebiopsy setting, the primary outcome of the analysis was to evaluate the diagnostic accuracy of PSMA PET as guidance for a targeted biopsy for the detection of csPCa on a per-patient level. Specifically, we evaluated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic odds ratio (DOR) of PSMA PET scans in patients undergoing a PSMA PET targeted biopsy with a concomitant systematic biopsy as the reference standard. If the data for both the PSMA PET targeted biopsy and the PSMA PET combined with the MRI targeted biopsy were available, these were extracted separately, along with the definition of PSMA PET/MRI positivity. Thereafter, PSMA PET/MRI included either the use of an integrated PET/MRI scanner or post hoc fusion of MRI and PSMA PET images.

Regarding the performance of PSMA PET as a metastatic staging tool before primary radical treatment, the primary outcome of the analysis was to assess the overall and risk-stratified rates of positivity of PSMA PET outside of the prostate in the context of primary staging of patients who were candidates for definitive treatment. When histological data from lymph node dissection (LND) were available, the sensitivity, specificity, PPV, NPV, and DOR of PSMA PET scans for the detection of lymph nodal invasion (LNI) were also assessed. Additional secondary outcomes and calculation of specific outcomes are summarized in the Supplementary material.

2.4. Data synthesis and statistical analyses

The evaluation of false and true positive and negative cases needed for the calculation of diagnostic and staging accuracy was derived through the results of biopsy and LND as compared with preoperative PSMA PET scan results, as described above. The statistical methodology for meta-analysis was described previously and is summarized in the Supplementary material [13].

Preplanned subgroups analyses were performed in studies reporting staging accuracy stratified according to different baseline risk groups if available (according to the specific definition used in each manuscript). Here, the overall study cohorts were stratified as those with mixed risk, high risk, intermediate risk, and not specified risk. Where possible, subgroup analyses were also performed after extracting subgroups of risk within each single study rely-

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ing on mixed cohorts of men with PCa. Additional subgroup analyses were performed after stratification according to a PSMA PET ligand (68Ga-PSMA vs 18F-PSMA). Univariable metaregression analyses using random-effect models were used to statistically test the differences in diagnostic accuracy between subgroups, and statistical significance was evaluated with the analysis of variance test.

In case of the presence of a consistent risk of bias, sensitivity analyses were performed after excluding studies with a high risk of bias [17]. Similarly, where the presence of heterogeneity was identified at metaregression or by the assessment of τ^2, further sensitivity analyses were performed after excluding the study cohorts that contributed significantly to heterogeneity and by adding meta-analyses with fixed-effect models to ensure the robustness of our findings. Additional sensitivity analyses were performed in studies that explicitly reported the use of the Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) criteria for a PSMA PET assessment [18]. Fagan plots were used to assess the impact of PSMA PET on post-test probability by estimating how much the result of the diagnostic test changes the probability that a patient has csPCa or LNI [19]. Lastly, we tested the variation of PPV and NPV over LNI prevalence in those studies where the LNI prevalence could be estimated. Such variation was then represented graphically using a locally weighted scatterplot smoothing (LOWESS) plot [20], and the Pearson correlation coefficient was estimated.

Statistical significance for all analyses was defined as two-sided $p < 0.05$. A statistical analysis was performed with the R software (version 4.2.3; http://www.r-project.org/).

3. Results

3.1. Study selection flowchart

Fig. 1 shows the flow of studies through the screening process. Overall, 3878 papers were screened blindly by four reviewers working in pairs (D.C., L.Q., A.T., and D.C.C.), with 277 of these records being included for further evaluation based on the predefined eligibility criteria. At this point, final evaluation for the inclusion in the quantitative synthesis was carried out by two reviewers (E.M. and M.P.). At the end of the process, 12 and 99 studies were included for the meta-analysis on the diagnostic and staging performance, respectively (Supplementary Fig. 2 and 7).

3.2. Study quality and risk of bias

Supplementary Fig. 1 summarizes the quality criteria assessed for each study using the QUADAS 2.0 tool. Overall, 16 (53%), 23 (76%), 17 (57%), and 19 (63%) studies had a low risk of bias for the patient selection, index test, comparator test, and flow and timing domains for diagnosis, respectively. On the contrary, 62 (63%), 78 (79%), 53 (54%), and 63 (64%) studies had a low risk of bias for the patient selection, index test, comparator test, and flow and timing domains for staging, respectively.

3.3. Evidence synthesis—intraprostatic diagnosis

3.3.1. Population characteristics

Table 1 summarizes the general and design characteristics of the selected studies. The primary analysis included 12 papers for qualitative review and quantitative synthesis [6,7,21–30]. At baseline, the final screened manuscripts reported detection rates in biopsy-naïve patients (seven studies), patients with a prior negative biopsy (two studies), and mixed patient cohorts (three studies). Where possible, data on different patient subcohorts (ie, biopsy naïve or prior biopsy) were extracted from mixed cohorts. Overall, according to the primary outcome (ie, detection of csPCa), 1533 patients underwent a targeted biopsy for positive PSMA PET and were included in the pooled meta-analysis.

3.3.2. Overall diagnostic accuracy of PSMA PET for intraprostatic csPCa

In a univariate pooled meta-analysis adjusted for random effects, the pooled sensitivity of PSMA PET for the detection of csPCa was 82% (95% confidence interval [CI] 76–90%) and pooled specificity was 67% (95% CI 46–85%; Fig. 2 and Supplementary Fig. 2). At a bivariate analysis, which simultaneously takes into account both sensitivity and specificity, the diagnostic accuracy of PSMA PET estimated through a summary receiver operating characteristic curve (SROC)-derived area under the curve (AUC) was 84% (bivariate sensitivity 81% and specificity 70%; Supplementary Fig. 3).

In analyses testing for DOR, a meta-analysis using random-effect models demonstrated a pooled odds ratio (OR) of 12 (95% CI 2–51; Supplementary Fig. 4). In analyses testing for the predictive value, pooled meta-analyses using random-effect models demonstrated a PPV of 77% (95% CI 63–88%) and an NPV of 73% (95% CI 56–87%; Fig. 2 and Supplementary Fig. 2).

3.3.3. Diagnostic accuracy of PSMA PET combined with MRI for intraprostatic csPCa

Four studies including 466 patients explored the diagnostic accuracy of PSMA PET in combination with MRI (Supplementary Fig. 5). Here, in the pooled meta-analysis adjusted for random effects, the sensitivity of the combination of PSMA PET and MRI for the detection of csPCa was 91% (95% CI 80–98%) and pooled specificity was 68% (95% CI 43–89%). At the bivariate analysis, the diagnostic accuracy of PSMA PET estimated through an SROC-derived AUC was 88% (bivariate sensitivity 90% and specificity 69%; Supplementary Fig. 3).

In analyses testing for DOR, a meta-analysis using random-effect models demonstrated a pooled OR of 22 (95% CI 11–42; Supplementary Fig. 4). In analyses testing for the predictive value, pooled meta-analyses using random-effect models demonstrated a PPV of 78% (95% CI 62–91%) and an NPV of 86% (95% CI 70–96%; Supplementary Fig. 5).

3.3.4. Subgroup analyses according to previous biopsy status

In subgroup analyses testing the impact of previous biopsy status on diagnostic accuracy, data for quantitative comparison were extracted from seven studies for biopsy-naïve patients (1172 patients) and from two studies for patients

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Table 1 – Descriptive tables of the included studies assessing the role of PSMA PET for intraprostatic diagnostic assessment

Author (year of publication)	Study design	Study population	Number of patients who underwent PSMA PET before prostate biopsy	Age (dispersion), yr	Mean PSA (ng/ml)	Number of patients with positive PSMA PET	Definition of positive PSMA PET	csPCa prevalence, *n* (%)	csPCa definition	Type of ligand
Liu et al (2021) [26]	Prospective	Previous negative Bx	31	65 (53–81) [a]	18	18	Intense uptake higher than liver background	12 (38.7)	GG ≥2	68Ga-PSMA-617
Metser et al (2021) [29]	Prospective	Previous negative and positive Bx	55	65 (49–83) [b]	8.8	49	Intense uptake higher than normal prostate background	40 (72.7)	GG ≥ 2 or TCL 6 mm	18F-DCFPyL
Ferraro et al (2021) [23]	Prospective	Bx naïve	42	65 (59–68) [a]	8	28	Intense uptake higher than normal prostate background	31 (73.8)	GG ≥3 or TCL 6 mm, or GG ≥2	68Ga-PSMA-11
Emmett et al (2021) [6]	Prospective	Bx naïve	291	64 (59–70) [a]	5.6	211	SUVmax ≥4	163 (56)	ISUP ≥2	68Ga-PSMA-11
Margel et al (2021) [28]	Prospective	Bx naïve + previous negative Bx + AS	99	67 (62–71) [a]	6.7	47	SUVmax ≥2.5	25 (25.3)	GG ≥2	68Ga-PSMA-617
Lopci et al (2021) [27]	Prospective	Previous negative Bx	97	75 (43–81) [a]	7.6	64	Intense uptake higher than normal prostate background	15 (15.5)	GS ≥7	68Ga-PSMA
Zhang et al (2021) [22]	Prospective	Bx naïve	60	–	–	25	SUVmax ≥8	24 (40)		68Ga-PSMA-11
Pepe et al (2022) [30]	Retrospective	Previous negative and positive Bx	100	66 (49–79) [a]	7.5	62	SUVmax ≥5	44 (44)	GG ≥2	68Ga-PSMA-11
Gao et al (2023) [24]	Prospective	Bx naïve	206	65 (44–89) [a]	14.3	115	Intense uptake higher than normal prostate background	111 (53.9)	GS ≥7	68Ga-PSMA-617
Shi et al (2024) [7]	Prospective	Bx naïve	56	–	–	15	PRIMARY ≥3	8 (14.3)	Not reported	68Ga-PSMA
Wong et al (2024) [21]	Prospective	Bx naïve	236	65 (59–70) [a]	6.3	116	SUVmax ≥7	84 (35.6)	GG ≥2	18F-DCFPyL
Guo et al (2024) [25]	Retrospective	Bx naïve	343	67 (62–73) [a]	9.3	216	PRIMARY ≥3	141 (41.1)	Not reported	68Ga-PSMA-11

AS = active surveillance; Bx = biopsy; csPCa = clinically significant prostate carcinoma; DCFPyL = pifuflolastat; GG = Gleason grade; GS = Gleason score; ISUP = International Society of Urological Pathology; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; SUVmax = maximum standardized uptake value; TCL = total core length.

[a] Median (interquartile range).

[b] Mean (range).

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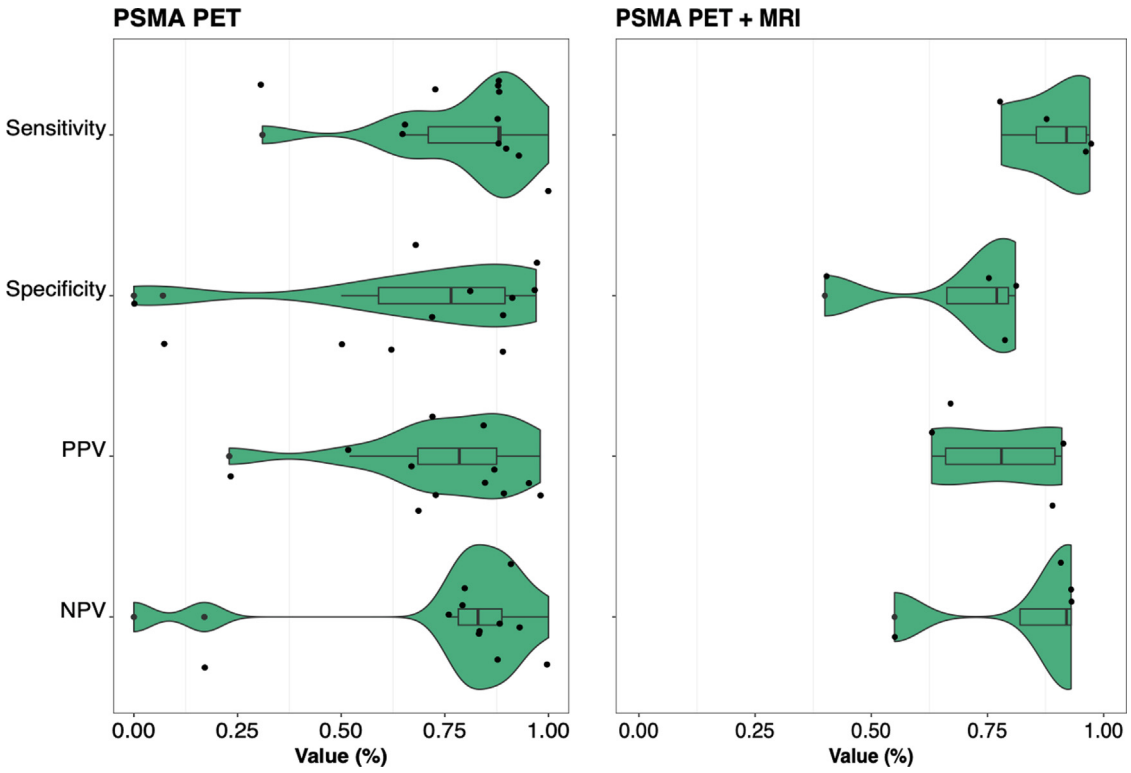

Fig. 2 – Summary of pooled meta-analyses testing the sensitivity, specificity, and positive and negative predictive values of PSMA PET and the combination of PSMA PET + MRI for the detection of clinically significant prostate cancer. MRI = magnetic resonance imaging; NPV = negative predictive value; PET = positron emission tomography; PPV = positive predictive value; PSMA = prostate-specific membrane antigen.

with at least one prior negative biopsy (128 patients). In pooled meta-analyses with random-effect models, sensitivity, specificity, PPV, and NPV were, respectively, 84%, 83%, 85%, and 82% in the biopsy-naïve cohorts, and 77%, 22%, 43%, and 50% in the previous negative biopsy cohort (Supplementary Fig. 6). No statistically significant differences were recorded in terms of sensitivity, specificity, PPV, or NPV at univariable metaregression.

3.3.5. *Investigating and addressing heterogeneity*

In subgroups analyses, τ^2 showed the presence of substantial heterogeneity in the previous negative biopsy cohort (τ^2 0.46, 0.47, and 1.22 for sensitivity, specificity, and NPV, respectively; Supplementary Fig. 2). Therefore, sensitivity analyses were performed including only the biopsy-naïve cohort (seven studies): here, meta-analyses with fixed-effect models showed sensitivity, specificity, PPV, and NPV of 88%, 78%, 84%, and 83%, respectively, consistent with the results of the analyses using random-effect models (Supplementary Fig. 7). Residual heterogeneity was identified (τ^2 varying from <0.01 to 0.05) but could not be addressed further due to limitation in data granularity.

3.3.6. *Variation in PPV and NPV over PCa prevalence and post-test probability of csPCa*

All the included studies reported sufficient data to estimate overall PCa prevalence, with a median prevalence of any PCa of 55% (interquartile range [IQR]: 46–67%). The PPV for csPCa significantly increased from 34% to 80% as the PCa prevalence increased from 25% to 70% (r = 0.69, p < 0.01). On the contrary, NPV decreased significantly from 98% to 87% as the PCa prevalence increased from 25% to 70% (r = –0.26, p < 0.01; Supplementary Fig. 8). The post-test effect in terms of csPCa likelihood is reported in Fig. 3 using Fagan plots. Notably, positive PSMA PET increased the post-test probability of having csPCa from 40% to 65% (positive likelihood ratio [PLR] of PSMA PET = 2.5; PLR of PSMA PET + MRI = 2.8). By contrast, in studies exploring the concomitant effect of PSMA PET and MRI, negative PSMA PET/MRI could substantially reduce the probability of having csPCa (from a mean probability of 64% to a post-test probability of 19%; negative likelihood ratio [NLR] of PSMA PET = 0.26; NLR of PSMA PET + MRI = 0.13).

3.4. *Evidence synthesis—primary staging*

3.4.1. *Patient characteristics*

Supplementary Table 1 summarizes the general and design characteristics of the selected studies. The primary analysis included 99 papers for qualitative review and quantitative synthesis [4,22,31–129]. At baseline, the final screened manuscripts reported detection rates in high-risk patients (18 studies), intermediate-risk patients (five study), and mixed patient cohorts (72 studies). Only four studies did not specify preoperative risk categories. Where possible, data on different patient subcohorts (ie, those with a high or an intermediate risk) were extracted from mixed cohorts. The majority of the included studies (n = 83) were based on patient cohorts receiving PSMA PET using 68-gallium as a radionuclide ligand for PSMA. Overall, in the final cohort of the included studies, 17 116 patients received preoperative PSMA PET. Among these men, 7713 included in 51 stud-

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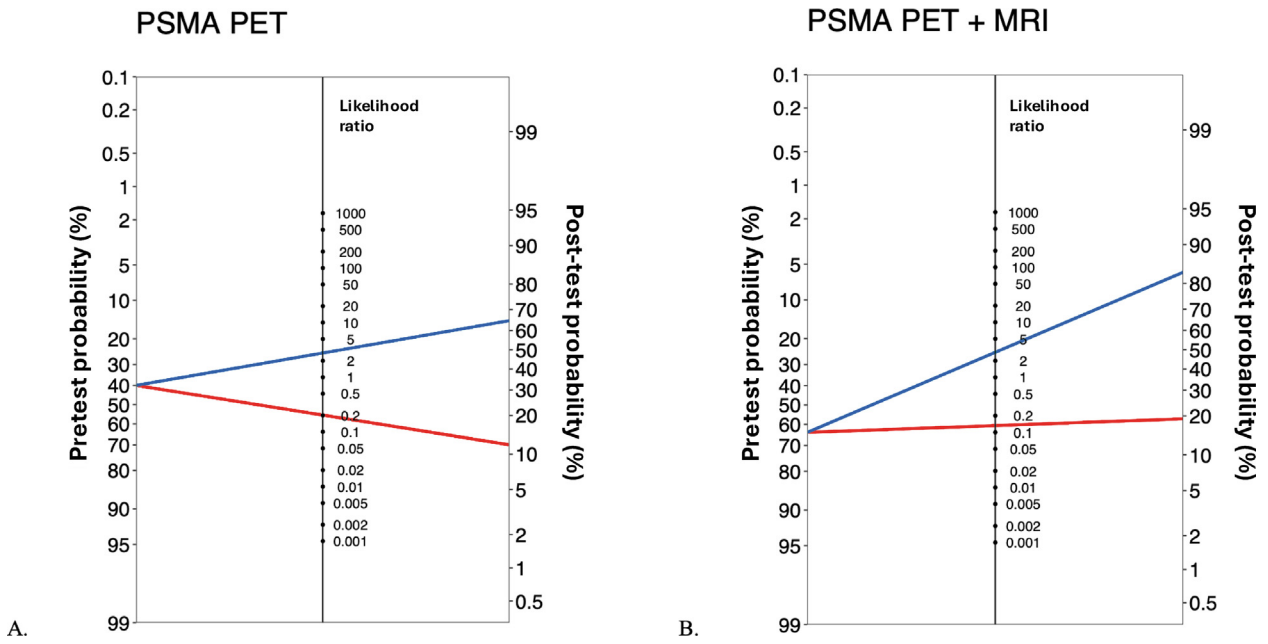

Fig. 3 – Fagan plots assessing the impact of (A) PSMA PET and (B) PSMA PET/MRI on post-test probability of csPCa in patients undergoing targeted prostate biopsy. The left axis shows the pretest probability, the right axis shows the post-test probability, and the central axis shows the likelihood ratios. The blue line traces the variation from pre- to post-test probability after intercepting the positive likelihood ratio (PLR; PLR PSMA PET = 2.5; PLR PSMA PET + MRI = 2.8), while the red line traces the variation from pre- to post-test probability of csPCa after intercepting the negative likelihood ratio (NLR; NLR PSMA PET = 0.26; NLR PSMA PET + MRI = 0.13). The pretest probability was calculated as the mean csPCa prevalence among the included studies. csPCa = clinically significant prostate cancer; MRI = magnetic resonance imaging; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.

ies underwent subsequent radical prostatectomy with PLND and were included in the final primary quantitative synthesis assessing diagnostic accuracy for LNI using a reference standard (ie, PLND).

3.4.2. Rates, predictors, and location of PSMA PET extraprostatic positivity

In the final cohort of studies included in a meta-analysis, PSMA PET showed a positive uptake outside the prostate in 24% (95% CI 0.21–0.27) of patients undergoing primary staging before the primary treatment for PCa (Supplementary Fig. 9). Based on the overall cohort stratification, the pooled estimate of PSMA PET positivity outside the prostate in five studies including patients with intermediate-risk disease was 15% (95% CI 6–27%), which was statistically significantly lower at metaregression when compared with the positivity rate in high-risk patients included in 18 studies (31%, 95% CI 22–39%, $p = 0.03$; Supplementary Fig. 9). Similarly, when comparing high- and intermediate-risk subgroups extracted from the main patient cohorts of the studies, the pooled estimate of positivity from 22 studies including intermediate-risk patients was lower than that extracted from 35 studies including high-risk patents only (12% vs 35%, $p < 0.01$; Supplementary Fig. 10). Interestingly, two studies including a low-risk cohort showed no PSMA PET uptake outside the prostate, while a single study including a cohort of very-high-risk patients demonstrated a positivity rate of 74%. In a sensitivity analysis including only studies with a low risk of bias ($n = 59$), positivity rates of PSMA PET uptake outside the prostate were consistent with those of the primary analysis (24%, 95% CI 20–28%; Supplementary Fig. 11).

Ninety-two studies involving 4476 patients were available for an evaluation of PSMA PET positivity in regional lymph nodes and 67 studies for various distant anatomical sites. The pooled estimate of positivity in the pelvic lymph nodal region was 21% under the random-effect assumption, with proportions being very low in sites outside the pelvis (Supplementary Fig. 12). Specifically, the estimates of positivity were 4% in extrapelvic lymph nodes, 7% in bone, and 1% in distant viscera. Pooled estimates were observed to be generally different among risk subgroups: the proportion of PSMA PET positivity observed in pelvic lymph nodes in high-risk patients was significantly higher than that in their intermediate-risk counterparts (25% vs 10%, $p < 0.001$). Notably, PSMA PET positivity outside the pelvic area in intermediate-risk patients was negligible (all <1%), while the positivity rate in high-risk patients was 5% in both extrapelvic lymph nodes and bone (Fig. 4 and Supplementary Fig. 13). In sensitivity analyses relying on studies using the PROMISE criteria (eight studies), PSMA PET showed a positive uptake outside the prostate in 32% (95% CI 0.22–0.42) of patients receiving primary staging before the primary treatment for PCa (Supplementary Fig. 14). When exploring the anatomical site of positivity, rates were generally higher among all sites when compared with the results from the main meta-analysis (regional nodes 31%, distant nodes 9%, and bone 12%; Supplementary Fig. 14).

3.4.3. Diagnostic accuracy of PSMA PET scans for local staging (extracapsular extension and seminal vesicle invasion)

In the univariate pooled meta-analysis using random-effect models (five studies), the pooled sensitivity of PSMA PET for the detection of extracapsular extension was 71% (95% CI

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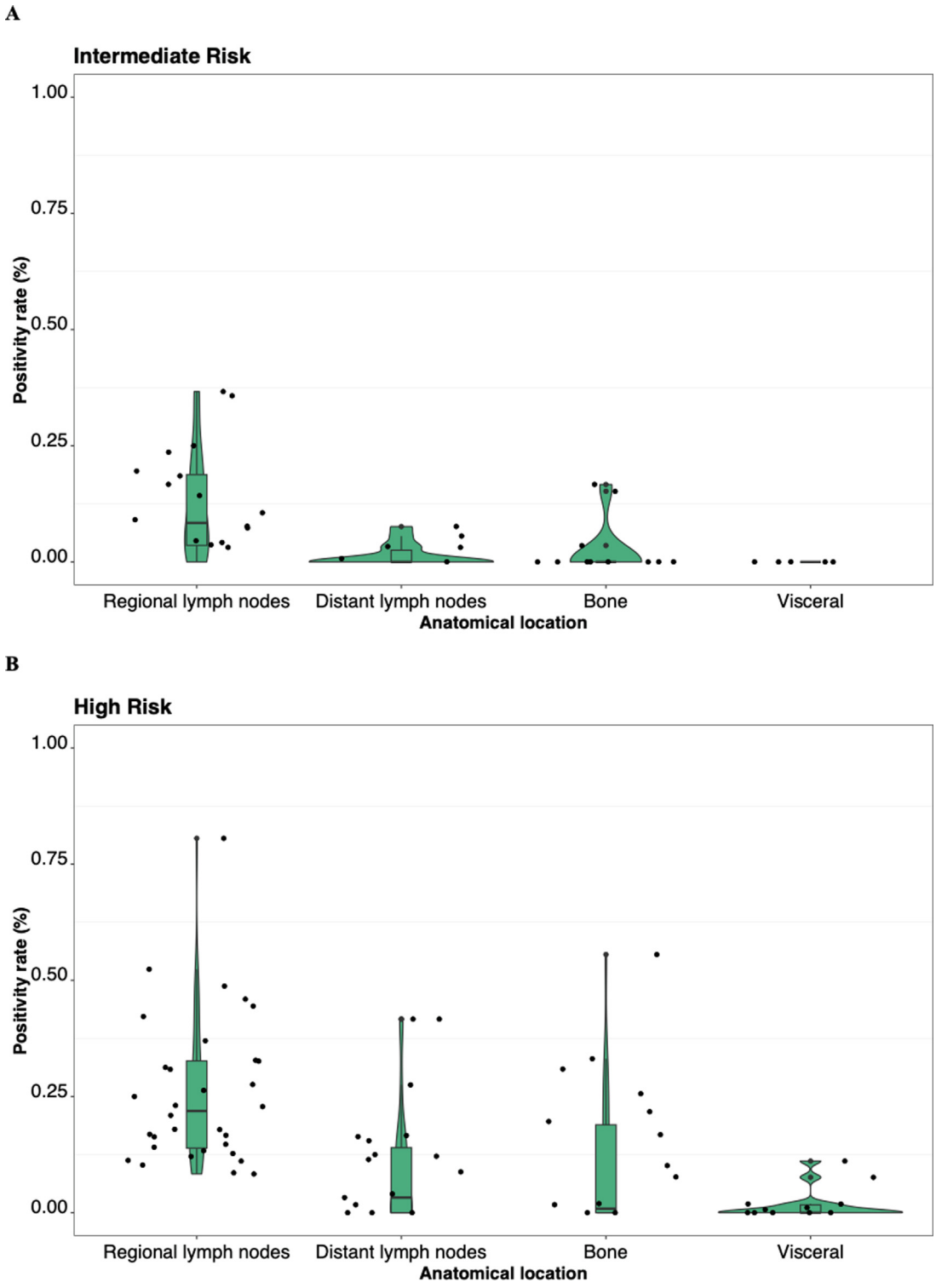

Fig. 4 – Subgroup analyses of the rate of positive uptake of PSMA PET in (A) intermediate-risk and (B) high-risk patients stratified according to anatomical location. PET = positron emission tomography; PSMA = prostate-specific membrane antigen.

46–61%) and the pooled specificity was 84% (95% CI 67–95%), while the PPV and NPV were 80% (95% CI 70–88%) and 79% (95% CI 64–91%), respectively (Supplementary Fig. 15). Regarding the detection of seminal vesicle invasion (SVI) by PSMA PET (six studies), the pooled sensitivity was 71% (95% CI 46–61%) and the pooled specificity was 93% (95% CI 88–96%). Similarly, the PPV and NPV were 73% (95% CI 62–83%) and 91% (95% CI 84–96%), respectively (Supplementary Fig. 15).

3.4.4. Diagnostic accuracy of PSMA PET scans for LNI

In the univariate pooled meta-analysis using random-effect models, the pooled sensitivity of PSMA PET for the detection of LNI was 54% (95% CI 48–60%) and the pooled specificity

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was 94% (95% CI 93–96%; Supplementary Fig. 16). At the bivariate analysis, the diagnostic accuracy of PSMA PET estimated through an SROC-derived AUC was 87% (95% CI 81–87%; bivariate sensitivity 52% and specificity 93%; Supplementary Fig. 17). In order to address the risk of biases, we performed a subsequent sensitivity analysis that included only studies with a low risk for bias, showing results consistent with those of the primary analysis (n = 36; sensitivity 52% [95% CI 45–59%] and specificity 95% [95% CI 93–96%]; Supplementary Fig. 16).

In analyses testing for DOR, a meta-analysis using random-effect models demonstrated a pooled OR of 16 (95% CI 12–20). In analyses testing for the predictive value, pooled meta-analyses using random-effect models demonstrated a PPV of 77% (95% CI 72–82%) and an NPV of 86% (95% CI 84–88%; Supplementary Fig. 16). In a sensitivity analysis including only studies with a low risk of bias (n = 36), the PPV (78%, 95% CI 71–84%), NPV (86%, 95% CI 84–89%), and DOR (OR 14.7, 95% CI 10.4–20.9) were consistent with those of the primary analysis (Supplementary Fig. 18). Similarly, in sensitivity analyses testing the diagnostic accuracy for LNI among studies using the PROMISE criteria (four studies), sensitivity (49%, 95% CI 25–73%), specificity (93%, 95% CI 87–97%), PPV (70%, 95% CI 57–82%), and NPV (82%, 95% CI 78–85%) were all substantially in line with the results of the main analysis (Supplementary Fig. 19).

3.4.5. Subgroup analyses according to overall risk group cohorts

In subgroup analyses testing the impact of different risk groups in the overall study cohorts, data for quantitative comparison were extracted from nine studies for high-risk patients (1387 patients), four studies for intermediate-risk patients (199 patients), 37 studies for mixed cohorts (6037 patients), and one study for unspecified risk cohorts (90 patients). In pooled meta-analyses with random-effects model, the sensitivity, specificity, PPV, and NPV for LNI were, respectively, 57%, 96%, 86%, and 86% in the high-risk cohorts; 57%, 94%, 61%, and 93% in the intermediate-risk cohorts; 57%, 94%, 75%, and 85% in the mixed risk cohorts; and 57%, 94%, 85%, and 80% in the unspecified risk cohorts (Supplementary Fig. 20). Univariable metaregression demonstrated absence of statistically significant differences (p = 0.8) in sensitivity and specificity between the overall risk cohorts, while differences in PPV and NPV were statistically significant (p < 0.01).

3.4.6. Subgroup analyses according to subgroups extracted from the main patient cohorts

For subgroups analyses comparing high- and intermediate-risk subgroups extracted from the main patient cohorts of the studies, data for a quantitative comparison were extracted from 14 studies exploring high-risk cohorts (1116 patients) and from seven studies testing the accuracy of PSMA in intermediate-risk cohorts (332 patients; Fig. 5 and Supplementary Fig. 21). In pooled meta-analyses with random-effect models, the sensitivity, specificity, PPV, and NPV for LNI were, respectively, 52%, 95%, 83%, and 82% in the high-risk cohorts, and 52%, 95%, 57%, and 91% in the intermediate-risk cohorts. Univariable metaregression confirmed the absence of statistically significant differences (p = 0.9) in sensitivity and specificity between the high- and intermediate-risk cohorts, while significant differences were recorded in PPV and NPV (p < 0.01).

3.4.7. Subgroups analyses according to PSMA PET ligand

In subgroup analyses testing the impact of PSMA PET ligand type, data for a quantitative comparison were extracted from 74 (10149 patients) and 20 (6240 patients) studies using 68Ga- and 18F-PSMA PET, respectively. The overall positivity rate was comparable among the two cohorts, with no relevant differences even after stratification according to anatomical sites (Supplementary Fig. 22 and 23). In pooled meta-analyses with random-effect models testing for accuracy in detecting LNI (49 studies), the sensitivity, specificity, PPV, and NPV for LNI were, respectively, 57%, 95%, 80%, and 87% in the 68Ga-PSMA PET cohort, and 42%, 94%, 85%, and 80% in the 18F-PSMA PET cohort (Supplementary Fig. 24). Univariable metaregression demonstrated a statistically significant difference (p = 0.03) in sensitivity in favor of 68Ga-PSMA (57% vs 42%), while no significant differences were recorded for specificity, PPV, and NPV (all p > 0.05).

3.4.8. Investigating and addressing heterogeneity

Univariable metaregression showed significant difference in sensitivity based on the ligand used (sensitivity in favor of 68Ga-PSMA: 57% vs 42%, p = 0.03; Supplementary Fig. 24); therefore, sensitivity analyses were performed including only studies using 68Ga-PSMA (39 studies): here, meta-analyses with fixed-effect models showed sensitivity, specificity, PPV, and NPV of 54%, 95%, 78%, and 87%, respectively, consistent with the results of the analyses using random-effect model (Supplementary Fig. 25). Residual heterogeneity was identified (τ^2 varying from <0.01 to 0.03) but could not be addressed further due to limitation in data granularity.

3.4.9. Variation of PPV and NPV over LNI prevalence and post-test probability of LNI

The overall median prevalence of LNI across the included studies was 20% (IQR: 11–34%, range: 2–82%), while it was 12% in studies relying on intermediate-risk cohorts and 24% in studies of high-risk cohorts. The PPV increased significantly from 56% to 88% as the LNI prevalence increased from 5% to 40% (r = 0.69, p = 0.02). On the contrary, NPV decreased significantly from 95% to 79% as the prevalence of LNI increased from 5% to 40% (r = –0.43, p = 0.03; Supplementary Fig. 26). The post-test effect in terms of LNI likelihood was reported in Fig. 6 using Fagan plots. Notably, in high-risk patients, positive PSMA PET increased the post-test probability of having LNI significantly from 24% to 77% (PLR of PSMA PET = 9.5). By contrast, in intermediate-risk patients, negative PSMA PET halves the risk of LNI (NLR of PSMA PET = 0.45).

4. Discussion

This systematic review was aimed at updating and corroborating evidence from previous works, providing initial evi-

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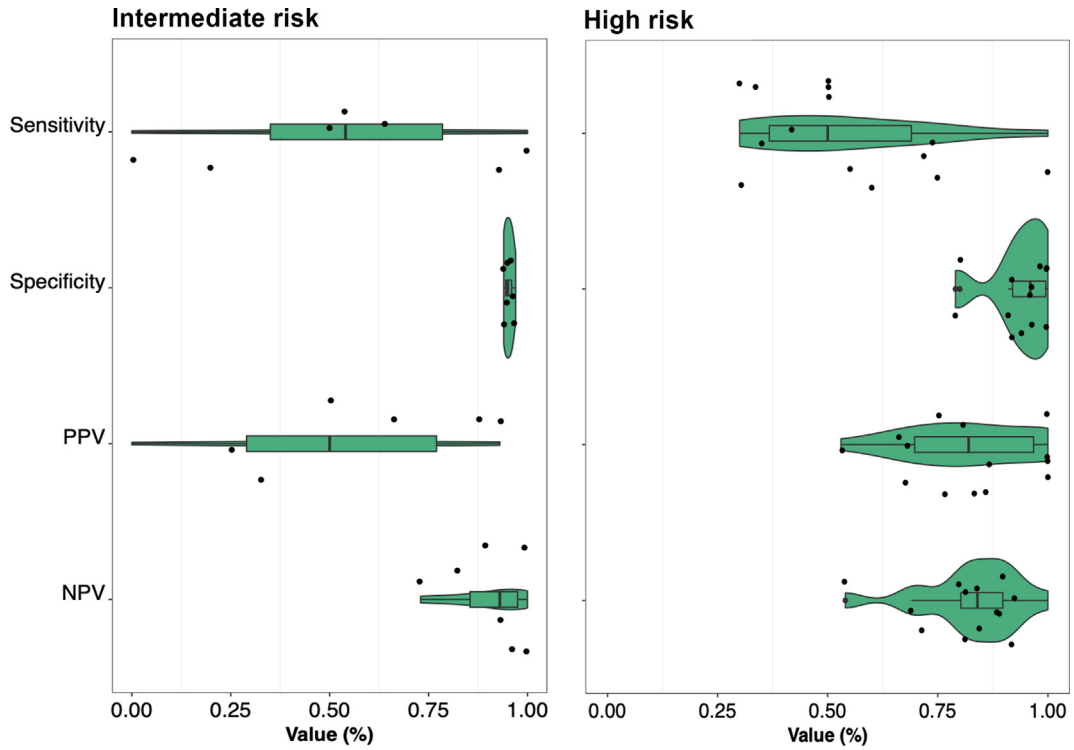

Fig. 5 – Summary of pooled meta-analyses testing the sensitivity, specificity, and positive and negative predictive values of PET PSMA for the detection of LNI stratified according to risk groups. LNI = lymph nodal invasion; NPV = negative predictive value; PET = positron emission tomography; PPV = positive predictive value; PSMA = prostate-specific membrane antigen.

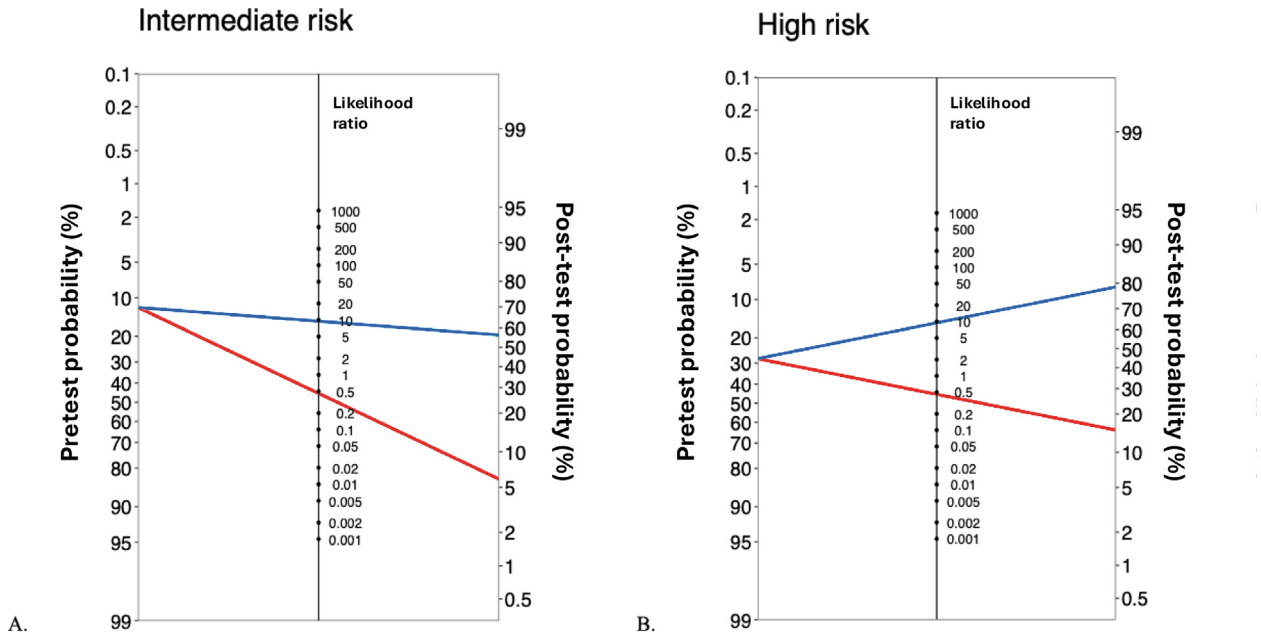

Fig. 6 – Fagan plots assessing the impact of PSMA PET on the post-test probability of LNI in patients with (A) intermediate-risk and (B) high-risk prostate cancer undergoing radical prostatectomy with pelvic lymph node dissection. The left axis shows the pretest probability, the right axis shows the post-test probability, and the central axis shows the likelihood ratios. The blue line traces the variation from pre- to post-test probability of LNI after intercepting the positive likelihood ratio of 9.5, while the red line traces the variation from pre- to post-test probability of LNI after intercepting the negative likelihood ratio of 0.45. The pretest probability was calculated as the mean LNI prevalence among the included studies stratified according to risk group. LNI = lymph nodal invasion; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.

dence about the role of PSMA PET in diagnosis and staging of PCa [11,13,14]. In the current review, given the increasing interest and utilization of PSMA PET in multiple disease stages and particularly in earlier stages, the initial data collection included a significant number of records (3878) of patients undergoing initial screening, followed by a more

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targeted evaluation that culminated in 12 studies being included for an intraprostatic diagnostic assessment and 100 for metastatic staging analyses. The rigorous methodology implemented, including multiple reviewers working independently and adhering to the predefined criteria, enhanced the reliability and robustness of the findings. As a result of this thorough process, several results of interest were recorded and deserve accurate discussion.

First, PSMA PET demonstrates good accuracy for diagnosing intraprostatic csPCa, with the meta-analysis showing pooled sensitivity and specificity of 82% and 67%, respectively. The high sensitivity (82%) indicates that PSMA PET is particularly effective at identifying true positives, making it a useful tool for detecting csPCa in patients in whom traditional imaging or biopsies have failed. These results are in line with previous systematic reviews and meta-analyses [11], thus reinforcing the option of using PSMA PET as a viable alternative to MRI for biopsy targeting. Moreover, the combination of PSMA PET and MRI appears to enhance the diagnostic performance further, with sensitivity improving to 91% and specificity remaining comparable at 68%. The pooled OR of 22 suggests a notably improved diagnostic value when both modalities are used together. This synergistic effect may arise from the complementary strengths of PSMA PET in molecular imaging and MRI in high-resolution anatomical imaging. As a consequence, the combined use of PSMA PET and MRI could also reduce unnecessary biopsies, thus corroborating most recent efforts to omit a biopsy in specific prediction constellations building upon PSMA PET [6,130]. The variation in NPV and PPV based on cancer prevalence (ie, as PCa prevalence increased, PPV increased while NPV decreased) suggests that the utility of PSMA PET might be enhanced or constrained depending on the population it is applied to. This finding aligns with the results from a post-test probability analysis, where PSMA PET results altered the likelihood of csPCa significantly: for example, PSMA PET can assist in the decision-making process in cases with borderline indication for a biopsy, such as when elevated prostate-specific antigen (PSA) levels are not corroborated by consistent MRI findings (eg, Prostate Imaging Reporting and Data System score $\leq$3), thanks to its robust NLR of =0.26. However, a negative result alone is insufficient to definitively rule out the need for a biopsy in patients at risk, particularly when post-test probabilities remain above the commonly used risk thresholds. NPV is influenced by several factors, including the prevalence of csPCa and study heterogeneity. Therefore, integration of PSMA PET results with MRI findings and additional clinical parameters is essential to establish more reliable criteria for avoiding unnecessary biopsies.

Regarding metastatic staging, the meta-analysis highlights the ability of PSMA PET to detect metastatic disease outside the prostate, with notable variation based on patient risk stratification. Here, high-risk patients demonstrated a PSMA PET positivity rate of 31%, compared with just 15% in intermediate-risk patients. When looking at the anatomical location of metastasis, the pooled estimate of pelvic lymph node positivity in high-risk patients was 25%, while intermediate-risk patients had a much lower positivity rate of 10% for pelvic nodes. Similarly, the risk of metastasis beyond the pelvic area was negligible in intermediate-risk patients (<1%), while high-risk patients showed a 5% positivity rate in extrapelvic nodes and bone. This difference reinforces the idea that PSMA PET is most valuable in high-risk cohorts, where the likelihood of metastasis is higher and the need for accurate staging is more important in the setting of a potential multimodal treatment plan. In this context, future studies aimed at developing an optimal definition of oligometastatic disease are warranted to clarify which patients might benefit from upfront or early salvage multimodal treatments [131–134]. The significantly lower positivity rates in intermediate-risk patients also raise questions about whether PSMA PET should be used routinely for staging in this group, or whether it should be reserved for patients with other indications of high-risk disease.

When considering pathology as the reference standard, PSMA PET demonstrated very high specificity, making it a valuable integrative tool for ruling out lymph nodal metastasis or presence of SVI when combined with additional clinical information. However, the relatively lower sensitivity suggests that it may miss some positive cases, particularly in the presence of micrometastatic disease [135]. However, whether these micrometastases missed at PSMA PET might significantly impact the patient prognosis is still unknown [136]. Of note, in subgroup analyses, the use of 68Ga-PSMA seemed to be associated with higher sensitivity than the use of 18F-PSMA (57% vs 42%). We also confirmed that the performance of PSMA PET is influenced by baseline LNI prevalence, where PPV increased significantly with a higher prevalence, while NPV decreased. This data might still support the utility of preoperative nomograms determining the preoperative risk of LNI, which might be particularly important in patients with unfavorable intermediate-risk features [137]. In fact, while we could not perform a specific subanalysis for unfavorable intermediate risk, reporting of the variation of the predictive value of PSMA PET according to baseline risk could provide the closest approximation to the goal of exploring different subsets of risk profiles. In this context, our analysis represents a key addition to the available evidence and to a key debate where consensus is still lacking [138].

From a clinical perspective, the main implications for clinical practice from our meta-analyses can be summarized as follows: (1) PSMA PET is a valuable tool for the detection of csPCa and should be considered as a viable alternative to MRI or in combination with MRI to enhance diagnostic accuracy; nonetheless, its NPV alone is insufficient to omit a biopsy, requiring integration with MRI and clinical parameters; (2) staging PSMA PET provides important information for treatment planning, especially in high-risk patients with higher positivity rates; these patients may benefit from upfront or early salvage multimodal treatment, warranting further research into targeted therapies such as stereotactic ablative radiotherapy; (3) when considering to perform LND, PSMA PET provides useful information to confirm or revise the surgical plan, but integration with additional patient data (such as PSA, and Gleason grade or stage) is still recommended.

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Taken together, our findings highlight the important role of PSMA PET in diagnosis and primary staging. As largely discussed in the literature, several additional challenges still need to be considered when aiming for a broad implementation of PSMA PET in this disease setting; these include and are not limited to cost effectiveness, equipment and tracer availability, the true clinical benefit compared with the current gold standard in the diagnostic pathway (ie, MRI), and the potential for combining this test with novel biomarkers [139]. For instance, recent and ongoing studies evaluating the accuracy of PSMA PET and its impact on outcomes, such as the PRIMARY 2 study [140] or the follow-up analyses form the proPSMA study [141], might provide further guidance regarding indications and clinical implications. However, well-designed and targeted prospective studies are still required to address existing knowledge gaps. Last but not least, a closer evaluation of the use of standardized reporting systems will also be a crucial point of research and discussion [8]. For instance, only a limited proportion of studies included in the current review relied exclusively on the PROMISE tumor, node, metastasis (TNM) criteria for a PSMA PET assessment [18,142]. By providing a structured approach to defining disease stages, the PROMISE TNM criteria minimize interobserver variability, ensure comparability across studies, and facilitate more reliable clinical decision-making. Therefore, we believe that a routine implementation of these criteria might further improve the accuracy of a preoperative assessment.

Despite the clinical relevance of our findings, a few limitations of our study need to be mentioned. First, the use of different combinations of radioligands and anatomical imaging modalities (ie, CT or MRI) might represent a residual confounder that is not accounted for in the current analysis. Second, our analysis does not provide a specific focus on the impact of the quality chain for a PSMA PET assessment (ie, imagine quality, readout quality, data processing, and image registration), which may determine further variability in the diagnostic and staging accuracy. Third, despite investigating and addressing heterogeneity based on the available data, we reported residual heterogeneity between studies likely due to differences in sampling techniques, populations, protocols, and experience of clinicians. Furthermore, different definitions of csPCa and positivity at PSMA PET might also have contributed to residual heterogeneity among studies. For csPCa, thresholds such as Gleason grade $\geq$3 + 4 or tumor core length are applied variably, complicating comparisons across studies. Similarly, there is no consensus on the cutoffs of the maximum standardized uptake value for PSMA PET positivity, which may influence sensitivity and specificity significantly. Standardization of these definitions across future studies is critical to improving the generalizability and clinical applicability of PSMA PET results. As a consequence, the clinical value of PSMA PET should be interpreted in the context of potential marginal residual heterogeneity, which remained unexplored due to limited data granularity: for instance, the estimated post-test probabilities may vary based on different clinical scenarios and settings, and the values reported in the current study represent only an average. Therefore, we reinforce the need to integrate PSMA PET with additional individual information to determine clinical recommendation. This said, meta-analytic estimates of the current study can still be considered a robust assessment of the available evidence given the structured approach to investigate and address heterogeneity. Lastly, a detailed histopathological evaluation, including cellular PSMA expression and the use of immunohistochemistry to identify micrometastatic disease, was reported rarely in the reviewed studies. This gap may partially explain the limited sensitivity of PSMA PET for the detection of micrometastases. Future studies should incorporate comprehensive pathological workup, correlating imaging findings with histopathological data to refine PSMA PET diagnostic thresholds.

5. Conclusions

The current systematic review and meta-analysis provides updated evidence on the diagnostic and staging accuracy of PSMA PET in PCa. We reported good accuracy of PSMA PET, particularly when combined with MRI, to distinguish csPCa, but NPV alone is insufficient to omit a biopsy. Regarding staging, PSMA PET cannot be used alone to determine the need for LND; thus, a combination of PSMA PET with additional patient information, such as PSA, stage, or grade, is recommended. Notably, these findings primarily apply to biopsy-naïve patients and men staged with PSMA PET using 68Ga-based ligands, given the lower yet persistent study heterogeneity compared with the overall cohort. Taken together, further research should develop and validate models that incorporate PSMA PET to reliably inform biopsy or LND.

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

Study conception and design: Mazzone, Murphy, Briganti, Perera.
Acquisition of data: Cannoletta, Quarta, Chen, Thomson.
Analysis and interpretation of data: Mazzone, Cannoletta, Quarta, Chen, Thomson, Barletta, Stabile.
Drafting of the manuscript: Mazzone, Cannoletta, Perera.
Critical revision of the manuscript for important intellectual content: Moon, Eapen, Lawrentschuk, Montorsi, Siva, Hofman, Chiti.
Statistical analysis: Mazzone.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Murphy, Briganti, Perera.
Other: None.

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Supplementary material

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