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Extraprostatic Lesion Detection, Anatomic Distribution, and Disease Burden on PSMA PET/CT for Initial N/M Staging of Newly Diagnosed Unfavorable Intermediate- and High-Risk Prostate Cancer: A Systematic Review and Meta-analysis

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 October 2026 and was last updated on 20 October 2026.

INTRODUCTION

Review question / Objective To synthesize extraprostatic detection, miN/miM distribution, pelvic nodal diagnostic performance, and quantitative disease burden.

Condition being studied Newly diagnosed unfavorable intermediate-risk, high-risk, and very-high-risk prostate cancer, with a focus on extraprostatic disease detected by prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT). The review evaluates the detection and anatomical distribution of regional pelvic lymph-node metastases, nonregional lymph-node metastases, bone metastases, and visceral or other distant-organ metastases during initial staging. It also examines the diagnostic performance of PSMA PET/CT for pelvic nodal metastases and the quantitative burden of extraprostatic disease. The review aims to characterize the clinical yield and limitations of

PSMA PET/CT in identifying nodal and distant disease before definitive local therapy or initial systemic treatment.

METHODS

Participant or population Adults with histologically confirmed, newly diagnosed, treatment-naïve prostate cancer classified as unfavorable intermediate-risk, high-risk, very-high-risk, or locally advanced disease who undergo PSMA PET/CT for initial staging before definitive local therapy or initial systemic treatment. Studies involving mixed-risk populations will be eligible when the relevant risk subgroup can be extracted separately or clinically interpretable risk-stratified outcomes are available. Eligible studies must include at least 40 relevant patients. Selected metastatic cohorts may contribute to disease-distribution or disease-burden analyses but will not contribute to initial-detection prevalence estimates when metastatic status is an eligibility requirement.

Intervention Prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT) performed for initial staging of newly diagnosed prostate cancer. Eligible examinations must use a gallium-68- or fluorine-18-labelled PSMA-targeted radiotracer. The review evaluates patient-level detection of extraprostatic disease, anatomical distribution of regional and distant metastases, pelvic nodal diagnostic accuracy, quantitative disease-burden measures (including lesion count, PSMA-derived tumor volume, total tumor volume, and total-lesion uptake), and management changes attributable to metastatic staging.

Comparator For diagnostic-accuracy analyses of pelvic nodal metastases, the preferred reference standard is histopathological examination following pelvic lymph-node dissection. For other disease-distribution and burden outcomes, clinical imaging interpretation, longitudinal follow-up, or an appropriate composite reference standard will be accepted as reported by the original studies. No single active comparator intervention is required for the detection-prevalence and disease-distribution analyses. Studies comparing PSMA PET/CT with other imaging modalities may contribute relevant outcomes when these meet the review's eligibility criteria.

Study designs to be included Original prospective or retrospective studies published as full articles, including prospective diagnostic-accuracy cohorts and phase 2/3 or phase 3 trials, retrospective surgical or staging cohorts, analytical cross-sectional imaging-biomarker studies, and prognostic disease-burden cohorts. Eligible studies must include at least 40 relevant patients and report at least one prespecified outcome.

Eligibility criteria Studies must be full-text original research articles first published online between January 1, 2020, and July 1, 2026. Eligible participants must be adults with histologically confirmed, newly diagnosed, treatment-naïve prostate cancer undergoing PSMA PET/CT before definitive local therapy or initial systemic treatment. The relevant population must comprise unfavorable intermediate-risk, high-risk, very-high-risk, or locally advanced disease, or provide an extractable relevant subgroup or interpretable risk-stratified results. Studies must include at least 40 relevant patients, use a gallium-68- or fluorine-18-labelled PSMA PET/CT tracer, and report at least one eligible patient-level outcome. Eligible outcomes include extraprostatic nodal or metastatic positivity, site-specific miN/miM distribution, diagnostic accuracy, lesion number,

disease-burden measures, or management changes attributable to metastatic staging. Mixed primary-staging and recurrence cohorts are eligible only when the primary-staging subgroup can be extracted independently.

Exclusion criteria include studies limited to biochemical recurrence, post-treatment restaging, treatment-response assessment, nonmetastatic castration-resistant disease, or radioligand-therapy eligibility; inseparable primary and recurrent cohorts; studies reporting only intraprostatic detection or local T staging; PET/MRI-only studies without separable PET/CT data; cohorts with fewer than 40 relevant patients; lesion-level diagnostic results without patient-level denominators; abstracts without corresponding eligible full-text articles, editorials, reviews, protocols, case reports, and small case series; overlapping cohorts without unique data; and studies for which the required events, denominators, or quantitative summaries cannot be recovered. Selected metastatic cohorts may be included for descriptive disease-distribution or burden analyses but excluded from initial-detection prevalence pooling when metastatic status was an entry criterion.

Information sources The following electronic databases will be searched: PubMed/MEDLINE, Embase, Web of Science Core Collection, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL). Searches will cover studies first published online from January 1, 2020, through July 1, 2026.

The search strategy will combine terms relating to prostate cancer, prostate-specific membrane antigen (PSMA), positron emission tomography (PET) or PET/computed tomography (PET/CT), initial or primary staging, lymph-node involvement, metastases, anatomical distribution, lesion count, and quantitative disease burden. Database-specific search strategies, including field tags and publication-date limits, are provided in the supplementary material.

Reference lists of eligible studies, recent systematic reviews, imaging procedural standards, and relevant clinical guidelines will be screened to identify additional reports. Conference abstracts will be used only to identify corresponding full-text articles. When multiple publications describe potentially overlapping patient cohorts, the most complete report will be retained unless distinct denominators and outcomes justify separate inclusion. The manuscript does not specify additional author contact, trial-register searches, or a separate grey-literature search.

Main outcome(s) The main outcomes are:

1. Extraprostatic disease detection: Patient-level proportion of patients with any PSMA-positive disease outside the prostate, including regional nodal and/or distant metastatic disease, expressed as a pooled proportion with a 95% confidence interval (CI).

2. Anatomical distribution of metastases: Patient-level proportions of pelvic regional nodal disease (miN1), nonregional nodal metastases (miM1a), bone metastases (miM1b), visceral or other distant-organ metastases (miM1c), and any distant M1 disease, each reported separately with pooled proportions and 95% CIs.

3. Pelvic nodal diagnostic accuracy: Patient-level sensitivity and specificity of PSMA PET/CT for pelvic lymph-node metastases, using histopathology after pelvic lymph-node dissection as the preferred reference standard. Summary sensitivity, specificity, false-positive rate, and the summary receiver operating characteristic (SROC) area under the curve will be reported with 95% CIs.

4. Quantitative disease burden: Lesion count, single or oligometastatic disease, diffuse skeletal involvement, PSMA-derived tumor volume (PSMA-TV), whole-body total tumor volume (PSMA-TTV), total-lesion uptake (PSMA-TL or PSMA-TTL), and spatial dissemination. Compatible measures will be pooled where feasible; otherwise, medians and interquartile ranges will be summarized descriptively.

5. Clinical management impact: Changes in management attributable to metastatic staging will be described when reported.

The primary assessment time point is initial staging before definitive local therapy or initial systemic treatment. Disease-distribution outcomes will use the full eligible initial-staging cohort as the denominator. Diagnostic outcomes will use patient-level 2 × 2 data. Follow-up timing will be recorded where relevant and available in the original studies.

Quality assessment / Risk of bias analysis

Methodological quality and risk of bias will be assessed using tools appropriate to each primary study design. Diagnostic-accuracy studies will be evaluated using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool, covering patient selection, index test, reference standard, and flow and timing, with separate assessments of applicability concerns.

Studies reporting detection prevalence or anatomical disease distribution will be assessed using the Joanna Briggs Institute (JBI) prevalence checklist. Analytical cross-sectional imaging-biomarker studies will be evaluated using the JBI analytical cross-sectional checklist. Prognostic

disease-burden studies will be assessed using the Quality In Prognosis Studies (QUIPS) tool, covering study participation, study attrition, prognostic-factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. Judgements will be supported by written justifications. Overall risk will be classified as high when at least one domain is likely to materially affect the target estimate; moderate concern will indicate unresolved limitations without a dominant high-risk mechanism. Results will be summarized descriptively using domain-level and overall assessments. Because the tools address different study designs, their categories will not be treated as directly equivalent. Risk-of-bias assessments will inform interpretation of the findings rather than be used as statistical weights in the meta-analysis.

Strategy of data synthesis A systematic review with outcome-specific quantitative meta-analyses will be conducted. All eligible studies will be included in the systematic review, while each meta-analysis will include only studies reporting compatible outcomes with exact numerators and denominators or reconstructable patient-level diagnostic 2 × 2 tables.

Patient-level detection and disease-distribution proportions will be synthesized using random-intercept logistic regression models with a logit transformation. Exact Clopper–Pearson confidence intervals will be calculated for individual studies. Pooled proportions will be reported with 95% CIs, between-study variance (tau-squared), I-squared, Cochran's heterogeneity test, and 95% prediction intervals when at least three studies are available. Cohorts in which metastatic or nonmetastatic status was fixed by eligibility criteria will be excluded from the primary detection-prevalence models.

Pelvic nodal diagnostic accuracy will be synthesized using a bivariate random-effects Reitsma model estimated by restricted maximum likelihood. Summary sensitivity and false-positive rate, corresponding specificity, between-study variance components, the summary receiver operating characteristic curve, and its area under the curve will be reported. Study-specific sensitivity and specificity will also be presented in forest plots. Bone diagnostic accuracy will be analyzed separately when available and will not be combined with pelvic nodal accuracy when reference standards differ.

Disease-burden measures will be pooled only when at least three studies use sufficiently compatible metrics, anatomical scopes, units, segmentation thresholds, and summary statistics. Otherwise, medians and interquartile ranges will be presented descriptively. Primary-tumor PSMA-TV,

whole-body PSMA-TTV, and uptake-volume measures will be treated as distinct outcomes. Potentially overlapping cohorts will be handled separately for each outcome, and the patient will be the unit of analysis. Site-specific miN/miM outcomes will be analyzed separately because categories may overlap within patients. All analyses will be performed in R version 4.4.2 using the meta, metafor, mada, ggplot2, and robvis packages. Two-sided P values below .05 will be considered statistically significant.

Subgroup analysis Prespecified subgroup analyses will compare gallium-68-labelled and fluorine-18-labelled PSMA PET/CT tracers for pelvic miN1 positivity and bone metastasis (miM1b), provided that at least two studies are available in each subgroup. These analyses will explore potential differences in detection and disease-distribution estimates according to tracer class.

Subgroup findings will be interpreted cautiously because tracer type may be confounded by differences in patient risk profiles, study centres, acquisition protocols, image-reading methods, and reference standards. The small number of studies available for some outcomes may limit statistical power and the reliability of between-subgroup comparisons. No firm comparative conclusions will be drawn when the evidence is insufficient.

Disease-distribution and diagnostic-accuracy outcomes will remain separate, and pelvic nodal and bone diagnostic results will not be combined when their reference standards differ.

Sensitivity analysis Leave-one-study-out sensitivity analyses will be conducted for sufficiently populated proportion meta-analyses, including pelvic miN1 positivity, any distant M1 disease, miM1a disease, and miM1b disease, to assess the influence of individual studies on pooled estimates.

Additional sensitivity analyses will include selected metastatic cohorts in the relevant disease-distribution analyses to examine potential spectrum effects. Such cohorts will be excluded from primary initial-detection prevalence estimates when metastatic status was an eligibility requirement.

For studies with multiple reader interpretations, the prespecified primary or majority interpretation will be used in the main analysis, with alternative reader interpretations examined in sensitivity analyses when data are available. Potentially overlapping cohorts will be handled by outcome, and diagnostic accuracy analyses will use the prespecified reference standards.

Small-study effects will be explored only for outcomes represented by at least 10 studies. Deeks-type asymmetry regression will be used for diagnostic-accuracy analyses, while regression analyses for pooled proportions will be considered exploratory. Funnel plots will be interpreted cautiously because the number of studies may be limited.

Disease-burden measures will not be combined in sensitivity analyses when their definitions, anatomical scopes, units, segmentation thresholds, or summary statistics are incompatible. Results will be compared with the primary analyses to assess the robustness and interpretability of the findings.

Country(ies) involved China.

Keywords Prostatic Neoplasms; Positron-Emission Tomography; Lymphatic Metastasis; Neoplasm Metastasis.

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