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ADMINISTRATIVE INFORMATION**Support** - N/A.**Review Stage at time of this submission** - Completed but not published.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2025100084

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 October 2025 and was last updated on 23 October 2025.

INTRODUCTION

Review question / Objective Multiple PSMA-targeted PET radiotracers have been developed and are increasingly utilized in clinical practice. These agents differ in their physicochemical characteristics, biodistribution, and diagnostic performance, and the question of which tracer offers optimal clinical utility remains unresolved. Network meta-analysis (NMA) is a robust statistical method that enables simultaneous comparison of multiple diagnostic tests by integrating both direct and indirect evidence. Unlike traditional pairwise meta-analysis, NMA allows inference even in the absence of head-to-head comparisons and can increase statistical power and precision. This NMA aims to evaluate and compare the detection rates of different PSMA PET tracers in detecting both recurrent and primary prostate cancers.

Rationale Prostate-specific membrane antigen (PSMA), a transmembrane glycoprotein highly expressed on prostate cancer cells, has revolutionized prostate cancer management via PSMA positron emission tomography (PET) imaging, especially for biochemical recurrence (BCR) and primary staging. Multiple PSMA-targeted PET radiotracers have been developed and are increasingly utilized in clinical practice. These agents differ in their physicochemical characteristics, biodistribution, and diagnostic performance, and the question of which tracer offers optimal clinical utility remains unresolved.

Condition being studied Multiple PSMA-targeted PET radiotracers have been developed and are increasingly utilized in clinical practice. These agents differ in their physicochemical characteristics, biodistribution, and diagnostic performance, and the question of which tracer offers optimal clinical utility remains unresolved. Network meta-analysis (NMA) is a robust statistical method that enables simultaneous comparison of

multiple diagnostic tests by integrating both direct and indirect evidence. Unlike traditional pairwise meta-analysis, NMA allows inference even in the absence of head-to-head comparisons and can increase statistical power and precision.

METHODS

Search strategy Two authors (YEH and CKH) independently conducted electronic searches in the PubMed, Embase, Cochrane, and ClinicalTrail.gov Library databases. This search was updated to March 2025. We used a search algorithm based on a combination of the following keywords: ((PSMA) OR (“prostate-specific membrane antigen”) OR (DCFPyL)) AND (“prostate cancer”) OR (“prostate carcinoma”)) AND ((PET) OR (“positron emission tomography”)). Both evaluators screened the titles and abstracts of all identified records.

Participant or population Studies comparing two PET imaging radiotracers for evaluating prostate cancer recurrence or primary staging were included. Eligible study types comprised clinical studies, phase II-IV clinical trials, comparative studies, controlled clinical trials, pragmatic clinical trials, and randomized controlled trials. The additional filters had no language or publication year restrictions.

Intervention Eighteen of the 19 studies on recurrent prostate cancer reported overall patient-level DRs and were included in the NMA to compare DRs across different PET tracers. Among these studies focusing on PSMA-targeted PET tracers, a total of eight PSMA tracers (68Ga-PSMA-11, 18F-PSMA-1007, 18F-DCFPyL, 64Cu-PSMA-617, 68Ga-P16-093, 68Ga-PSMA I&T, 68Ga-THP-PSMA, and 68Ga-PSMA-617) were included. In addition, two non-PSMA tracers (18F-Fluciclovine and choline-based tracers) were also incorporated, resulting in ten PET tracers being analyzed overall.

Comparator Except for 68Ga-THP-PSMA, all PSMA tracers demonstrated superior RR of detection rates compared to non-PSMA tracers. 64Cu-PSMA-617 exhibited the highest estimated detection rate, followed by the three most common PSMA tracers: 18F-DCFPyL, 18F-PSMA-1007, and 68Ga-PSMA-11. Compared to 68Ga-PSMA-11 (the most common tracer), forest plot analysis showed 18F-PSMA-1007, 18F-DCFPyL, and 64Cu-PSMA-617 had superior detection rates.

Study designs to be included Two authors (YEH and CKH) independently conducted electronic

searches in the PubMed, Embase, Cochrane, and ClinicalTrail.gov Library databases. This search was updated to March 2025. We used a search algorithm based on a combination of the following keywords: ((PSMA) OR (“prostate-specific membrane antigen”) OR (DCFPyL)) AND (“prostate cancer”) OR (“prostate carcinoma”)) AND ((PET) OR (“positron emission tomography”)). Both evaluators screened the titles and abstracts of all identified records.

Eligibility criteria Studies comparing two PET imaging radiotracers for evaluating prostate cancer recurrence or primary staging were included. Eligible study types comprised clinical studies, phase II-IV clinical trials, comparative studies, controlled clinical trials, pragmatic clinical trials, and randomized controlled trials. The additional filters had no language or publication year restrictions.

Information sources Two authors (YEH and CKH) independently conducted electronic searches in the PubMed, Embase, Cochrane, and ClinicalTrail.gov Library databases. This search was updated to March 2025. We used a search algorithm based on a combination of the following keywords: ((PSMA) OR (“prostate-specific membrane antigen”) OR (DCFPyL)) AND (“prostate cancer”) OR (“prostate carcinoma”)) AND ((PET) OR (“positron emission tomography”)). Both evaluators screened the titles and abstracts of all identified records.

Main outcome(s) The primary outcome was the detection rate of recurrent prostate cancer among the evaluated PET tracers.

Additional outcome(s) The additional outcome was the detection rate of recurrent prostate cancer among the evaluated PET tracers.

Data management Two authors (YEH and CKH) independently extracted data, including patient characteristics, study design, PET radiotracers, PET/CT or PET/MRI imaging protocols, and outcome measures. Data extraction, transformation, and result merging followed the Cochrane Handbook for Systematic Reviews of Interventions and relevant medical literature. When required data were unavailable in published articles, corresponding authors were contacted for original materials.

Quality assessment / Risk of bias analysis The quality of the included studies was critically appraised by 2 authors independently, according to the revised Quality Assessment of Diagnostic

Accuracy Studies (QUADAS-2) tool. QUADAS-2 assesses risk of bias and applicability concerns on 4 key domains including patient selection, index text, reference standard, and flow and timing, respectively. To reach a judgment on the risk of bias the provided signaling questions of the QUADAS-2 tool were used. Risk of bias and applicability concerns were judged as low, high, or unclear risk or concern for the various QUADAS domains.

Strategy of data synthesis Data extraction, transformation, and result merging followed the Cochrane Handbook for Systematic Reviews of Interventions and relevant medical literature. When required data were unavailable in published articles, corresponding authors were contacted for original materials. Data extraction, transformation, and result merging followed the Cochrane Handbook for Systematic Reviews of Interventions and relevant medical literature. When required data were unavailable in published articles, corresponding authors were contacted for original materials. The DRs of different PET radiotracers were compared using relative risk (RR) with 95% confidence intervals (CIs). RR was calculated by dividing the DR of each PET tracer group by that of the control group, which was the most frequently utilized tracer in this study. Forest plots were generated to illustrate pairwise comparisons of RR across studies. The Effect sizes were reported as point estimates with 95% CIs. PET tracer DRs were ranked with numerical values for direct and indirect comparisons. Inconsistency tests were performed to assess data disparities. Statistical significance was set at a two-tailed p-value of <0.05.

Subgroup analysis N/A.

Sensitivity analysis To confirm the robustness of the meta-analysis, the sensitivity analyses were performed using one-study removal method to see if there was a significant change in the summary effect size after removing a particular trial from the analysis.

Language restriction No language limit.

Country(ies) involved Taiwan.

Other relevant information N/A

Keywords prostate cancer, PSMA, PET, positron emission tomography, Network meta-analysis.

Dissemination plans N/A.

Contributions of each author

Author 1 - Yu-Erh Huang - contributed on drafting and revising of the manuscript.

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