Radiology: Imaging Cancer

ORIGINAL RESEARCH

^{18}F-Fluciclovine versus PSMA PET Imaging in Primary Tumor Detection during Initial Staging of High-Risk Prostate Cancer: A Systematic Review and Meta-Analysis

Divya Yadav, MD • Hyunsoo Hwang, MS, PhD • Wei Qiao, MS, PhD • Rituraj Upadhyay, MD • Brian F. Chapin, MD • Chad Tang, MD • Ana Aparicio, MD • Maria A. Lopez-Olivo, MD • Stella K. Kang, MD • Homer A. Macapinlac, MD • Tharakeswara K. Bathala, MD • Devaki Shilpa Surasi, MD

From the Departments of Radiation Oncology (D.Y., R.U., C.T.), Biostatistics (H.H., W.Q.), Urology (B.F.C.), Genitourinary Medical Oncology (A.A.), Health Services Research (M.A.L.O.), Nuclear Medicine (H.A.M., D.S.S.), and Abdominal Imaging (T.K.B.), The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 483, Houston, TX 77030; and Department of Radiology, NYU Langone Health, New York, NY (S.K.K.). Received August 11, 2021; revision requested September 27; revision received December 28; accepted January 20, 2022. **Address correspondence to** D.S.S. (e-mail: *dssurasi@mdanderson.org*).

Authors declared no funding for this work.

Conflicts of interest are listed at the end of this article.

Radiology: Imaging Cancer 2022; 4(2):e210091 • https://doi.org/10.1148/rycan.210091 • Content codes: GU OI

Purpose: Fluorine 18 (^{18}F)–fluciclovine and prostate-specific membrane antigen (PSMA) tracers are commonly used for localizing biochemical recurrence of prostate cancer, but their accuracy in primary tumor detection in the initial staging of high-risk prostate cancer has not been established.

Materials and Methods: A systematic review was performed of the electronic databases for original studies published between 2012 and 2020. Included studies were those in which ^{18}F-fluciclovine or PSMA PET was used for initial staging of patients with high-risk prostate cancer. The diagnostic performance data were collected for primary tumor with histopathologic results as reference standard. The Quality Assessment of Diagnostic Accuracy Studies–2 tool was used for quality appraisal. A random-effects model was used to summarize the effect sizes and to evaluate the difference between two groups.

Results: Overall, 28 studies met the eligibility criteria, and 17 were included in the meta-analysis (^{18}F-fluciclovine = 4, PSMA = 13). Of these 17 studies, 12 (70%) were judged to have high risk of bias in one of the evaluated domains, and nine studies were deemed to have applicability concerns. The pooled sensitivity, specificity, and diagnostic odds ratio for ^{18}F-fluciclovine versus PSMA were 85% (95% CI: 73%, 92%) versus 84% (95% CI: 77%, 89%) (P = .78), 77% (95% CI: 60%, 88%) versus 83% (95% CI: 76%, 89%) (P = .40), and 18.88 (95% CI: 5.01, 71.20) versus 29.37 (95% CI: 13.35, 64.60) (P = .57), respectively, with no significant difference in diagnostic test accuracy.

Conclusion: ^{18}F-fluciclovine and PSMA PET demonstrated no statistically significant difference in diagnostic accuracy in primary tumor detection during initial staging of high-risk prostate cancer.

Supplemental material is available for this article.

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Prostate cancer is the most common noncutaneous cancer and second leading cause of cancer death in men in the United States (1). About 15% of patients with prostate cancer present with high-risk disease, which has a high propensity for local or systemic recurrence despite optimal treatment (2). High-risk prostate cancer is defined as a "clinical T category greater than or equal to T3, Gleason score … greater than or equal to 8, or serum prostate-specific antigen … greater than 20 ng/mL prior to definitive therapy," adapted from criteria proposed by D'Amico et al (3,4). The identification and timely stratification of these patients with accurate workup is crucial for appropriate management, which may further improve survival (5). The staging system developed by the American Joint Committee on Cancer acknowledges the use of imaging for preoperative local T staging of prostate cancer and MRI as the current standard (5,6). However, as the need to accurately identify these high-risk patients has shifted the focus to functional imaging, PET has shown superior accuracy, especially in suspicious cases (6).

^{18}F-fluciclovine is a synthetic amino acid radiotracer that enters the cell via the human L-type amino acid transporters, which are upregulated in certain malignancies like prostate cancer, particularly in aggressive disease (7,8). ^{18}F-fluciclovine (Axumin; Blue Earth Diagnostics) (9) has been approved by the U.S. Food and Drug Administration for localization of biochemical recurrence of prostate cancer after definitive therapy but not for initial staging. Turkbey et al showed that combining the information from ^{18}F-fluciclovine PET with multiparametric MRI (mpMRI) increased the positive predictive value for detecting prostate cancer from 76% for mpMRI alone to 82% (10). While ^{18}F-fluciclovine PET/MRI has definite value in the initial staging of primary prostate cancer, it also demonstrated potential to predict aggressiveness of prostate cancer (11–13).

Another group of PET tracers uses prostate-specific membrane antigen (PSMA), a transmembrane type II glycoprotein expressed by prostate cancer cells. Gallium 68 (^{68}Ga)–labeled PSMA tracers (PSMA N,N′-bis-[2-hydroxy-5-(carboxyethyl) benzyl]

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Abbreviations

AUC = area under the ROC curve, DOR = diagnostic odds ratio, mpMRI = multiparametric MRI, PRISMA-DTA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Diagnostic Test Accuracy Studies, PSMA = prostate-specific membrane antigen, QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies–2, ROC = receiver operating characteristic

Summary

Fluorine 18–fluciclovine and prostate-specific membrane antigen–based PET tracers show comparable yet satisfactory diagnostic test accuracy in detection of primary prostate tumor during the initial staging of high-risk prostate cancer.

Key Points

- In patients with high-risk prostate cancer, prostate-specific membrane antigen (PSMA) PET revealed a pooled sensitivity of 84% (95% CI: 77%, 89%) and specificity of 83% (95% CI: 76%, 89%) for assisting initial evaluation of primary tumor.
- In the same clinical setting, fluorine 18–fluciclovine PET also enabled similar diagnostic accuracy for primary prostate cancer, with a pooled sensitivity and specificity of 85% (95% CI: 73%, 92%) (P = .78) and 77% (95% CI: 60%, 88%) (P = .40), respectively.

Keywords

PET, Prostate, Molecular Imaging–Cancer, Staging

ethylenediamine-N,N′-diacetic acid, or HBED-CC [^{68}Ga PSMA-11] and ^{68}Ga PSMA-617), 2-(3-{1-carboxy-5-[(6-[^{18}F] fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid (^{18}F-DCFPyL), *N*-[*N*-[(S)-1,3-dicarboxy-propyl] carbamoyl]-4–^{18}F-fluorobenzyl-L-cysteine (^{18}F-DCFBC), and newer 18F-PSMA-1007 have shown superior accuracy in detection of prostate cancer (14,15). Furthermore, PET can be used as a single "one-stop" staging modality, and it has now been recognized in the American Society of Clinical Oncology guidelines for staging newly diagnosed, clinically high-risk prostate cancers (16). However, the evidence has not been summarized on the performance of PET tracers in the initial staging of high-risk prostate cancer. We therefore performed a systematic review and meta-analysis to compare diagnostic test accuracy of ^{18}F-fluciclovine and PSMA-targeted PET tracers in the detection of primary prostatic lesions during initial staging in patients with high-risk prostate cancer.

Materials and Methods

A systematic review of the literature was performed and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Diagnostic Test Accuracy Studies (PRISMA-DTA) guidelines. No financial support of any kind was provided for this article, and the authors had full control of the data and the information submitted for publication. None of the authors have any relevant conflicts of interest to disclose. There was no protocol registered online for the study. The current study retrieved and analyzed data from previously published studies, and hence, institutional review board approval was not needed.

Eligibility Criteria

We included studies evaluating the diagnostic efficacy of PET/CT or PET/MRI with ^{18}F-fluciclovine or PSMA-based tracers for initial staging of patients with high-risk prostate cancer before definitive therapy. We included controlled studies (prospective as well as retrospective) in the specified high-risk population that gave information on the primary prostate lesion(s) during the initial T staging, with or without comparison with conventional imaging (CT or MRI). We excluded studies performed for restaging or biochemical recurrence evaluation. Studies with a mixed population (ie, imaging for initial staging, restaging and biochemical recurrence, or multiple risk levels) and ones in which the data for initial staging were not provided separately or the risk status was not mentioned were also excluded. If there were multiple published studies from the same group with possible overlapping of the patient population, then only the most recent publication was included.

Information Sources

Systematic searches were independently conducted in PubMed, Embase, Scopus, and Web of Science databases. Search results were managed using EndNote X9.3.3 reference manager software (Clarivate Analytics). Duplicate articles were identified, reviewed, and removed from the database by the software.

Search Strategy and Study Selection

The search strategy was developed by the study team in consultation with a health sciences librarian, and a detailed search string is provided in Appendix E1 (supplement). We used terms related to the following: "Positron Emission Tomography (PET)," PET tracers "(Fluciclovine) or (Axumin) or (FACBC)" or "(^{68}Ga-PSMA) or (^{68}Ga-PSMA-11) or (^{68}Ga-HBED-CC) or (^{18}F-PSMA) or (^{18}F-DCFPyl) or (^{18}F-DCFBC)," and "High risk prostate cancer." The search was restricted to original articles published in English in or after 2012. Two reviewers (D.Y., R.U.) independently screened titles and abstracts separately to identify relevant citations. The full texts of the included relevant citations were independently reviewed by the same reviewers, disagreements between reviewers were resolved by consensus, and reasons for exclusion were documented.

Risk of Bias and Applicability

We used the Quality Assessment of Diagnostic Accuracy Studies–2 (QUADAS-2) tool to assess the risk of bias in four domains: patient selection, index test, reference standard, and reference test timing. For the first three domains, applicability concerns were also assessed. The quality of evidence was performed and confirmed independently by two reviewers (D.Y., D.S.S.) in consensus. Deeks funnel plot asymmetry test was performed to test for any publication bias (17).

Data Extraction and Collection Process

We extracted basic study characteristics in terms of author, year of publication, study origin (country), design (prospective vs retrospective, multicenter vs single center), detection rate, and PET tracer (^{18}F-fluciclovine vs PSMA). The

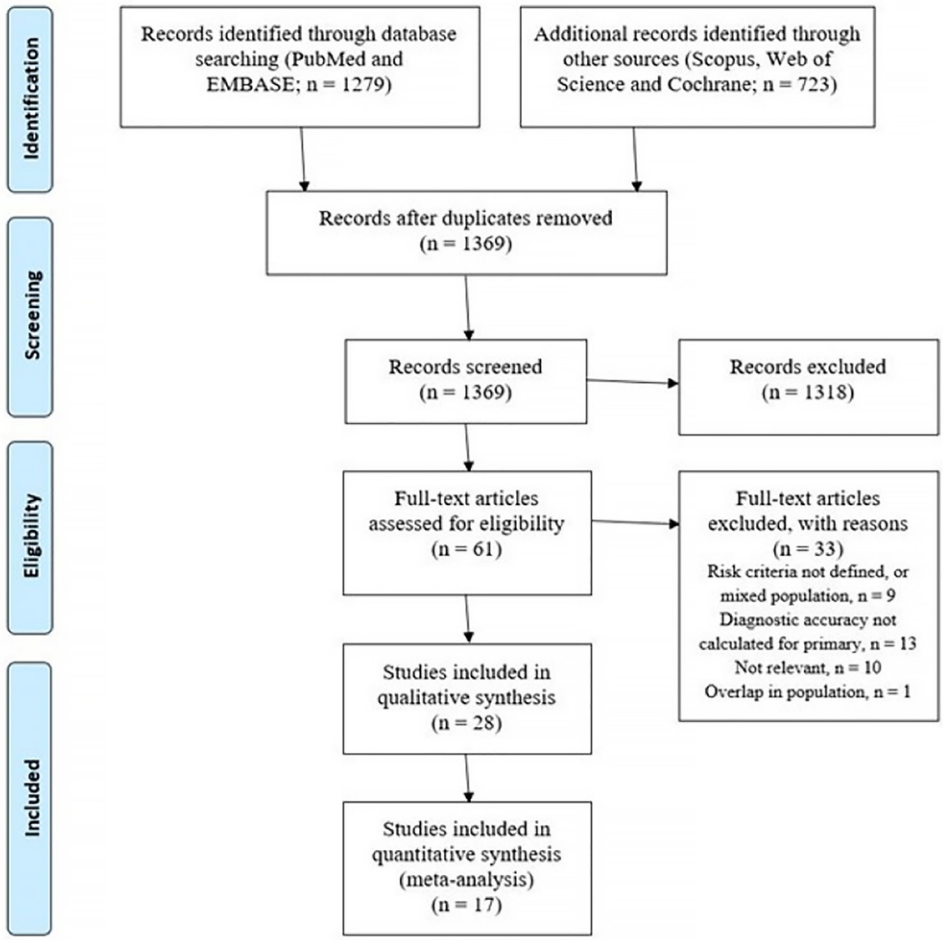


Figure 1: PRISMA flow diagram depicts the selection of studies. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

PSMA-targeted tracers included ^{68}Ga-PSMA-11, ^{18}F-DCFPyL, ^{18}F-DCFBC, ^{68}Ga-PSMA inhibitor for imaging and therapy (or, ^{68}Ga-PSMA-I&T), ^{18}F-rhPSMA-7.3, and ^{18}F-PSMA-1007. We also collected clinicopathologic information, for example, number of patients, median age, Gleason score, prostate-specific antigen levels, and histopathologic results. The histopathologic results were considered the reference standard, and diagnostic parameters for the individual studies were collected for primary disease localization, extraprostatic extension, and seminal vesicle invasion, where available. For diagnostic accuracy data, the number of true-positive results, true-negative results, false-positive results, and false-negative results were collected when available to attain 2 × 2 contingency tables. Data extraction was performed and confirmed independently by two reviewers (D.Y., D.S.S.), and discrepancies were resolved with two-person consensus.

Diagnostic Accuracy Measures

The diagnostic test accuracy measures—that is, sensitivity, specificity, and diagnostic odds ratio (DOR)—were calculated for the studies on a per-patient basis when 2 × 2 contingency table data were available for both ^{18}F-fluciclovine and PSMA tracers.

Synthesis of Results

The meta-analysis was performed in the studies with calculated accuracy measures for both tracers to summarize the evidence. The random-effects model was used to summarize the test accuracy, and results were displayed as forest plots. The heterogeneity of studies was examined using Higgins I^2 and Cochran Q test. A continuity correction of 0.5 was applied in studies with zero cell frequencies.

Additional Analyses

To jointly analyze sensitivity and specificity, we created a summary receiver operating characteristic (ROC) curve and calculated the area under the ROC curve (AUC). Metaregression was used to explore the sources of heterogeneity across the studies between subgroups. Several covariates, such as difference in tracers (^{18}F-fluciclovine vs PSMA), difference among various PSMA tracers (^{68}Ga-labeled PSMA-11 vs ^{18}F-labeled DCFPyL, ^{18}F-DCFBC, and ^{18}F-PSMA-1007), study type (prospective or retrospective), and study population (only high risk vs mixed intermediate to high risk), were analyzed.

Statistical Analysis

All statistical analyses were performed using R 3.6.1 *(https://www.r-project.org/)* (18). R packages meta and mada were used

Table 1: Characteristics of Studies Included in Systematic Review

Author	Year of Publication	Country of Origin	Study Type	Tracer Used	No. of Total Patients	No. of High-Risk Patients	Median Age (y)	Sensitivity (%)	Specificity (%)
Anttinen et al (19)	2020	Finland	Single center, prospective	^{18}F-PSMA-1007	80	80	70	86	90
Demirci et al (20)	2019	Turkey	Single center, retrospective	^{68}Ga PSMA-11	141	141	65	78	81
Donato et al (21)	2019	Australia	Single center, Retrospective	^{68}Ga PSMA-11	58	13	66	96	NA
El Hajj et al (22)	2019	Lebanon	Single center, Retrospective	^{68}Ga PSMA-11	23	10	69	83	99
Elschot et al (23)	2018	Norway	Single center, retrospective	^{18}F-fluciclovine	28	28	66	85	86
Galgano et al (24)	2021	United States	Single center, prospective	^{18}F-fluciclovine	14	14	66	100	NA
Gaur et al (25)	2020	United States	Single center, prospective	^{18}F-DCFPyL	26	26	70	91	NA
Hicks et al (26)	2018	United States	Single center, retrospective	^{68}Ga PSMA-11	32	30	68	67	71
Hirmas et al (27)	2019	Jordan	Single center, retrospective	^{68}Ga PSMA-11	21	21	66	85	NA
Hofman et al (28)	2020	Australia	Multicenter, prospective	^{68}Ga PSMA-11	302	148	70	85	98
Jambor et al (29)	2018	Germany	Single center, prospective	^{18}F-fluciclovine	26	25	65	87	56
Kesch et al (30)	2017	Germany	Single center, retrospective	^{18}F-PSMA-1007	10	10	67	71	81
Kroenke et al (31)	2020	Germany	Single center, retrospective	^{18}F-rhPSMA-7.3	58	58	68	72	93
Kuten et al (32)	2020	Israel	Single center, prospective	^{68}Ga PSMA-11	16	4	69	100	98
Liu et al (33)	2018	China	Single center, retrospective	^{68}Ga PSMA-617	40	30	67	88	50
Lopci et al (34)	2018	Italy	Single center, prospective	^{18}F-PSMA-1007	45	25	64	100	76
Muehlematter et al (35)	2019	Switzerland	Single center, retrospective	^{68}Ga PSMA-11	40	32	63	69	67
Pallavi et al (36)	2020	India	Single center, prospective	^{68}Ga PSMA-11	35	26	64	100	NA
Park et al (37)	2018	United States	Single center, prospective	^{68}Ga PSMA-11	33	15	66	85	90
Rahbar et al (38)	2016	Germany	Single center, retrospective	^{68}Ga PSMA-11	6	6	65	92	92
Rogasch et al (39)	2018	Germany	Single center, retrospective	^{68}Ga PSMA-11	108	89	72	95	25
Rowe et al (40)	2015	United States	Single center, prospective	^{18}F-DCFBC	13	8	62	80	100
Suzuki et al (41)	2016	Japan	Multicenter, prospective	^{18}F-fluciclovine	67	44	66	93	90
Thalgott et al (42)	2018	Germany	Single center, retrospective	^{68}Ga PSMA-11	102	73	68	94	45
Turkbey et al (43)	2016	United States	Single center, prospective	^{18}F-fluciclovine	21	8	62	69	NA

Table 1 (*continues*)

Table 1 (*continued*): Characteristics of Studies Included in Systematic Review

Author	Year of Publication	Country of Origin	Study Type	Tracer Used	No. of Total Patients	No. of High-Risk Patients	Median Age (y)	Sensitivity (%)	Specificity (%)
von Klot et al (44)	2017	Germany	Single center, prospective	^{68}Ga PSMA-I&T	21	19	68	95	75
Zhang et al (45)	2017	China	Single center, retrospective	^{68}Ga PSMA-11	42	24	69	93	96
Zhao et al (46)	2020	China	Single center, retrospective	^{68}Ga PSMA-11	31	22	63	89	77

Note.—^{18}F = fluorine 18, ^{18}F-DCFBC = *N*-[*N*-[(S)-1,3-dicarboxy-propyl] carbamoyl]-4–^{18}F-fluorobenzyl-L-cysteine, ^{18}F-DCFPyL = 2-(3-{1-carboxy-5-[(6-[^{18}F] fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentane-dioic acid, ^{68}Ga = gallium 68, I&T = inhibitor for imaging and therapy, NA = not applicable, PSMA = prostate-specific membrane antigen.

for meta-analysis, and statistical significance was set at *P* less than .05.

Results

Study Selection

The search revealed a total of 1369 studies, and the exclusion process is elaborated in the PRISMA flowchart (Fig 1).

Study Characteristics

In total, 28 studies with 1029 patients with high-risk prostate cancer underwent qualitative analysis, and Table 1 summarizes the basic features of all included studies (19–46). Regarding study design, 13 studies were prospective and 15 were retrospective. The majority (*n* = 26) of these studies were performed in a single center; only two studies came from multicenter trials (one each with ^{18}F-fluciclovine [41] and PSMA [28]). ^{18}F-fluciclovine was used in all five ^{18}F-fluciclovine studies. Of the 23 PSMA studies, 15 were performed with ^{68}Ga-PSMA-11, four were performed with ^{18}F-PSMA-1007, and the remaining four studies each used one of ^{68}Ga-PSMA-617, ^{68}Ga-PSMA-I&T, ^{18}F-DCFPyl, and ^{18}F-DCFBC. Initial staging PET scans were obtained in a specific high-risk patient population in 12 studies, while the remaining 16 studies were obtained in a mixed intermediate- to high-risk population.

Risk of Bias and Applicability

The results of quality assessment of 13 PSMA studies and four ^{18}F-fluciclovine studies as evaluated by QUADAS-2 are shown in Figure 2. Eight (47%) of all 17 studies were judged to have high risk of bias in more than one of the evaluated domains. Eight studies showed high risk of bias in patient selection, and six were deemed to have applicability concerns among them. The Deeks funnel plot for the DOR for the entire cohort suggested absence of any publication bias (*P* = .06) (Fig 3). Similarly, the funnel plots for the DOR of the four studies evaluating ^{18}F-fluciclovine and the 13 studies evaluating PSMA did not suggest presence of publication bias (*P* = .91 and *P* = .07, respectively).

Results of Individual Studies

The diagnostic accuracy of PET for extraprostatic extension, including extracapsular extension (T3a tumor) and seminal vesicle invasion (T3b tumor), was also evaluated in a few PSMA studies (Table 2). PET demonstrated higher diagnostic efficacy than conventional imaging (CT and MRI) in a few of the studies (Table 3). PSMA PET was shown to influence the management of cases that underwent primary staging in four studies. In a study by Gaur et al, ^{18}F-DCFPyL PET/CT findings showed an incremental detection contribution in 11 patients (42.3%) compared with mpMRI (25). In a study by Demirci et al, ^{68}Ga-PSMA PET maximum standardized uptake values at a cutoff of 9.1 could help detect high-risk disease with a high sensitivity (78%) and specificity (81%) and could have helped predict upstaging in 10 of 16 (62.5%) patients who were moved from the low-risk to the high-risk group (20). In the proPSMA study, PSMA PET/CT conferred management change more frequently than first-line conventional imaging did (23 [15%] patients vs 41 [28%] patients; *P* = .008) (28).

Synthesis of Results

There were 20 studies for which the data to make 2 × 2 contingency tables was available (19,21,23,25–31,35–38,41–46). However, three studies did not have relevant information (false-positive results + true-negative results = 0) to calculate specificity (21,27,36). After filtering out those studies, a total of 17 studies, for which sensitivities and specificities could be calculated, underwent meta-analysis. This analysis included 104 high-risk patients with a median age of 65.5 years (interquartile range, 3.17) in four ^{18}F-fluciclovine studies (23,29,41,43) and 543 high-risk patients with a median age of 68 years (interquartile range, 3.45) in 13 PSMA studies (19,25,26,28,30,31,35,37,38,42,44–46). The Higgins I^2 in the sensitivity, specificity, and DOR analyses was 84% (95% CI: 76%, 90%), 87% (95% CI: 80%, 91%), and 89% (95% CI: 83%, 92%), respectively, and the *P* value of Cochrane Q statistics was less than .0001 for all analyses, indicating the evidence of heterogeneity.

Sensitivity.— The pooled sensitivity for the 17 studies (regardless of the tracer used) was 84% (95% CI: 78%, 0.89%) (Fig

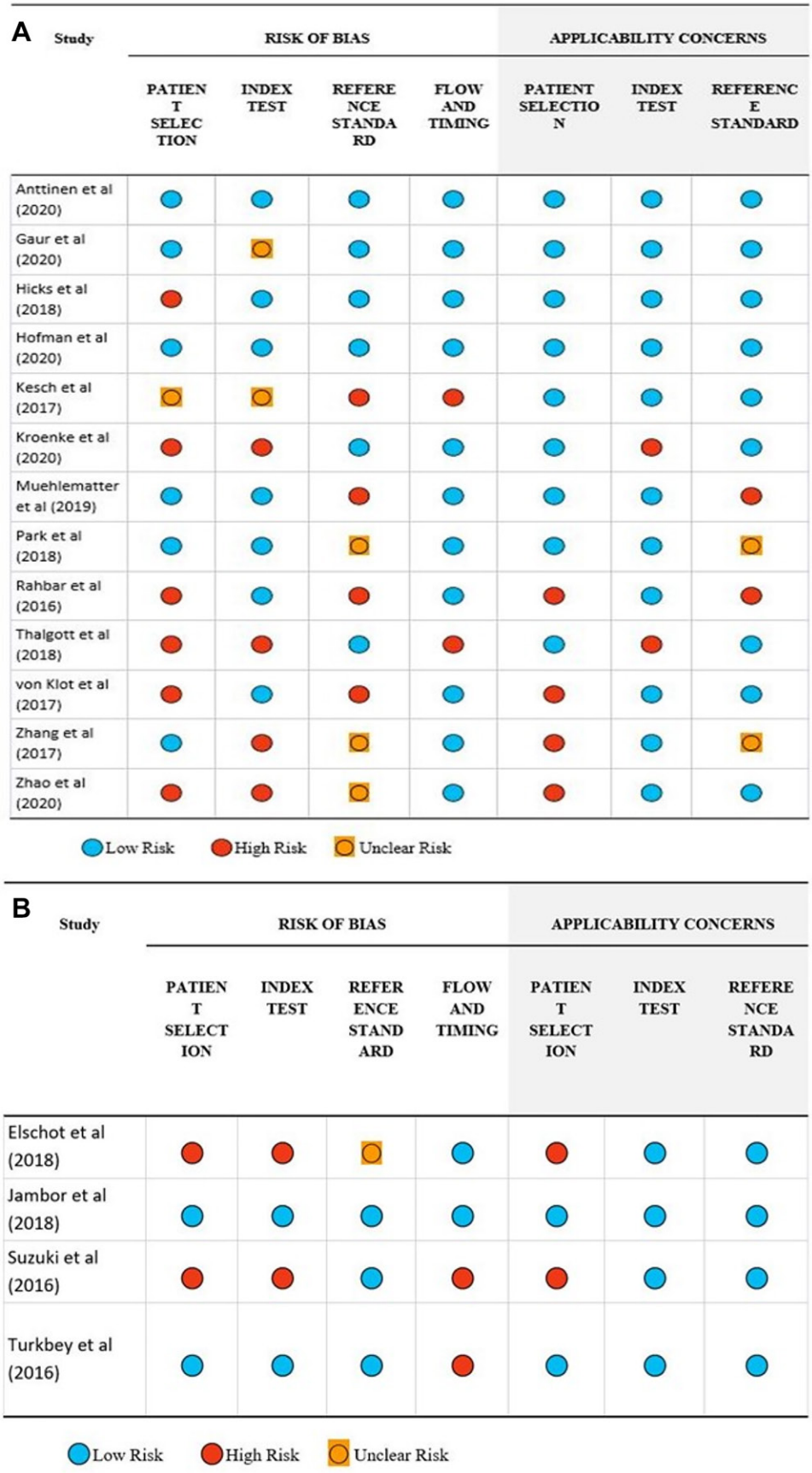


Figure 2: Quality Assessment of Diagnostic Accuracy Studies–2 analysis of **(A)** prostate-specific membrane antigen and **(B)** fluorine 18–fluciclovine studies shows risk of bias and applicability concerns.

4). We did not observe evidence of a difference between the pooled sensitivity for the four ^{18}F-fluciclovine studies and the 13 PSMA studies (85% [95% CI: 73%, 92%] vs 84% [95% CI: 77%, 89%], respectively; P = .78).

Specificity.— The pooled specificity for the 17 studies (regardless of the tracer used) was 81% (95% CI: 75%, 87%) (Fig 5). We found no evidence of a difference between the pooled specificity for the four studies evaluating ^{18}F-fluciclovine and the pooled specificity for the 13 studies evaluating PSMA (77% [95% CI: 60%, 88%] vs 83% [95% CI: 76%, 89%]; respectively, P = .40).

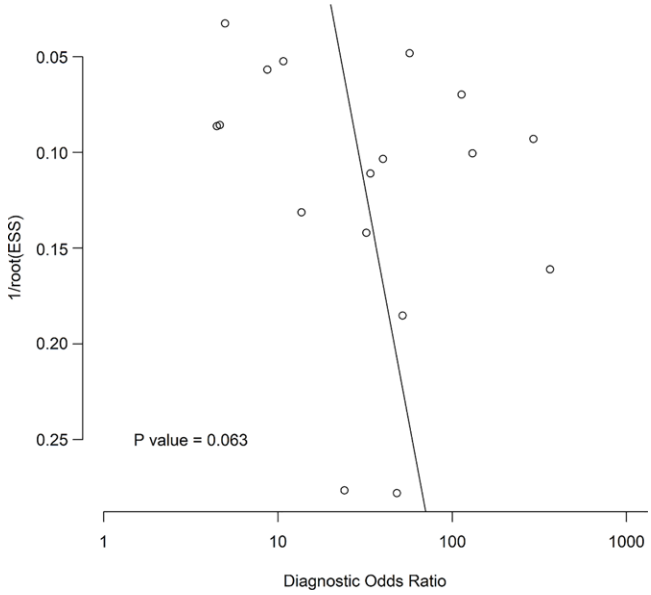


Figure 3: Deeks funnel plot asymmetry test plotted between effect size measure (diagnostic odds ratio) and the inverse of the square root of the effective sample size (ESS) shows that there is no significant publication bias (P = .06).

Diagnostic odds ratio.— The pooled DOR for the 17 studies (regardless of the tracer used) was 25.51 (95% CI: 13.49, 48.23) (Fig 6). We observed no evidence of a difference between the pooled DOR for the ^{18}F-fluciclovine and the PSMA groups (18.88 [95% CI: 5.01, 71.20] vs 29.37 [95% CI: 13.35, 64.60], respectively; P = .57).

Additional Analyses

The summary ROC curve revealed the AUC for the 17 studies (regardless of the tracer used) as 0.90 and the summary sensitivity and specificity as 84% (95% CI: 79%, 88%) and 82% (95% CI: 74%, 88%), respectively (Fig 7). Metaregression performed to explore sources of heterogeneity did not show evidence of a difference when we evaluated the difference among tracers used, study design, and study participant characteristics. The difference among PSMA tracers (^{68}Ga-PSMA-11 vs ^{18}F-DCFBC, ^{18}F-DCFPyl, and ^{18}F-PSMA-1007) did not appear to contribute to heterogeneity for sensitivity, specificity, and DOR (P = .56, .34, and .98, respectively). The difference in study population (only high-risk vs mixed intermediate- to high-risk population) also did not appear to contribute to heterogeneity of sensitivity, specificity, and DOR (P = .47, .18, and .82, respectively).

Table 2: Diagnostic Efficacy of PET for Extraprostatic Extension in Patients with High-Risk Prostatic Cancer

Study	PET Tracer Used	ECE Sensitivity (%)	ECE Specificity (%)	SVI Sensitivity (%)	SVI Specificity (%)
Muehlematter et al, 2019 (35)	^{68}Ga PSMA-11	69	67	35	98
Pallavi et al, 2020 (36)	^{68}Ga PSMA-11	75	100	60	96
Thalgott et al, 2018 (42)	^{68}Ga PSMA-11	94	45	81	80
von Klot et al, 2017 (44)	^{68}Ga PSMA-I&T	90	91	75	100

Note.—ECE = extracapsular extension, ^{68}Ga = gallium 68, PSMA = prostate-specific membrane antigen, SVI = seminal vesicle invasion.

Table 3: Studies Comparing Diagnostic Efficacy of PET versus Conventional Imaging in Initial Staging of High-Risk Prostate Cancer

Author	Year of Study	Tracer	No. of High-Risk Patients	PET Sensitivity (%)	PET Specificity (%)	CI Sensitivity (%)	CI Specificity (%)
Anttinen et al (19)	2020	^{18}F-PSMA-1007	80	86	90	67	96
Gaur et al (25)	2020	^{18}F-DCFPyL	26	91	NA	86	NA
Hicks et al (26)	2018	^{68}Ga PSMA-11	30	67	71	50	90
Hirmas et al (27)	2019	^{68}Ga PSMA-11	21	85	NA	87	NA
Hofman et al (28)	2020	^{68}Ga PSMA-11	148	85	98	38	91
Jambor et al (29)	2018	^{18}F-fluciclovine	25	87	56	77	99

Note.—Conventional imaging was performed as CT in one study (Hofman et al) and MRI in the rest of the studies. CI = conventional imaging, ^{18}F = fluorine 18, ^{18}F-DCFPyL = 2-(3-{1-carboxy-5-[(6-[^{18}F] fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentane-dioic acid, ^{68}Ga = gallium 68, NA = not applicable, PSMA = prostate-specific membrane antigen.

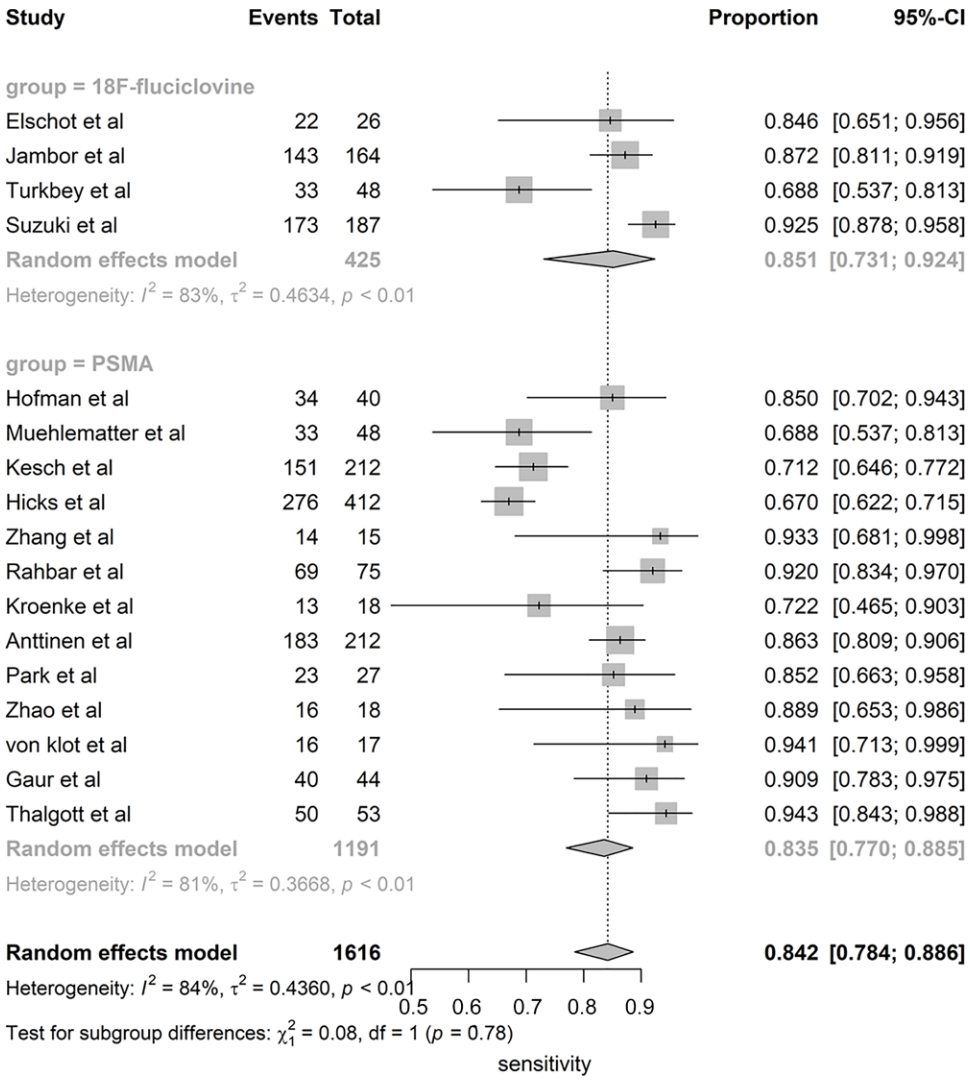


Figure 4: Forest plot for sensitivity of PSMA (coded as test group = 0), fluorine 18 ([18]F)–fluciclovine (test group = 1), and combined whole cohort of studies shows the results of random-effects model, heterogeneity analysis, and metaregression analysis. PSMA = prostate-specific membrane antigen.

Discussion

The goal of initial staging is to detect primary prostatic foci and their local extensions along with metastatic burden. It has been well established in literature that PET can help detect and localize primary prostate tumors, along with its excellent ability to help detect distant metastases. In this systematic review, we focused on the diagnostic efficacy of PET in helping detect primary prostatic lesions in patients with high-risk prostate cancer. The pooled sensitivity, specificity, and DOR for [18]F-fluciclovine versus PSMA were 85% versus 84% (P = .78), 77% versus 83% (P = .40), and 18.88 versus 29.37 (P = .57), respectively. These data suggest that both [18]F-fluciclovine and PSMA PET have high diagnostic accuracy for primary prostatic lesions in the initial evaluation among patients with high-risk prostate cancer.

Similar results for [18]F-fluciclovine were described in the literature for primary prostate cancer (47,48). For example, in meta-analysis by Bin et al, the pooled sensitivity, specificity, and DOR of [18]F-fluciclovine in prostate cancer were 88%, 73%, and 20, respectively (49). While they included studies with a mixed population, we have focused on studies with high-risk patients, but the results are still comparable. There are limited studies using [18]F-fluciclovine PET for initial staging of prostate cancer, because it is not a Food and Drug Administration–approved indication.

PSMA PET is being investigated in the initial staging of high-risk prostate cancer, and it helped correctly predict the intraprostatic tumor foci in 92% of patients (14). The retrospective analysis of 56 patients with high-risk prostate cancer revealed that [18]F-rhPSMA-7 PET/CT demonstrated a high sensitivity, specificity, and diagnostic accuracy of 81%, 88%, and 86%, respectively (31). Similarly, our meta-analysis of studies with various PSMA tracers resulted in a pooled sensitivity and specificity of 84% and 83%, respectively. The odds of positive results among patients with clinically significant prostate cancer was approximately 29.36 times higher than the odds of positive results among persons with no disease. PSMA PET demonstrated higher diagnostic odds than [18]F-fluciclovine, but the difference was not statistically significant (P = .57).

In terms of local extension of newly diagnosed prostate cancer, Woo et al found that PSMA PET had moderate sensitivity and

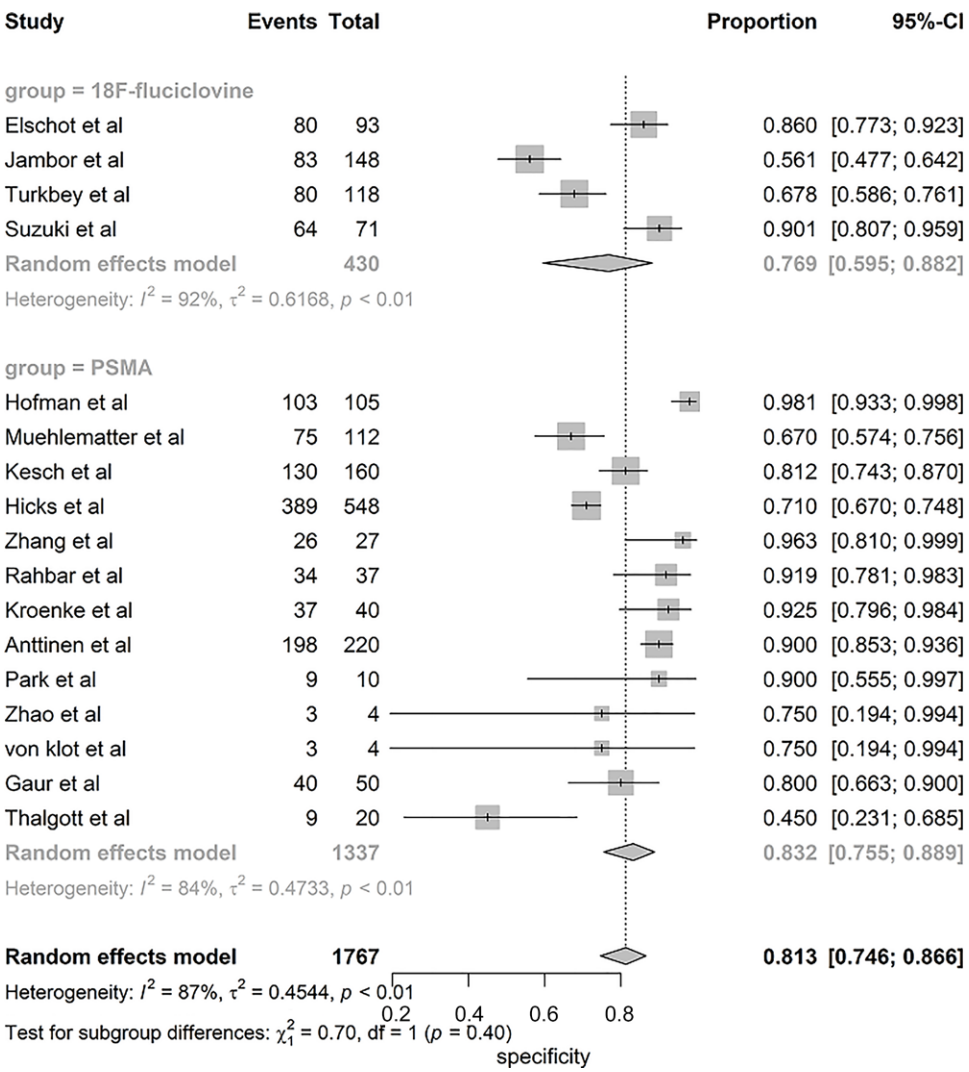


Figure 5: Forest plot for specificity of PSMA (group 0), fluorine 18 (^{18}F)–fluciclovine (group 1), and combined whole cohort of studies shows the results of random-effects model, heterogeneity analysis, and metaregression analysis. PSMA = prostate-specific membrane antigen.

excellent specificity for both seminal vesicle invasion (69% and 94%) and extraprostatic extension (72% and 87%) (50). Similar findings were seen among the four included PSMA studies in high-risk patients (Table 2). The accurate assessment of extraprostatic extension further supports the incorporation of PSMA PET in the initial workup of patients with high-risk prostate cancer. A review by Corfield et al suggested that PSMA PET enables accurate staging of primary prostate cancer and alters management of newly diagnosed prostate cancer compared with conventional imaging alone (51). Additionally, Hofman et al found a lower sensitivity (38% [95% CI: 24%, 52%] vs 85% [95% CI: 74%, 96%]) and specificity (91% [95% CI: 85%, 97%] vs 98% [95% CI: 95%, 100%]) for conventional imaging compared with PSMA PET/CT in a prospective randomized controlled trial (Table 3) (28). While ^{18}F-fluciclovine and PSMA PET have diagnostic accuracy similar to mpMRI (35,52), they can also help predict aggressiveness and assist in prognostication (13,42).

The difference between ^{18}F-fluciclovine and PSMA tracers has been explored in the detection of biochemical recurrence for a long time but not, to our knowledge, for primary prostate cancer (53). For detection of biochemical recurrence after definitive therapy, PSMA tracers revealed a significantly higher detection rate of 80% than with ^{18}F-fluciclovine PET/CT (62%) but not a significantly different rate when prostate-specific antigen level was less than 1.0 ng/mL (54). Although PSMA showed superiority over ^{18}F-fluciclovine in aiding detection of biochemical recurrence (55), the results of our metaregression did not reveal any significant difference in the diagnostic test accuracy between the two tracer groups in primary setting. With the approval of the use of PSMA tracer (Pylarify; Lantheus Medical Imaging) in the primary staging of patients with prostate cancer, there is hope for future studies evidencing its clinical impact and survival benefit in high-risk patients.

There were important limitations to this review. First, the strength of evidence was considered weak given that most included studies were limited by retrospective design. Additionally, there was substantial heterogeneity across all the studies, which could arise from heterogeneous patient populations, institutions,

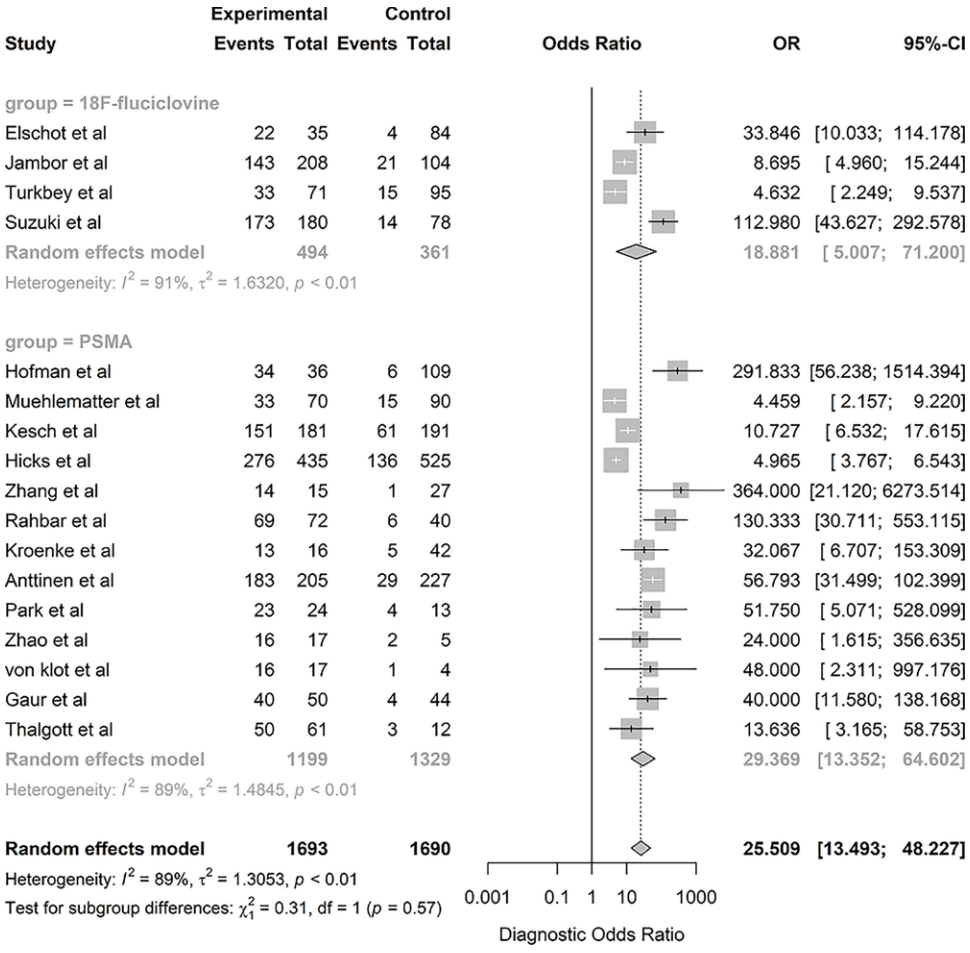


Figure 6: Forest plot for diagnostic odds ratio of PSMA (group 0), fluorine 18 ([18]F)–fluciclovine (group 1), and the combined whole cohort of studies shows the results of random-effects model, heterogeneity analysis, and metaregression analysis. OR = odds ratio, PSMA = prostate-specific membrane antigen.

methods, PET/CT scanners, and reporting. However, differences in tracers and study design were not found to be the source of heterogeneity. Mixed populations with intermediate- to high-risk patients were difficult to segregate in literature search and data extraction, which might have limited the inclusion of studies. Finally, the small number of included [18]F-fluciclovine studies possibly limited the study power for high-risk patients.

In conclusion, both [18]F-fluciclovine and PSMA PET can help detect primary prostate cancer and its local extension with no significant difference. With satisfactory diagnostic accuracy and increased detection rates with respect to conventional imaging modalities, PET may provide substantial clinical impact in disease management. Thus, for initial evaluation of primary prostatic tumor, [18]F-fluciclovine and PSMA PET could serve as accurate imaging modalities that might benefit the management of patients with high-risk prostate cancer.

Acknowledgments: We would like to acknowledge Kate Krause, MLIS, AHIP, senior librarian, Research Services Team and Sarah Bronson, ELS, scientific editor, Editing Services Team at The University of Texas MD Anderson Cancer Center.

Author contributions: Guarantors of integrity of entire study, D.Y., H.H., R.U., A.A., T.K.B., D.S.S.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all

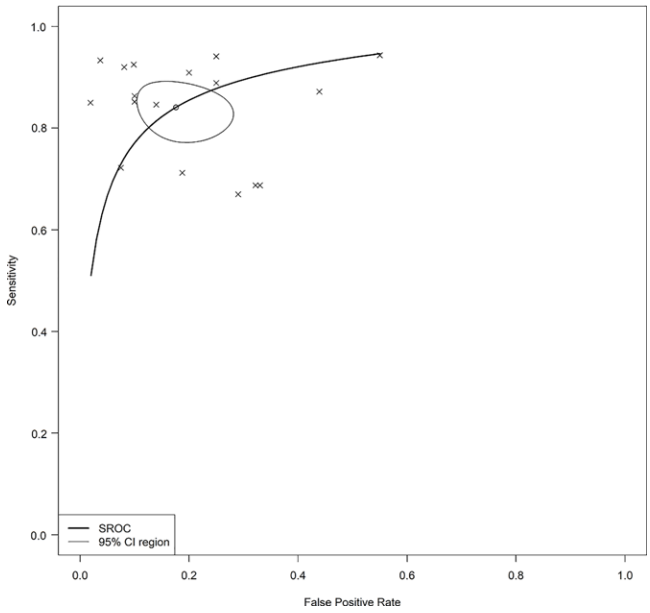


Figure 7: The summary receiver operating characteristic (SROC) curve for diagnostic test accuracy for the whole cohort, plotted using bivariate diagnostic random-effects meta-analysis and restricted maximum likelihood, gave an area under SROC curve of 0.90, sensitivity of 84% (95% CI: 79%, 88%), and specificity of 82% (95% CI: 74%, 88%).

authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, **D.Y., R.U., S.K.K., H.A.M., T.K.B., D.S.S.**; clinical studies, **D.Y., C.T., H.A.M., T.K.B., D.S.S.**; statistical analysis, **D.Y., H.H., W.Q., R.U., S.K.K., T.K.B., D.S.S.**; and manuscript editing, **D.Y., H.H., R.U., B.F.C., C.T., A.A., M.A.L.O., S.K.K., T.K.B., D.S.S.**

Disclosures of conflicts of interest: D.Y. No relevant relationships. **H.H.** No relevant relationships. **W.Q.** No relevant relationships. **R.U.** No relevant relationships. **B.F.C.** Institution has contract with Blue Earth Diagnostics as lead site for international clinical trial of rh–prostate-specific membrane antigen and has contracts with the industry sponsor; advisory board consulting fee from Blue Earth Diagnostics; leadership or fiduciary role on American Urological Association guidelines committee and NCCN guidelines committee. **C.T.** No relevant relationships. **A.A.** Consulting fees, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events, and support for attending meetings and/or travel from Amgen, Astellas Pharma US, American Cancer Society, Janssen Research and Development, Daiichi Sankyo, AstraZeneca Pharmaceuticals, Bayer Healthcare Pharmaceuticals, and Sanofi US Services. **M.A.L.O.** Grants or contracts from National Cancer Institute (grant no. CA237619) and Rheumatology Research Foundation. **S.K.K.** Grant support from National Institutes of Health (NIH)/National Institute of Dental and Craniofacial Research, NIH/National Cancer Institute, the Doris Duke Foundation, and the Agency for Healthcare Research and Quality; royalties from Wolters Kluwer; honorarium from the American Roentgen Ray Society for editorial work; chair of the American College of Radiology steering committee for incidental findings and expert panel on obstetric and gynecological imaging. **H.A.M.** No relevant relationships. **T.K.B.** No relevant relationships. **D.S.S.** Grant support from Blue Earth Diagnostics, not related to this work; receipt of radiotracer from Blue Earth Diagnostics, not related to this work.

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