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The role of ^{18}F-fluciclovine PET in the management of prostate cancer: a systematic review and meta-analysis

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AIM: To investigate the diagnostic performance of ^{18}F-fluciclovine positron-emission tomography (PET) or combined PET and computed tomography (PET/CT) for diagnosis of primary cancer, preoperative lymph node (LN) staging, and detection of recurrent disease of prostate cancer (PCa) through a systematic review and meta-analysis.

MATERIALS AND METHODS: The PubMed and EMBASE databases were searched from the earliest available date of indexing through 31 December 2018, for studies evaluating the diagnostic performance of ^{18}F-fluciclovine PET or PET/CT for the management of PCa patients. The sensitivities, specificities, and positive and negative likelihood ratios (LR+ and LR-) across the studies were calculated and summary receiver operating characteristic curves were constructed.

RESULTS: Across 13 studies (563 patients), the pooled sensitivity for ^{18}F-fluciclovine PET or PET/CT for diagnosis of primary PCa was 0.87 (95% confidence interval [CI]: 0.77–0.93) and a pooled specificity of 0.84 (95% CI: 0.68–0.93). For LN staging, the pooled sensitivity was 0.56 (95% CI: 0.37–0.74) and a pooled specificity of 0.98 (95% CI: 0.88–1.00). For detection of recurrent disease, the pooled sensitivity was 0.79 (95% CI: 0.60–0.91) and a pooled specificity of 0.69 (95% CI: 0.59–0.77). In meta-regression analysis, no definite variable was the source of the study heterogeneity.

CONCLUSION: The current meta-analysis showed the moderate sensitivity and specificity of ^{18}F-fluciclovine PET or PET/CT for the diagnosis of primary cancer, preoperative LN staging, and detection of recurrent PCa. Further large multicentre studies will be necessary to substantiate the diagnostic accuracy of ^{18}F-fluciclovine PET/CT for management of PCa patients.

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Introduction

Prostate cancer (PCa) is the most common cancer in men and the second most common cause of death in developed countries.[1] In 2018, an estimated 164,690 men were diagnosed with PCa and 29,430 men will die of the disease in the United States.[2] Early diagnosis of localised PCa has a good prognosis and accurate staging is important for treatment strategy and patient management.[3] Exact local and systemic staging of PCa is crucial to provide optimal treatment and exact assessment of lymph node (LN) status is essential to accurate staging of PCa.[3] After treatment, the recurrence of PCa occurs in 20–50% based on levels of prostate specific antigen (PSA).[4–6] In addition, 25% of PCa patients reported to have biochemical recurrence (BCR) progress to metastatic disease associated with significantly increased morbidity and mortality rates.[7,8] Therefore, the detection of the exact site of recurrent disease is essential as it determines the subsequent salvage treatment.[3]

The new synthetic non-metabolised leucine derivate anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid (^{18}F-fluciclovine, ^{18}F-FACBC) is known to accumulate in PCa.[9] Previous preliminary studies showed promising results in the detection of primary PCa and recurrent disease in PCa patients with BCR after initial curative intent treatment.[10–14]

The purpose of the present study was to meta-analyse published data on the diagnostic accuracy of ^{18}F-fluciclovine PET or PET/CT for the diagnosis of primary cancer, preoperative LN staging, and detection of recurrent PCa in order to provide more evidence-based data and to address further studies in the management of PCa patients.

Materials and methods

Data sources and search strategy

Electronic English-language literature searches of the PubMed and EMBASE databases from the earliest available date of indexing through to 31 December 2018 were conducted. The reference lists were also hand-searched to identify publications for additional studies. A search algorithm based on a combination of terms: (1) “PET” OR “positron emission tomography” OR “positron emission tomography/computed tomography” OR “PET/CT” OR “positron emission tomography-computed tomography” OR “PET-CT” AND (2) “fluciclovine” OR “FACBC” AND (3) “prostatic neoplasms” OR “prostate cancer” OR “prostate carcinoma” was used.

Study selection

The inclusion criteria for relevant studies were as follows: ^{18}F-fluciclovine PET or PET/CT had been used to diagnose the primary cancer, preoperative LN staging, and detection of recurrent PCa; sufficient data to calculate the sensitivity and specificity of ^{18}F-fluciclovine PET or PET/CT for the management of PCa or absolute numbers of true positive, true negative, false positive, and false negative data had been presented; and no data overlap.

Duplicated publications were excluded, as were publications such as review articles, case reports, conference papers, and letters, which did not contain the original data. Two researchers independently reviewed titles and abstracts of the retrieved articles, applying the above-mentioned selection criteria. Articles were rejected if clearly ineligible. The same researchers independently evaluated the full-text of the included articles to determine their eligibility for inclusion of the current review.

Data extraction and quality assessment

Information about basic study (authors, year of publication, and country of origin), study design (prospective or retrospective), patients’ characteristics, and technical aspects were collected. Each study was analysed to retrieve the number of true positive (TP), true negative (TN), false positive (FP), and false negative (FN) findings of ^{18}F-fluciclovine PET or PET/CT for diagnosis of primary cancer, preoperative LN staging, and detection of recurrent PCa, according to the reference standard. Only studies providing such complete information were finally included in the meta-analysis.

The overall quality of the included studies in this review was critically appraised by two authors independently, based on 15-item modified Quality Assessment of Diagnostic Accuracy Studies (QUADAS2).[15] Discrepancies between the researchers were resolved by discussion.

Data synthesis and analysis

All data from each eligible study were extracted. The primary objective was to estimate the sensitivity and specificity, and the positive and negative likelihood ratios (LR+ and LR−, respectively) with 95% confidence intervals (CIs), and diagnostic odds ratios (DORs) with 95% CIs. A DOR can be calculated as the ratio of the odds of positivity in a disease state relative to the odds of positivity in the non-disease state, with higher values indicating better discriminatory test performance.[16] Between-study statistical heterogeneity was assessed using I^2 and the Cochrane Q test on the basis of the random-effects analysis.[17] The bivariate random-effects model was used for analysis and pooling of the diagnostic performance measures across studies, as well as comparisons.[18,19] The bivariate model estimates pairs of logit transformed sensitivity and specificity from studies, incorporating the correlation that might exist between sensitivity and specificity. Each data point of the summary receiver operator characteristic (SROC) graph comes from an individual study; then, the SROC curve is formed based on these points to form a smooth curve to reveal pooled accuracy.[20] When statistical heterogeneity was substantial, meta-regression was performed to identify potential sources of bias.[21] Two-sided $p \leq 0.05$ was considered statistically significant. Statistical analyses were performed using Meta-Disc statistical software version 1.4[22] and commercial software programs (STATA, version 13.1; StataCorp LP, College Station, TX, USA).

Results

Literature search and selection of studies

After the comprehensive computerised search was performed and references lists were extensively cross-checked, 281 records, of which 46 records of duplicated abstracts were excluded after reviewing the title and abstract. In addition the following studies were also excluded: 62 non-relevant studies, 37 case reports, 58 conference abstracts, eight notes, three editorials, three letters, and 46 review articles. The remaining 18 full-text articles were assessed for eligibility and five articles were excluded due to insufficient data for the calculation of sensitivity and specificity of ^{18}F-fluciclovine PET/CT for management of PCa patients. Finally, 13 studies were selected and were eligible for the systematic review and meta-analysis and no additional studies were found screening the references of these articles.[9,12–14,23–31] The characteristics of the included studies are presented in Table 1. The detailed study selection procedure of the current meta-analysis is shown in Fig 1.

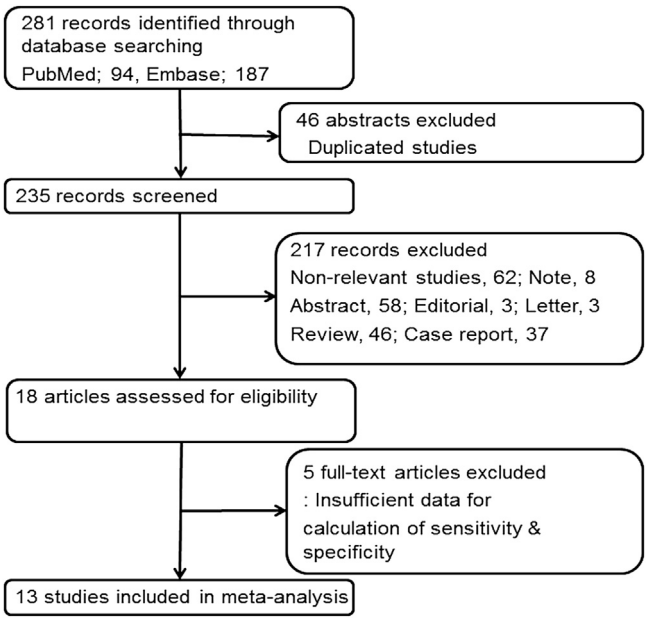

Figure 1 Flow chart of the search for eligible studies on the diagnostic performance of ^{18}F-fluciclovine PET or PET/CT for the diagnosis of primary cancer, preoperative LN staging, and detection of recurrent PCa.

Study description

All analyses were conducted based on per-patient and/or per-lesion data. Among those 13 studies included in the current review, 11 studies enrolled patients prospectively.[9,12–14,23,24,27–31] Other two studies enrolled patients retrospectively.[25,26] There was a total of 563 patients in the included studies, and the age ranged from 44 to 90 years. All 13 studies analysed the ^{18}F-fluciclovine PET or PET/CT images visually. One study[30] evaluated the diagnostic accuracy of ^{18}F-fluciclovine PET/CT for primary cancer diagnosis and preoperative LN staging in PCa patients. Six studies investigated the diagnostic role of ^{18}F-fluciclovine PET/CT in primary PCa detection.[9,24–26,30,31] Two studies evaluated the role of preoperative LN staging.[29,30] Six studies investigated diagnostic performance of ^{18}F-fluciclovine PET/CT for the detection of recurrent disease.[12–14,23,27,29] The principal characteristics of the 13 studies included in the meta-analysis are included in Table 1. To assess a possible publication bias, Deeks' funnel plot asymmetry tests were designed. The non-significant slope indicates that no significant bias was found (p=0.98; Fig 2). Fig 3 shows the risk of bias and applicability concerns summary of the included studies and overall. The quality of the included studies was deemed satisfactory.

Diagnostic performance of ^{18}F-fluciclovine PET/CT in the management of PCa

The diagnostic performance results of ^{18}F-fluciclovine PET or PET/CT for the diagnosis of primary cancer, preoperative LN staging, and detection of recurrent PCa are presented in Table 2.

Table 1
Characteristics of the studies included in the meta-analysis.

First author	Year	Country	Imaging	Analysis	Patient no.	Interpretation of ^{18}F-fluciclovine	Age (range)	Dose (MBq)	PSA (ng/ml, range)	GS	Study design
Akin-Akintayo	2018	USA	PET/CT	PB	24	Visual	70.8 (60–83)	370	8.5 (2.2–29.3)	7 (6–9)	P
Elschot	2018	Norway	PET/MRI	LB	28	Visual	66 (55–72)	NA	NA	NA	P
Jambor	2018	Finland	PET/CT	LB	32	Visual	65 (49–76)	370	12.0 (4.1–35)	7 (6–9)	R
Kairemo	2014	Finland	PET/CT	PB	26	Visual	68.1 (56–77)	328	7.9 (0.11–69)	7.1 (5–9)	R
Nanni	2015	Italy	PET/CT	PB	50	Visual	67 (55–78)	370	3.2 (0.24–15.6)	NA	P
Nanni	2016	Italy	PET/CT	PB	89	Visual	69 (55–83)	370	6.9 (0.2–20.7)	NA	P
Odewole	2016	USA	PET/CT	LB	53	Visual	67.5 (49–90)	358	7.2 (0.11–44.8)	NA	P
Schuster	2011	USA	PET/CT	PB	40	Visual	68.3 (50–90)	340	6.6 (0.11–44.7)	NA	P
Schuster	2013	USA	PET/CT	LB	10	Visual	60.8 (49–70)	347	8.2 (2.3–16.6)	6–10	P
Schuster	2014	USA	PET/CT	LB	93	Visual	68 (49–90)	322	9.8 (0.1–301.7)	7 (5–10)	P
Selnaes	2018	Norway	PET/MRI	PB	28	Visual	66.2 (55–72)	NA	14.6 (3.7–56.9)	7–11	P
Suzuki	2016	Japan	PET/CT	LB	68	Visual	67.3 (51–82)	185	88.6 (3.8–972.7)	6–10	P
Tukbey	2014	USA	PET/CT	LB	22	Visual	62.2 (44–73)	350	13.5 (3.5–37.3)	6–9	P

PET, positron-emission tomography; CT, computed tomography; MRI, magnetic resonance imaging; PB, patient based; LB, lesion based; GS, Gleason score; NA, not available; R, retrospective; P, prospective.

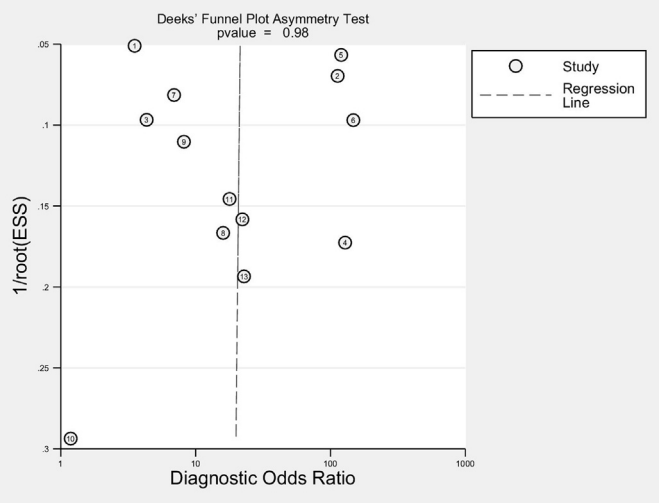

Figure 2 Results of Deeks' funnel plot of asymmetry test for publication bias. Non-significant slope indicates that no significant bias was found. ESS, effective sample size.

Diagnosis of primary cancer

The pooled sensitivity for ^{18}F-fluciclovine PET/CT for diagnosis of primary PCa was 0.87 (95% CI: 0.77–0.93) with heterogeneity (I^2=91.4, p<0.001) and a pooled specificity of 0.84 (95% CI: 0.68–0.93) with heterogeneity (I^2=96.3, p<0.001). Likelihood ratio (LR) syntheses gave an overall LR+ of 5.3 (95% CI: 2.4–11.7) and LR− of 0.16 (95% CI: 0.08–0.31). The pooled DOR was 34 (95% CI: 9–131). Fig 4a shows hierarchical SROC curve and indicates that the area under the curve was 0.92 (95% CI: 0.89–0.94).

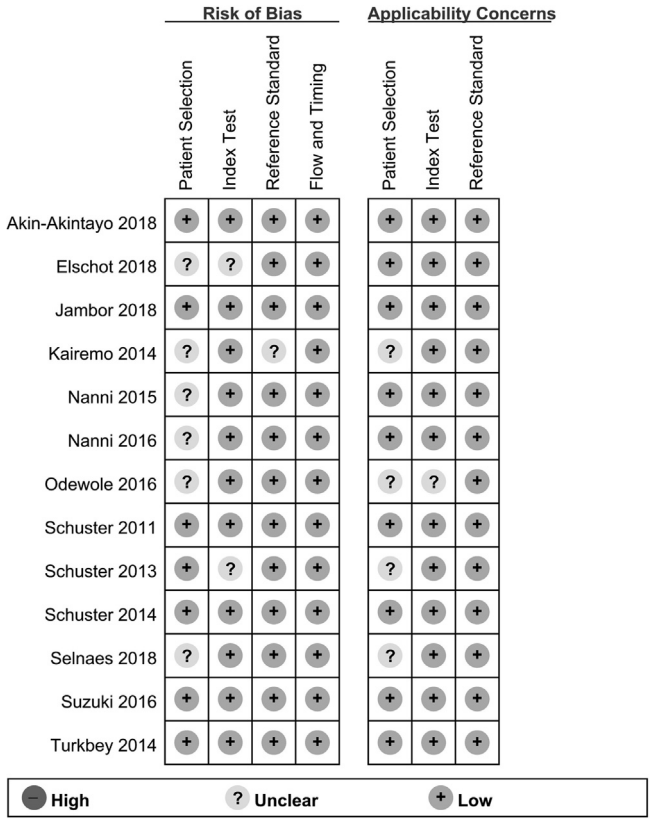

Figure 3 Risk of bias and applicability concerns summary.

Preoperative LN staging

The pooled sensitivity for ^{18}F-fluciclovine PET/CT for preoperative LN staging was 0.56 (95% CI: 0.37–0.74) without heterogeneity (I^2=41, p=0.193) and a pooled specificity of 0.98 (95% CI: 0.88–1.00) with heterogeneity (I^2=0, p=0.383). LR syntheses gave an overall LR+ of 19.3 (95% CI: 3.8–96.8) and LR− of 0.48 (95% CI: 0.27–0.82). The pooled DOR was 44 (95% CI: 7–265).

Detection of recurrent disease

The pooled sensitivity for ^{18}F-fluciclovine PET/CT for detection of recurrent PCa was 0.79 (95% CI: 0.60–0.91) with heterogeneity (I^2=93.1, p<0.001) and a pooled specificity of 0.69 (95% CI: 0.59–0.77) without heterogeneity (I^2=0, p=0.53). LR syntheses gave an overall LR+ of 2.5 (95% CI: 2.0–3.3) and LR− of 0.3 (95% CI: 0.15–0.6). The pooled DOR was 9 (95% CI: 4–19). Fig 4b shows hierarchical SROC curve and indicates that the area under the curve was 0.75 (95% CI: 0.71–0.79).

Heterogeneity evaluation and meta-regression analysis

Between-study heterogeneity was present for the sensitivity and specificity among studies of ^{18}F-fluciclovine PET/CT for diagnosis of primary PCa and detection of recurrent disease in the current study. A meta-regression analysis was performed to explore sources of heterogeneity included studies. Meta-regression showed that no definite variable was the source of heterogeneity in the current meta-analysis (Table 3).

Discussion

The synthetic amino acid, isoleucine analogue, ^{18}F-fluciclovine was developed for assessment of the anabolic component of tumour metabolism. The cellular uptake of ^{18}F-fluciclovine is mediated by the large-neutral amino acid transport system, and it is transported into cells but is not incorporated into proteins.[32] Because only a small amount of ^{18}F-fluciclovine is excreted into the urinary system and because amino acid uptake is enhanced in malignancies, ^{18}F-fluciclovine might play a crucial role in the diagnosis of PCa.

The current study showed the moderate diagnostic sensitivity and specificity of ^{18}F-fluciclovine for diagnosis of primary cancer, preoperative LN staging, and detection of recurrent PCa. Some previous studies reported the diagnostic performance of ^{18}F-fluciclovine for diagnosis of primary PCa. In the study of Jambor *et al.*, ^{18}F-fluciclovine PET/CT demonstrated a relatively low specificity of 56% because of increased tracer uptake in hyperplastic nodules, a feature typical of tracers depicting various metabolic pathways of PCa.[25] Turkbey *et al.*[31] reported that ^{18}F-fluciclovine shows higher uptake in intra-prostatic tumour foci than in normal prostate tissue; however, ^{18}F-fluciclovine uptake in tumours

Table 2
Diagnostic performance of ^{18}F-fluciclovine PET/CT for diagnosis of primary cancer, preoperative LN staging, and detection of recurrent disease in PCa.

First author, year	Test results, number of patients or lesions				Sensitivity (95% CI)	Specificity (95% CI)
	True positive	False positive	False negative	True negative		
Diagnosis of primary PCa						
Elschot 2018	38	9	2	72	0.95 (0.83–0.99)	0.89 (0.79–0.95)
Jambor 2018	139	6	27	140	0.84 (0.77–0.89)	0.96 (0.91–0.98)
Kairemo 2014	14	3	0	15	1.00 (0.77–1.00)	0.83 (0.59–0.96)
Schuster 2013	65	20	15	20	0.81 (0.71–0.89)	0.50 (0.34–0.66)
Suzuki 2016	173	7	14	64	0.93 (0.88–0.96)	0.90 (0.81–0.96)
Turkbey 2014	99	99	49	173	0.67 (0.59–0.74)	0.64 (0.58–0.69)
Combined	*528*	*144*	*107*	*482*	*0.87 (0.77–0.93)*	*0.84 (0.68–0.93)*
Preoperative LN staging						
Selnaes 2004	4	0	6	16	0.40 (0.12–0.73)	1.00 (0.79–1.00)
Suzuki 2016	13	1	7	34	0.65 (0.40–0.84)	0.97 (0.85–0.99)
Combined	*17*	*1*	*13*	*50*	*0.56 (0.37–0.74)*	*0.98 (0.89–1.00)*
Detection of recurrent disease						
Akin-Akintayo, 2018	20	9	1	10	0.95 (0.76–1.00)	0.53 (0.29–0.76)
Nanni, 2015	17	10	2	21	0.89 (0.67–0.99)	0.68 (0.49–0.83)
Nanni 2016	32	1	54	2	0.37 (0.27–0.48)	0.67 (0.09–0.99)
Odewole 2016	43	7	18	24	0.70 (0.57–0.81)	0.77 (0.59–0.90)
Schuster 2011	32	4	4	8	0.89 (0.74–0.97)	0.67 (0.35–0.90)
Schuster 2014	77	19	24	41	0.76 (0.67–0.84)	0.68 (0.55–0.80)
Combined	*221*	*50*	*1*	*106*	*0.79 (0.60–0.91)*	*0.69 (0.59–0.77)*

PET, positron-emission tomography; CT, computed tomography; PCa, prostate cancer; LN, lymph node; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; NA, not available.

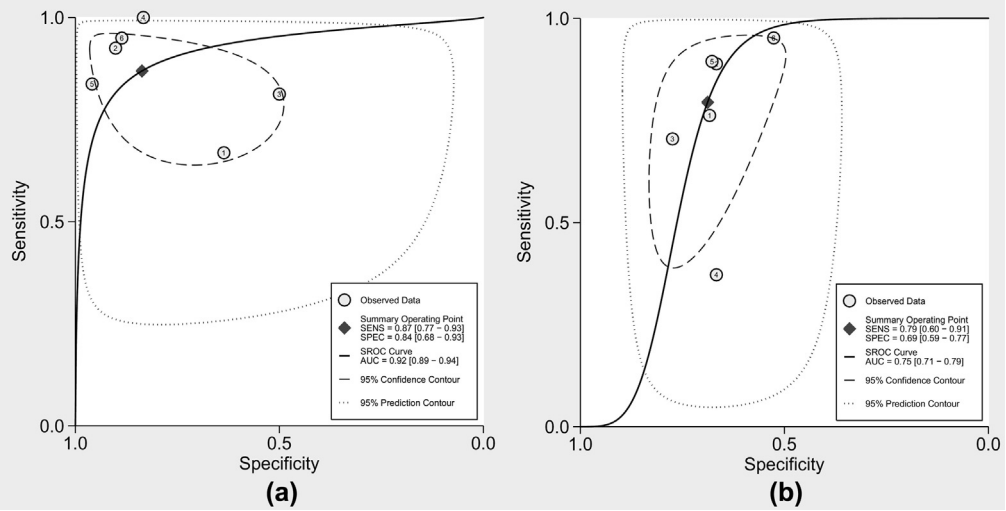

Figure 4 Hierarchical SROC curves of ^{18}F-fluciclovine PET or PET/CT for diagnosis of primary cancer and detection of recurrent PCa.

is similar to that in benign prostate hyperplastic nodules. They conclude that ^{18}F-fluciclovine may not specific for PCa and combined ^{18}F-fluciclovine PET/CT and T2-weighted magnetic resonance imaging (MRI) enable more accurate localisation of PCa lesions than either modality alone.[31] Similarly, another study showed that combined ^{18}F-fluciclovine PET/multiparametric MRI shows potential for improving detection and characterisation of high-risk PCa, in comparison to MRI and PET alone.[24] Schuster *et al.*,[9] reported that ^{18}F-fluciclovine PET should not be used alone for radiation therapy planning but may be useful to guide biopsy of the most aggressive lesion because there was no distinct separation between malignant and non-malignant sextants or between Gleason score levels.[9]

The current guideline of PCa recommends anatomical imaging, such as CT or MRI, to determine metastatic spread to the LNs in patients with newly diagnosed intermediate- to high-risk PCa[33]; however, the sensitivity of these anatomical imaging technique remains low with no significant difference in performance between modalities showing a limited ability to correctly identify malignant LNs.[34] ^{18}F-fluciclovine has shown promise in the detection of metastatic LNs among patients with BCR after prostatectomy.[35] The present study included only two studies reporting diagnostic accuracy of ^{18}F-fluciclovine PET or PET/CT for preoperative LN staging. Despite the small number of studies included, low sensitivity and high specificity of ^{18}F-fluciclovine PET or PET/CT was demonstrated for

Table 3
Effects of moderators.

Variables	Regression coefficient	SE	DOR	95% CI of DOR		*p*-Value[a]
Diagnosis of primary PCa						
Number of patients (>36 versus ≤36)	4.166	2.1673	64.4	0.00	5871.2	0.3054
PSA level (>8.2 versus ≤8.2 ng/ml)	-4.780	2.7026	0.01	0.00	98.8	0.3276
Analysis (patient versus lesion based)	3.483	2.5214	32.5	0.00	2669.7	0.3989
Detection of recurrent PCa						
Number of patients (>36 versus ≤36)	-0.922	1.3911	0.4	0.00	158.1	0.5757
PSA level (>8.2 versus ≤8.2 ng/mL)	-0.168	0.6285	0.85	0.06	12.6	0.8142
Analysis (patient versus lesion based)	0.244	0.7364	1.28	0.05	30.3	0.7716

Number of patients (1, >67 versus 0, ≤67); PSA level (1, >8.2 versus 0, ≤8.2 ng/mL); Analysis (1, Patient versus 0, Lesion based) DOR, diagnostic odds ratio; SE, standard error; CI, confidence interval; PCa, prostate cancer; PSA, prostate-specific antigen.

[a] *p*-Value of random effect meta-regression using maximum likelihood estimation (ML) between study variances and the weighted least squares of study size for regression model estimation.

preoperative LN staging of PCa. A recent study reported that patient- and region-based sensitivity/specificity for detection of pelvic LN metastases was 40%/87.5% and 35%/95.7%, respectively, for MRI and 40%/100% and 30%/100%, respectively, for PET.[29] They concluded that simultaneous ^{18}F-fluciclovine PET/MRI provides high specificity but low sensitivity for the detection of LN metastases in high-risk PCa patients and positive ^{18}F-fluciclovine PET/MRI for LN metastases indicates higher metastatic burden than a negative scan.[29]

After treatment of PCa, 30%–50% of patients experience recurrent disease after definitive local therapy.[36] Anatomical imaging such as CT, MRI, trans-rectal ultrasound have low diagnostic performance for the detection of recurrent PCa.[37,38] In addition, routine CT or MRI are limited for restaging of PCa.[34] Odewole *et al.* compared the diagnostic performance of ^{18}F-fluciclovine PET/CT with conventional CT for the recurrent PCa detection.[13] In 51 patients with sufficient follow-up to calculate diagnostic performance in the prostate bed, ^{18}F-fluciclovine PET/CT demonstrated a sensitivity of 88.6%, a specificity of 56.3%, an accuracy of 78.4%, a positive predictive value (PPV) of 81.6%, and a negative predictive value (NPV) of 69.2%; the respective values for CT were 11.4%, 87.5%, 35.3%, 66.7% and 31.1%. In 41 patients with sufficient follow-up to calculate diagnostic performance in extra-prostatic regions, fluciclovine PET/CT demonstrated a sensitivity of 46.2%, a specificity of 100%, an accuracy of 65.9%, a PPV of 100%, and an NPV of 51.7%; the respective values for CT were 11.5%, 100%, 43.9%, 100% and 39.5%. They concluded that the diagnostic performance of fluciclovine PET/CT in recurrent PCa is superior to that of CT and fluciclovine PET/CT provides better delineation of prostatic from extraprostatic recurrence. Nanni *et al.* conducted the prospective comparison of ^{18}F-fluciclovine and ^{11}C-choline PET/CT for detection of PCa relapse.[12] They reported that with ^{11}C-choline and ^{18}F-fluciclovine, sensitivities were 32% and 37%, specificities 40% and 67%, accuracies 32% and 38%, PPVs 90% and 97%, and NPVs 3% and 4%, respectively.[12] In that study, they concluded ^{18}F-fluciclovine could be considered an alternative tracer superior to ^{11}C-choline in the setting of patients with BCR after radical prostatectomy. A meta-analysis showed that ^{18}F-fluciclovine PET/CT had 87% pooled sensitivity, 66% pooled specificity, 0.93 the area under the ROC curve on a per-patient-based analysis in detecting PCa recurrence.[35]

The current meta-analysis showed considerable heterogeneity of sensitivity and specificity between studies for diagnosis of primary cancer and preoperative LN staging in PCa patients. The studies included in the meta-analysis were statistically heterogeneous in their estimates of sensitivity and specificity. This heterogeneity is likely to arise from diversity in methodological aspects between different studies and the basic differences among the patients in the studies included may have also contributed to the observed heterogeneity of the results; however, in the meta-regression analysis of the current review, no definite variable was the potential source of heterogeneity. Another major limitation of the present study is that there are many studies in which patient selection criteria was unclear and this would have had a major impact on the results of the current analysis. To minimise bias in the selection of studies and in the data extraction, reviewers who were blinded to the journal, author, institution, and date of publication independently selected articles based on the inclusion criteria, and scores were assigned to study design characteristics and examination results using a standardised form QUADAS2 tool.

In conclusion, the current meta-analysis showed the moderate sensitivity and specificity of ^{18}F-fluciclovine PET or PET/CT for the diagnosis of primary cancer, preoperative LN staging, and detection of recurrent PCa. Further large, multicentre studies would be necessary to substantiate the diagnostic accuracy of ^{18}F-fluciclovine PET or PET/CT for management of PCa patients.

Conflicts of interest

The authors declare no conflict of interest.

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