Original Paper

Influence of Four Radiotracers in PET/CT on Diagnostic Accuracy for Prostate Cancer: A Bivariate Random-Effects Meta-Analysis

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Key Words

PET/CT • Diagnosis • Prostate cancer • Meta-analysis

Abstract

Background/Aims: To date, several positron emission tomography/computed tomography (PET/CT) radiotracers including fluorine-18 fluorodeoxyglucose (18F-FDG), carbon-11 labeled choline (11C-choline), 18-F fluorocholine (18F-FCH) and carbon-11 acetate (11C-acetate) have already been assessed in the application of prostate cancer (PCa) diagnosis to some extent, the diagnostic efficiency of these radiotracers still remain controversial. As a result of this, we carried out this meta-analysis for the purpose of comparing the diagnostic accuracy among four PET/CT radiotracers. **Methods:** A systematical literature search for articles was performed until July 3, 2015. We implemented all analysis using the statistical software of STATA12 and quality assessment was performed using QUADAS-2. **Results:** A total of 56 studies containing 3,586 patients were included in this meta-analysis. Parameter estimates of the overall analysis are as follows: sensitivity, 0.80 (95% CI: 0.74-0.85); specificity, 0.84 (95% CI: 0.77-0.89) and area under roc curve-AUC of SROC, 0.89 (95% CI: 0.86-0.91), indicating a relatively high level of accuracy in diagnosis of PCa. When different radiotracers of PET/CT were compared, 18F-FCH-PET/CT was ranked as the most favorable with the highest value of AUC (AUC = 0.94; 95% CI: 0.92-0.96) whereas 18F-FDG was the least favorable (AUC = 0.73, 95% CI: 0.69-0.77). **Conclusion:** This study suggested that PET/CT imaging plays an invaluable role in the diagnosis of PCa and 18F-FCH-PET/CT was considered as a superior diagnostic tool over other radiotracers. More attention should be paid to the diagnostic efficiency of the four radiotracers particularly for PCa patients with different clinical stages.

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Introduction

Prostate cancer (PCa) is the most prevalent solid malignancy occurred in males over the world with an incidence rate of 70 cases per 100,000 males [1]. PCa has been considered as a severe health issue in developed countries compared with that in developing countries. The number of PCa cases in developed countries is approximately twice as high as that in developing countries as aging males are susceptible to the development of PCa [2, 3]. Early and accurate diagnosis of PCa is critical to the selection of optimal treatment and the prognosis of PCa patients. For example, radical prostatectomy is suitable for patients with organ-confined PCa whereas life extending therapy or systemic therapeutic regimen is appropriate for patients with impregnated or diffused PCa.

Primary imaging techniques such as bone scintigraphy and ultrasound have their own limitations, PET/CT has been sought to improve the staging of PCa [4-6]. The integrated imaging modality of PET/CT has substantial advantages in cancer localization and staging due to its combination of anatomic and metabolic information [7]. Several PET/CT radiotracers have been developed in the diagnosis of PCa, including fluorine-18 fluorodeoxyglucose (18F-FDG), carbon-11 labeled choline (11C-choline), 18-F fluorocholine (18F-FCH) and carbon-11 acetate (11C-acetate).

Although 18F-FDG, which is commonly used for diagnosing various kinds of tumor, has a suitable half-life (110 min) and presents excellent performance on tracking glucose metabolism in malignant lesions, it has very limited capacity in PCa work-up because PCa generally displays low glucose metabolism due to slow cancer growth [8-10]. Furthermore, urinary excretion of 18F-FDG could interrupt the molecular imaging and FDG accumulation may also occur in benign prostatic hypertrophy or inflammation, resulting in a low sensitivity in the detection of PCa [11-13].

Analogous imaging results are found in 11C-choline and 18F-FCH due to the same rationale for choline which is a vital portion of phosphatidylcholine that comprises the cell membrane. A rise in choline is attributable to an increase in cell proliferation and up-regulated choline-kinase activity [14-16]. Nevertheless, several distinctions between the two probes have been reported. For instance, 11C-choline provides clear images for pelvic regions for its feature of low urinary excretion and is considered to be limited for centers without on-site cyclotron because of its short half-life (20 min). By contrast, 18F-FCH possesses a longer half-life (110 min) which makes off-site transportation feasible, but it is subject to higher urinary activity [14, 17, 18].

As suggested by other studies, 11C-acetate was transformed into acetyl-CoA and then converted into fatty acid which has strength in visualizing the over-expressed fatty acid synthesis in PCa cells [19-21]. Moreover, the predominant elimination pathway of 11C-acetate is oxidized into carbon dioxide which explains the minimal bladder activity [19, 22, 23].

Comparison of imaging techniques among 18F-FDG PET/CT, 11C-choline PET/CT, 18F-FCH PET/CT and 11C-acetate PET/CT for PCa diagnosis has not been formerly reported. Therefore, this meta-analysis was designed for this specific purpose.

Materials and Methods

Search Strategy

A systematical literature search for relevant articles was performed in PubMed, Cochrane Library, Google Scholar, Medline and Embase with the key terms "prostate cancer; diagnosis; positron emission tomography/computed tomography" (updated to July 3, 2015).

Inclusion criteria and data extraction

In this meta-analysis, studies were included if matching the following criteria: studies focus on investigating the diagnostic performance of four PET/CT radiotracers in PCa; the values of true/false-

positive, true/false-negative can be calculated.

Two authors perused the full text of eligible studies and extracted the following relevant information: basic study information (first author, year of publication, publishing country), type of PET/CT and data needing for meta-analysis. When the data of sensitivity and specificity were not reported in the text, we estimated these figures by corresponding SROC curves. Missing data contained in eligible studies was sought from authors via e-mail request.

Quality assessment

Quality assessment was independently performed by two reviewers using QUADAS-2 which concerns about four key domains (patient selection, index test, reference standard and flow timing). [24]. The quality of the studies was evaluated by examining 10 questions and each question should be answered with “yes”, “no”, or “unclear”. An answer of “yes” gets one score, which means low risk of bias, whereas an answer of “no” or “unclear” gains a score of “0” which suggests that a high risk of bias may exist (Table 1).

Table 1. Main characteristics of included studies in the systematic meta-analyses

First author	Year	Country	Ethnicity	Type of PET/CT	TP	FP	FN	TN	Sensitivity (95%CI)	Specificity (95%CI)	QUADAS 2
Wachter	2006	Austria	Caucasian	11C-acetate	12	1	1	3	0.92 (0.64-1.00)	0.75 (0.19-0.99)	8/10
Jambor	2010	Finland	Caucasian	11C-acetate	28	5	7	2	0.80 (0.23-0.92)	0.29 (0.04-0.71)	7/10
Mena	2012	America	Caucasian	11C-acetate	47	37	17	66	0.73 (0.61-0.84)	0.64 (0.54-0.73)	9/10
Jambor	2012	Finland	Caucasian	11C-acetate	44	13	6	9	0.88 (0.76-0.95)	0.41 (0.21-0.64)	7/10
Haseebuddin	2013	America	Caucasian	11C-acetate	17	18	8	64	0.68 (0.46-0.85)	0.78 (0.68-0.86)	7/10
Kotzerke	2000	Germany	Caucasian	11C-choline	1	1	1	9	0.50 (0.01-0.99)	0.90 (0.55-1.0)	7/10
Farsad	2005	Italy	Caucasian	11C-choline	35	3	1	2	0.97 (0.85-1.0)	0.40 (0.05-0.85)	7/10
Reske	2006	Germany	Caucasian	11C-choline	363	61	86	426	0.81 (0.77-0.84)	0.87 (0.84-0.90)	7/10
Martorana	2006	Italy	Caucasian	11C-choline	107	15	56	80	0.66 (0.58-0.73)	0.84 (0.77-0.91)	8/10
Testa	2007	Italy	Caucasian	11C-choline	53	8	45	50	0.54 (0.44-0.64)	0.86 (0.75-0.94)	6/10
Scher	2007	Germany	Caucasian	11C-choline	32	8	5	13	0.86 (0.71-0.95)	0.62 (0.38-0.82)	7/10
Scattoni	2007	Italy	Caucasian	11C-choline	19	2	0	4	1.00 (0.82-1.00)	0.67 (0.22-0.96)	7/10
Igerc	2007	Austria	Caucasian	11C-choline	5	8	0	7	1.00 (0.48-1.00)	0.47 (0.21-0.73)	8/10
Rinnab	2007	Germany	Caucasian	11C-choline	38	6	2	4	0.95 (0.83-0.99)	0.40 (0.12-0.74)	8/10
Schiavina	2008	Italy	Caucasian	11C-choline	9	1	6	41	0.60 (0.32-0.84)	0.98 (0.87-1.00)	8/10
Reske	2008	Germany	Caucasian	11C-choline	23	4	10	12	0.70 (0.51-0.84)	0.75 (0.48-0.93)	7/10
Li	2008	China	Asian	11C-choline	19	4	2	24	0.90 (0.70-0.99)	0.86 (0.67-0.96)	6/10
Giovacchini	2008	Italy	Caucasian	11C-choline	48	27	19	20	0.72 (0.59-0.82)	0.43 (0.28-0.58)	6/10
Rinnab	2009	Germany	Caucasian	11C-choline	29	7	2	3	0.94 (0.79-0.99)	0.30 (0.07-0.65)	8/10
Winter	2009	Germany	Caucasian	11C-choline	9	2	0	12	1.00 (0.66-1.00)	0.86 (0.57-0.98)	7/10
Breeuwmsma	2010	Germany	Caucasian	11C-choline	57	0	13	10	0.81 (0.70-0.90)	1.00 (0.69-1.00)	8/10
Giovacchini	2010	Italy	Caucasian	11C-choline	65	10	10	85	0.87 (0.77-0.93)	0.89 (0.81-0.95)	6/10
Winter	2010	Germany	Caucasian	11C-choline	6	0	0	10	1.00 (0.54-1.00)	1.00 (0.69-1.00)	6/10
Giovacchini	2010	Italy	Caucasian	11C-choline	145	14	26	173	0.85 (0.79-0.90)	0.93 (0.88-0.96)	6/10
Fuccio	2010	Italy	Caucasian	11C-choline	19	0	3	3	0.86 (0.65-0.79)	1.00 (0.29-1.00)	8/10
Watanable	2010	Japan	Asian	11C-choline	19	7	7	10	0.73 (0.52-0.88)	0.59 (0.33-0.82)	7/10
Contractor	2011	UK	Caucasian	11C-choline	7	3	2	14	0.78 (0.40-0.97)	0.82 (0.57-0.96)	9/10
Bertagna	2011	Italy	Caucasian	11C-choline	6	3	4	32	0.60 (0.26-0.88)	0.91 (0.77-0.98)	7/10
Budiharto	2011	Belgium	Caucasian	11C-choline	3	1	13	19	0.19 (0.04-0.46)	0.95 (0.75-1.00)	6/10
Bergh	2011	Germany	Caucasian	11C-choline	363	390	106	317	0.77 (0.73-0.81)	0.45 (0.41-0.49)	7/10
Picchio	2012	Italy	Caucasian	11C-choline	24	0	3	51	0.89 (0.71-0.98)	1.00 (0.93-1.00)	7/10
Giovacchini	2012	Switzerland	Caucasian	11C-choline	63	3	7	2	0.91 (0.82-0.96)	0.40 (0.05-0.85)	8/10
Mitchell	2013	America	Caucasian	11C-choline	106	11	8	35	0.93 (0.87-0.97)	0.76 (0.61-0.87)	6/10
Jilg	2014	America	Caucasian	11C-choline	102	26	9	23	0.92 (0.85-0.96)	0.47 (0.33-0.62)	7/10
Heck	2014	Germany	Caucasian	11C-choline	8	3	6	30	0.57 (0.29-0.82)	0.91 (0.76-0.98)	9/10
Kitajima	2014	America	Caucasian	11C-choline	118	3	37	120	0.76 (0.69-0.83)	0.97 (0.97-0.99)	7/10
Minamimoto	2010	Japan	Asian	18F-FDG	27	36	25	112	0.52 (0.38-0.66)	0.76 (0.68-0.82)	8/10
Hwang	2012	Korea	Asian	18F-FDG	20	65	3	32	0.87 (0.66-0.97)	0.33 (0.24-0.43)	7/10
Shiba	2012	Japan	Asian	18F-FDG	58	18	36	72	0.62 (0.51-0.72)	0.80 (0.70-0.88)	7/10
Damle	2013	India	Asian	18F-FDG	23	0	9	17	0.72 (0.53-0.86)	1.00 (0.80-1.00)	7/10
Yang	2014	China	Asian	18F-FDG	13	25	7	55	0.65 (0.41-0.85)	0.69 (0.57-0.79)	8/10
Kwee	2005	America	Caucasian	18F-FCH	64	17	5	16	0.93 (0.84-0.98)	0.48 (0.31-0.66)	7/10
Hacker	2006	Austria	Caucasian	18F-FCH	1	2	9	8	0.10 (0.00-0.45)	0.80 (0.44-0.97)	8/10
Husarik	2007	Switzerland	Caucasian	18F-FCH	1	0	2	22	0.33 (0.01-0.91)	1.00 (0.85-1.00)	9/10
Pelosi	2007	Italy	Caucasian	18F-FCH	24	1	0	26	1.00 (0.86-1.00)	0.96 (0.81-1.00)	6/10
Vees	2007	Switzerland	Caucasian	18F-FCH	3	2	5	1	0.38 (0.09-0.76)	0.33 (0.01-0.91)	8/10
Pelosi	2008	Italy	Caucasian	18F-FCH	24	1	5	26	0.83 (0.64-0.94)	0.96 (0.81-1.00)	7/10
Beheshti	2010	Austria	Caucasian	18F-FCH	18	4	22	86	0.45 (0.29-0.62)	0.96 (0.89-0.99)	7/10
Steuber	2010	Germany	Caucasian	18F-FCH	0	0	31	254	0.00 (0.00-0.01)	1.00 (0.99-1.00)	7/10
Beheshti	2010	Austria	Caucasian	18F-FCH	207	3	56	96	0.79 (0.73-0.83)	0.97 (0.91-0.99)	8/10
Poulsen	2010	Denmark	Caucasian	18F-FCH	3	1	0	21	1.00 (0.29-1.00)	0.95 (0.77-1.00)	7/10
Langsteiger	2011	Austria	Caucasian	18F-FCH	20	2	2	16	0.91 (0.71-0.99)	0.89 (0.65-0.99)	8/10
McCarthy	2011	Austria	Caucasian	18F-FCH	150	1	6	26	0.96 (0.92-0.99)	0.96 (0.81-1.00)	6/10
Oprea-Lager	2012	Sweden	Caucasian	18F-FCH	35	1	2	16	0.95 (0.82-0.99)	0.94 (0.71-1.00)	6/10
Panebianco	2012	Italy	Caucasian	18F-FCH	48	2	4	1	0.92 (0.81-0.98)	0.33 (0.01-0.91)	7/10
Poulsen	2012	Denmark	Caucasian	18F-FCH	30	21	11	148	0.73 (0.57-0.86)	0.88 (0.82-0.92)	9/10

TP: true-positive; FP: false-positive; TN: true-negative; FN: false negative; CI: confidence interval; SEN: sensitivity; SPE: specificity; PET/CT: positron emission tomography/computed tomography; FCH: fluorocholine; FDG: fluoroglucose

Statistical methods

Statistical heterogeneity was evaluated by the statistic of Q and I^2 . $P < 0.01$ and $I^2 > 50\%$ indicates significant study heterogeneity [25], then the random-effects model would be performed to calculate the pooled estimates, otherwise a fixed-effect model would be carried out for the meta-analysis. The diagnostic accuracy of four PET/CT radiotracers was evaluated by several measures including the sensitivity, specificity, positive likelihood ratio-PLR, negative likelihood ratio-NLR, diagnostic odds ratio and AUC. Summary receiver operating characteristics (SROC) curves were generated to present parameter estimates using the method of inverse variance. Besides that, subgroup analyses by ethnicity and type of PET/CT were conducted to explore the potential source of heterogeneity. Publication bias of the included studies was assessed by Deeks' Funnel Plot and symmetry test which indicated significant publication bias if P value was less than 0.1. We performed all statistical analysis by STATA12.0 (StataCorp, College Station, Texas).

Results

Included studies

A total of 1,313 studies were identified during the stage of initial search, 326 of the articles were eliminated for duplicate data and 637 studies were judged as unavailable by screening their titles and abstracts. The rest of 385 studies were read for full-text review. Finally, 56 studies containing 3,586 patients were included according to the inclusion and exclusion criteria. The entire process of the literature search was presented in Fig. 1.

Study populations and their characteristics were summarized in Table 1. QUADAS-2 scores indicated that all of the admitted studies were reliable with scores ranging from 6 to 9 out of 10. The included studies were reported in different countries, of those, 42 studies were performed in Europe, 7 in Asia, and 7 in Australia. In total, there were 3,743 patients as the case group and 3,586 matched healthy people as the control group. All included studies were published between 2005 and 2015 (11C-choline: $n = 31$ [26-54], 18F-FCH: $n = 15$ [17, 55-68], 11C-acetate: $n = 5$ [69-73], 18F-FDG: $n = 5$ [74-78]).

Fig. 1. Literature selection flow chart.

Table 2. The pooled diagnostic performance related with 4 imaging techniques based on meta-analyses

Analysis	SEN (95%CI)	SPE (95%CI)	PLR (95%CI)	NLR (95%CI)	DOR (95%CI)	AUC (95%CI)
Ethnicity						
Asian	0.71 (0.60, 0.80)	0.74 (0.56, 0.86)	2.7 (1.5, 4.8)	0.39 (0.27, 0.57)	7 (3, 16)	0.77 (0.74, 0.81)
Caucasian	0.81 (0.74, 0.87)	0.85 (0.78, 0.90)	5.5 (3.7, 8.1)	0.22 (0.16, 0.30)	25 (15, 42)	0.90 (0.87, 0.92)
Type of PET/CT						
11C-choline PET/CT	0.83 (0.77, 0.88)	0.82 (0.73, 0.88)	4.50 (3.0, 6.8)	0.21 (0.16, 0.28)	22 (13, 37)	0.89 (0.86, 0.91)
18F-FCH PET/CT	0.76 (0.49, 0.91)	0.93 (0.84, 0.97)	11.70 (4.9, 27.9)	0.26 (0.10, 0.63)	46 (13, 165)	0.94 (0.92, 0.96)
11C-acetate PET/CT	0.79 (0.70, 0.86)	0.59 (0.43, 0.73)	1.90 (1.4, 2.7)	0.35 (0.25, 0.49)	6 (3, 10)	0.78 (0.74, 0.81)
18F-FDG PET/CT	0.67 (0.55, 0.77)	0.72 (0.50, 0.87)	2.40 (1.3, 4.5)	0.46 (0.34, 0.6)	5 (2, 12)	0.73 (0.69, 0.77)
Overall	0.80 (0.74, 0.85)	0.84 (0.77, 0.89)	5.0 (3.5, 7.1)	0.23 (0.18, 0.31)	21 (13, 34)	0.89 (0.86, 0.91)

CI: confidence interval; SEN: sensitivity; SPE: specificity; PLR: positive likelihood ratio; NLR: negative likelihood ratio; DOR: diagnostic odds ratio; AUC: area under the curve.

Fig. 2. Forest plots of sensitivity and specificity for 11C-acetate PET/CT.

Summary of the diagnostic performance

First of all, test of heterogeneity was performed to assess whether the included studies were homogeneous and then the pooled diagnostic statistics were evaluated. I^2 values for sensitivity and specificity was 90.24% (95% CI: 88.31-92.16%, $P < 0.001$) and 95.60% (95% CI: 94.91-96.28%, $P < 0.001$), respectively. A random-effects model was adopted to assess the pooled data due to the existence of significant heterogeneity among studies. As suggested by Table 2, the overall parameter estimates are as follows: sensitivity, 0.80 (95% CI: 0.74-0.85); specificity, 0.84 (95% CI: 0.77-0.89); PLR, 5.0 (95% CI: 3.5-7.1); NLR, 0.23 (95% CI: 0.18-0.31); and DOR, 21 (95% CI: 13-34). The pooled AUC was 0.89 (95% CI: 0.86-0.91), suggesting a relatively high level of accuracy for PCa diagnosis by PET/CT.

Subgroup analysis

Subgroup analysis by types of PET/CT was performed to assess whether there was significant heterogeneity among the four PET/CT radiotracers in respect of diagnostic accuracy. We implemented a random-effects model for 11C-PET/CT, 18F-FCH-PET/CT and 18F-FDG due to the presence of significant heterogeneity ($I^2 > 50\%$, $P < 0.001$) (Fig. 2-5).

Fig. 3. Forest plots of sensitivity and specificity for 11C-choline PET/CT.

Fig. 4. Forest plots of sensitivity and specificity for 18F-FDG PET/CT.

By contrast, a fixed-effect model was adopted for the sensitivity of 11C-acetate PET/CT ($I^2 = 42.47$, $P = 0.140$). The pooled sensitivities of the four diagnostic techniques were ordered in a descending order: 11C-PET/CT (sensitivity = 0.83; 95% CI: 0.770-0.88), 11C-Acetate PET/CT (sensitivity = 0.79; 95% CI: 0.70-0.86), 18F-FCH-PET/CT (sensitivity = 0.76; 95% CI: 0.49-0.91), 18F-FDG PET/CT (sensitivity = 0.67; 95% CI: 0.55-0.77). Moreover, 18F-FCH-PET/CT had the highest specificity (specificity = 0.93; 95% CI = 0.84-0.97) followed

Fig. 5. Forest plots of sensitivity and specificity for 18F-FCH PET/CT.

11C-PET/CT (specificity = 0.82, 95% CI: 0.73-0.88), 18F-FDG PET/CT (specificity = 0.72; 95% CI: 0.50-0.87) and 11C-Acetate PET/CT (specificity = 0.59; 95% CI: 0.43-0.73). Besides that, 18F-FCH-PET/CT had the highest AUC (AUC = 0.94; 95% CI: 0.92-0.96) followed by 11C-PET/CT (AUC = 0.89, 95% CI: 0.86-0.91), 11C-Acetate PET/CT (AUC = 0.78, 95% CI: 0.74-0.81) and 18F-FDG PET/CT (AUC = 0.73, 95% CI: 0.69-0.77) (Fig. 6).

Table 2 also revealed the pooled diagnostic results obtained from subgroup analysis by ethnicity. The diagnostic accuracy in Caucasian was higher (sensitivity = 0.81, 95%CI: 0.74-0.87; specificity = 0.85, 95%CI: 0.78-0.90; AUC = 0.90, 95%CI: 0.87-0.92) compared to that in Asian (sensitivity = 0.71, 95%CI: 0.60-0.80, specificity = 0.74, 95% CI: 0.56-0.86; AUC = 0.77, 95% CI: 0.74-0.81). The corresponding SROC curve was showed in Fig. 7.

Discussion

PET/CT has been developed as a new technology to improve the accuracy of clinical molecular imaging, especially for phymatology [7]. Moreover, the development of PET/CT radiotracers is critical to the early diagnosis of cancer which may enhance the chance of survival for cancer patients. Major radiotracers including 18F-FDG, 11C-choline, 18F-FCH and 11C-acetate enabled us to visualize tumor metabolisms and hence precisely assess the stage of cancer. As one of the first radiotracers, 18F-FDG is associated with low sensitivity and specificity especially in diagnosing well-differentiated PCa as its diagnostic accuracy is related to urinary excretion. Hence, 18F-FDG has limited performance on PCa diagnosis [10]. Other PET radiotracers, such as 18F-FCH, 11C-choline and 11C-acetate have been recommended and encouraging results were obtained [79-84]. Although, a systematic review has investigated the application of 18F-FCH PET/CT in PCa diagnosis [85], these recommendations remained unclear and the overall diagnostic performance remained vague.

Fig. 6. SROC curves of four PET/CT radiotracers, a: 11C-acetate PET/CT; b: 11C-choline PET/CT; c: 18F-FDG PET/CT; d: 18F-FCH PET/CT.

Therefore, the diagnostic accuracy of the four radiotracers in PET/CT were compared and assessed in this meta-analysis in order to address the issue of inconsistency resulted from study heterogeneity.

Our study indicated that 11C-acetate was more accurate than 18F-FDG with respect to the diagnostic accuracy of PCa and this was consistent with those results from previous studies [81, 86]. The diagnostic superiority of 11C-acetate over 18F-FDG may be explained by several facts. Firstly, 18F-FDG was mainly excreted through kidneys, urinary bladder and urethra which may result in the obscure of the urinary bladder. On the contrary, 11C-carbon dioxide

Fig. 7. SROC curves of overall and subgroup by ethnicity.

which is the primary metabolite of ^{11}C -acetate rapidly exhales through the respiratory system and the remaining ^{11}C -acetate filtered through kidney are almost negligible. Hence, the visualization of PCa tissues is not interfered with the elimination of ^{11}C -acetate, especially for regional lymph node metastasis and local recurrence PCa. Indeed, ^{11}C -acetate could contribute to prostate-specific citrate metabolism which may be beneficial to tumor detection for localized PCa [81].

Both ^{18}F -FCH and ^{11}C -choline PET/CT and the result indicated that they were significantly better than ^{11}C -acetate. Since choline is an important component in synthesizing phospholipids, the activity of choline has substantial influence on the activity of the enzyme choline kinase and PCa cell proliferation. Therefore, an elevated activity of choline and kinase could be detected in malignant cells [87]. Moreover, the promising results were also obtained in the preoperative staging of pelvic lymph nodes for PCa patients [84]. However, ^{11}C -choline radiotracers have a relatively short half-life which could be overcome by ^{18}F -FCH. Hence, ^{18}F -FCH seems to be more accurate than ^{11}C -choline in respect of PCa diagnosis [88, 89].

Subgroup analysis by ethnicity revealed that Caucasian population (AUC = 0.90) had significantly higher diagnostic accuracy than Asian (AUC = 0.77). The significant diagnostic difference between the two ethnicities may be attributable to the fact that almost all of the Asian populations in our study were diagnosed by ^{18}F -FDG whose diagnosis efficiency was relatively low.

Despite of the innovation and potential advantages in our meta-analysis, certain limitations still existed. First of all, the synthesized results were not applicable to other ethnicity since there were no African populations involved in our study. Secondly, subgroup analysis by radiotracers was not feasible due to insufficient data. Thirdly, some potential factors that affect the diagnostic accuracy of PCa were not assessed due to the clinical and biological complexity of PCa. For instance, the diagnostic accuracy is likely to be affected by different clinical stages of PCa, including locally recurrent, metastatic and loco regional lymph nodes PCa and this kind of information was not available. In addition, the absence of a thorough histopathological analysis for tumor tissues further reduces the credibility of the results.

For summary, our meta-analysis assessed four radiotracers employed in PET/CT for PCa detection. The results obtained from this study suggested that PET/CT imaging plays an irreplaceable role in PCa diagnosis. Among the four radiotracers, Choline PET/CT particularly ^{18}F -FCH PET/CT were more favorable than others in respect of PCa diagnostic accuracy. Still, we strongly recommended that future studies which are applicable to all ethnicities and adjusted for potential confounding factors should be designed to confirm our conclusion.

Disclosure Statement

The authors declare no commercial or financial conflict of interest.

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