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The Diagnostic Accuracy of 18F-FDG PET/CT in Prostate Cancer: A Systemic Review and Meta-analysis

Xue Liu[1]*, Qi-lian Ran[2], Shi-liang Zhou[1], Tao Jiang[1], Zhen Su[1], Jiang Wu[1], You-cheng Li[1], Huai-wei Xu[1], Da-ang Liu[1] and Zong-qun Zhao[1]

[1]Department of Nuclear Medicine, the First People's Hospital of Huaihua, Huaihua, Hunan, China
[2]Department of General Surgery, First Affiliated Hospital of Hunan University of Medicine, Huaihua, Hunan, China

Abstract

Objectives: A systematic review process was adopted to derive more robust estimates of the diagnostic accuracy of 18F-fluorodeoxyglucose(18F-FDG) positron emission tomography /computed tomography (PET/CT) for prostate cancer we pooled published studies.

Methods: A comprehensive literature search about published studies till November 2017 was performed. Methodological quality of each study was assessed. A meta-analysis was used to analyze the sensitivity, specificity, diagnostic odds ratio (DOR), area under the curve (AUC), summary receiver operating characteristic (sROC) curve and Q* indexes with statistical software.

Results: Ten articles including 364 patients and 505 lesions, which published between 2009 and 2017, met the inclusion criteria for the meta-analysis. The pooled sensitivity and specificity of 18F-FDG PET-CT in prostatic cancer were 0.65 (95% CI, 0.47-0.79) and 0.85 (95% CI, 0.71-0.93), respectively. The overall PLR, NLR and DOR were 4.3 (95% CI, 2.0-9.2), 0.41 (95% CI, 0.25-0.68) and 10 (95% CI, 3-32), respectively. The area under the summary ROC curve was 0.84. There is not exist publication bias in the included studies according to the Deek's test.

Conclusions: The results of our meta-analysis suggested that 18F-FDG PET-CT were imaging methods with high accuracy in differential diagnosis of prostate cancer patients.

Keywords: Prostate cancer; PET/CT; 18F-FDG; Meta-analysis

Introduction

Prostate cancer is the most common malignant tumor elderly male in the reproductive system [1]. Recently, the incidence of prostate cancer is very high and account for the highest incidence of all male cancers and the mortality rate is second in the Europe and American countries [2]. Early detection, early diagnosis and early treatment are the key to improve survival and quality of life for prostate cancer patients [2]. In terms of diagnosis, traditional medical imaging techniques, such as CT, MRI and ultrasound, have certain limitations in identified diagnosis of prostate cancer [3]. With the development of medical molecular biology technology, molecular imaging PET/CT is being used to diagnose prostate cancer. Compared with traditional medical diagnosis technology, PET/CT can detect early malignant lesions and evaluate the therapeutic effect after treatment [4]. Relevant studies [5-7] reported that the PET/CT has high application value on prostate cancer, but because of the different study results are huge so that there is not inconsistent conclusion because of the diversity of research population, different design method，and various regions. In order to derive more robust estimates of the diagnostic accuracy of 18F-FDG PET/ CT for prostate cancer in this setting we pooled published studies. A systematic review process was adopted in ascertaining studies, thereby avoiding selection bias.

Materials and Methods

Data sources and search strategies

A comprehensive computer literature search of PubMed, MEDLINE, and web of science and Embase databases were searched from January 1990 to November 2017 using the following searching strategy: ("fluorodeoxyglucose F18"[MeSH Terms] OR ("fluorodeoxyglucose"[All Fields] AND "F18"[All Fields]) OR "fluorodeoxyglucose F18"[All Fields] OR ("18F"[All Fields] AND "FDG"[All Fields]) OR "18F FDG"[All Fields]) AND PET/CT[All Fields] AND ("prostatic neoplasms"[MeSH Terms] OR ("prostatic"[All Fields] AND "neoplasms"[All Fields]) OR "prostatic neoplasms"[All Fields] OR ("tumor"[All Fields] AND "prostate"[All Fields]) OR "tumor of prostate"[All Fields]) OR ("cancer"[All Fields] AND "prostate"[All Fields]). Only articles in English language were considered. Besides, to expand our search, references of the retrieved articles were also screened for additional studies.

Study selection

Two investigators independently reviewed titles and abstracts of the eligible articles based on the inclusion criteria for this study: (a) articles which were open access English scientific literature; (b) articles which used 18F-FDG PET-CT to identify as prostatic cancer; (c) articles which used histopathology or follow-up at least 3 months as the reference standard; (d) articles which presented complete data to construct 2 × 2 tables [this is, true positive (TP), true-negative (TN), false-positive (FP), and false-negative (FN)]; (e) sample size was more than 10; (f) the main object of articles were prostate disease and primary tumor. In contrast, articles were excluded if: (a) articles which were unable to

get the full text; (b) articles that were duplicates, conferences, reviews or case reports.

Data extraction

Data abstracted from each eligible article were collected in homemade Excel spread sheet included the following details: title, authors, year of publication, country, sample sizes(patients or lesions), age, design, reference, standard of diagnosis, Gleason scores, dose of 18F-FDG, et al. Each study was analyzed to retrieve the number of TP, FP, FP and TN findings of 18F-FDG PET/CT in patients with prostatic disease, according to the standard of diagnosis. Only studies providing such complete information were finally included in the meta-analysis. If the study analyzed the number of per-patient and per-lesion, we will extract the latter.

Quality assessment

The QUADAS (Quality Assessment of Diagnostic Accuracy Studies) checklist was used to assess independently the methodological quality by the same investigators [8]. This table is an evidence-based quality assessment tool which developed for systematic reviews about the diagnostic accuracy of studies [8].

Statistical methods

Statistically, the χ^2-based **Q** statistic test (Cochran's **Q** statistic) was used to estimate whether existing study heterogeneity or not, and the I^2 statistic was used to measure the magnitude of the heterogeneity. Generally, the smaller the P value of **Q** test, the larger the I^2 statistic [9].

The I^2 index was calculated to assess between-study heterogeneity. The values of I^2 of 25%, 50% and 75% were considered as evidence of low, moderate, and high heterogeneity, respectively [10]. If the heterogeneity was low, the fixed-effects model was used to pool the results; otherwise, the random-effects model was used when I^2 was more than 50% [10].

The pooled results included the items: sensitivity TP/(TP+FN), specificity TN/(TN+FP), positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR) and 95% confidence interval (95% CI). The results of the individual studies were displayed in receiver operating characteristic (ROC) space, a weighted symmetric sROC curve with 95% CI was computed with the Moses' constant of linear mode, and the value of AUC and Q* indexes (the point on the curve at which sensitivity and specificity are equal) as estimated [11]. Besides, if the heterogeneity of the study was caused by the threshold effect, the best method of pooling data is using summary receiver operating characteristic (sROC) curve and calculating the area under the curve (AUC) of ROC. If heterogeneity is caused by the non-threshold effect, the data was combined by subgroup analysis or meta-regression analysis. Besides, publication bias was assessed by using Deek's test [12].

Statistical analyses were performed with STATA software (version 12.0) [12] for the eligible studies.

Results

Literature search

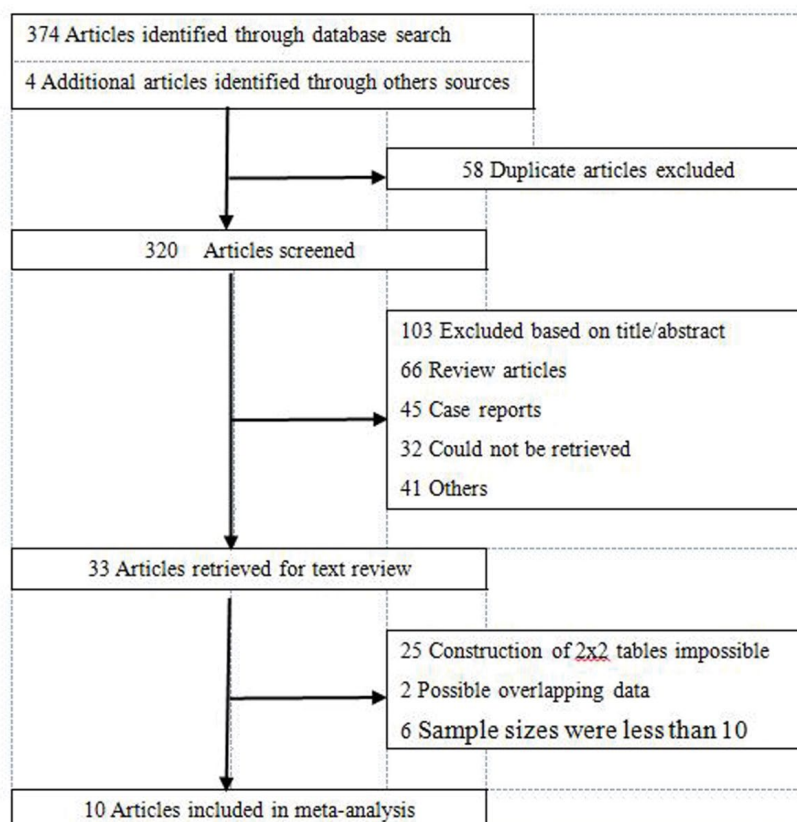The comprehensive computer literature search from the databases

Figure 1: Literature Search of Eligible Studies.

Authors	Publication year	Country	Age (years)	No. of patients	No. of lesions	Level of PSA (ng/ml)	Type	Reference	Gleason scores	Dose of FDG (MBq)	SUV
LIU et al. [5]	2014	USA	61 ± 9	25	NG	291±363	R	Biopsy	6-9	NG	>3.0
Richter et al. [14]	2017	Spain	41– 78	73	NG	2.7	R	Biopsy	8-10	370	4.8±1.9
Kit et al. [7]	2015	Sweden	63-78	10	70	0.12-15	R	Biopsy, CT	7-8	4 MBq/kg	NG
García et al. [15]	2009	Spain	63.8 ± 6.9	38	NG	0.8-9.5	R	Biopsy	8-10	656 ± 119	NG
Beauregard et al. [13]	2010	USA	51-77	16	NG	0.09-795	P	Biopsy	6-9	300	NG
Minamimoto et al. [6]	2015	Canada	68.3 ± 9.4	30	129	8.6 ± 10.1	P	Pathology, clinical follow-up	NG	370.1 ± 24.7	NG
Hossein et al. [17]	2012	Canada	71.1	37	NG	53.5-86.9	P	Biopsy	6-9	525.4 ± 25.9	NG
Yi et al. [16]	2016	China	60-88	36	106	10.91-1000	P	Pathology, clinical follow-up	8-10	5.18 MBq/kg	Higher than iliac fossa fat
Ryogo et al. [18]	2011	Japan	41-82	50	200	15.9 ± 14.9	P	biopsy	>7	2.5 MBq/kg	>2.9
Nishikant et al. [19]	2013	India	50-84	49	NG	NG	P	Biopsy	8-10	370–555	Increased metabolism

NG: Not Given; R: Retrospective; P: Perspective; PSA: Prostate Specific Antigen; CT: Computed Tomography; FDG: Fluorodeoxyglucose; SUV: Standardized Uptake Value.

Table 1: Characteristics of Studies Included in the meta-analysis.

Study	QUADAS criteria													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
LIU et al. [5]	Y	Y	Y	Y	Y	U	Y	Y	Y	N	N	Y	Y	Y
Richter et al. [14]	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	U	Y	Y
Kit et al. [7]	Y	Y	Y	Y	Y	N	Y	U	U	Y	Y	Y	Y	Y
García et al. [15]	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y
Beauregard et al. [13]	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y
Minamimoto et al. [6]	Y	Y	Y	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y
Hossein et al. [17]	Y	Y	Y	Y	Y	U	Y	Y	Y	N	N	Y	Y	Y
Yi et al. [16]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Ryogo et al. [18]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y
Nishikant et al. [19]	Y	Y	Y	Y	Y	U	Y	N	N	Y	Y	Y	Y	Y

QUADAS: Quality Assessment of Diagnostic Accuracy Studies; N: no; U: Unclear; Y: Yes.

Table 2: QUADAS (appraisal) tool results.

revealed 378 articles. Reviewing titles and abstracts, 294 articles were excluded because of reviews, editorials or letters, case reports or case series. 25 articles were excluded due to absence of data to construct or calculate 2 × 2 tables. Six articles were excluded because of the sample sizes were less than 10. Finally, ten articles including 364 patients and 505 lesions, which published between 2009 and 2017, met the inclusion criteria for the meta-analysis [5-7,13-19]. The screenings of excluded articles were presented in Figure 1. The characteristics of the enrolled studies are presented in Table 1. The mean age of patients ranged from 41 to 88 years. Of the ten included trials, four [5,7,14,15]were retrospective trial and six [13,6,16-19] were perspective trail. Nine studies [5,7,13,19] have reported the Gleason scores which the scores were between 6 and 10 point. Only one study [6] has not given the Gleason scores. In terms of interpreted the positive of 18F-PET/CT imaging, three [5,14,18]of the included trials were semi-quantitative method, two trails[16,19] were qualitative method, and the other studies not given the interpreted method. There were nine studies reported the dose of 18-F FDG, and one study [5] has not given.

The methodological quality of the eligible 10 studies was assessed by the 'QUADAS' quality assessment tool (Table 2), and a total of 14 questions were applied for each study. Scores of all studies were more than 9, indicating high quality.

1. Was the spectrum of patient's representative of the patients who will receive the test in practice?

2. Were the selection criteria clearly described?

3. Is the reference standard likely to correctly classify the target condition?

4. Is the time period between the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests?

5. Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis?

6. Did patients receive the same reference standard regardless of the index test result?

7. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?

8. Was the execution of the index test described in sufficient detail to permit replication of the test?

9. Was the execution of the reference standard described in sufficient detail to permit its replication?

10. Were the index test results interpreted without knowledge of the results of the reference standard?

11. Were the reference standard results interpreted without knowledge of the results of the index test?

12. Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice?

13. Were uninterpretable/intermediate test results reported?

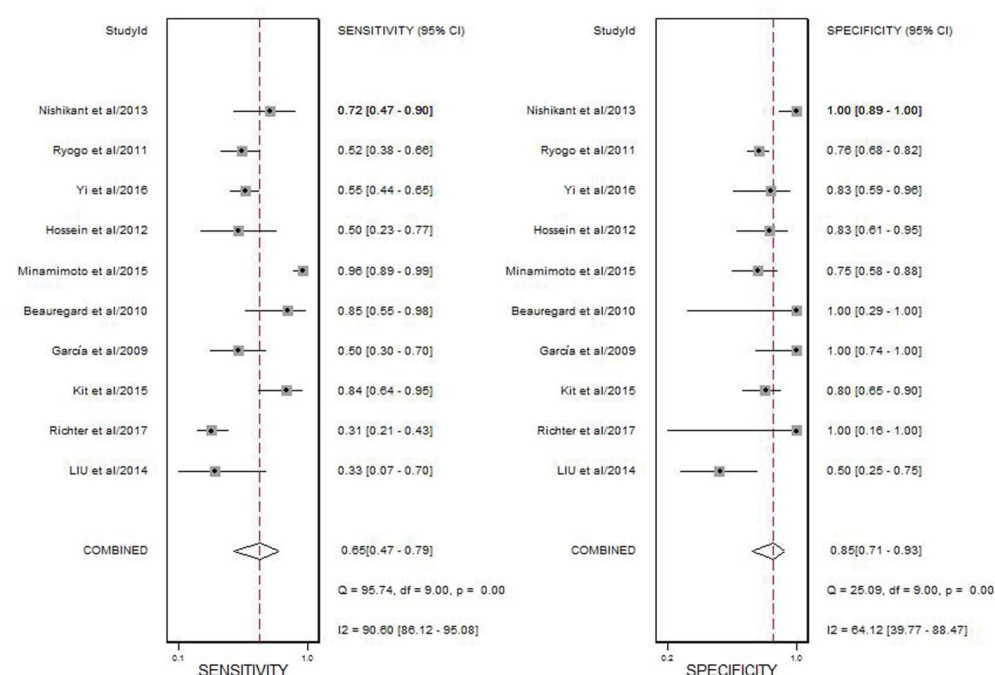14. Were withdrawals from the study explained?

Figure 2: Forest plot of the sensitivity and specificity of 18F-FDG-PET/CT for the diagnosis of prostate cancer.
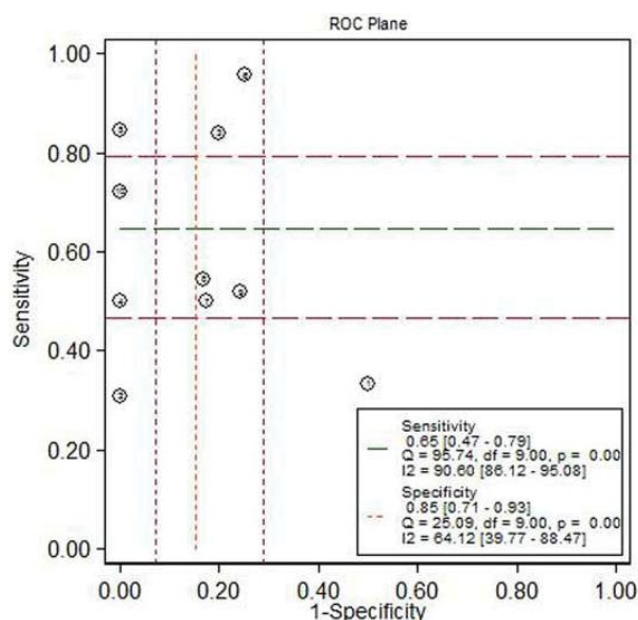

Figure 3: Receiver-operating characteristic plane plot of the sensitivity and specificity of 18F-FDG-PET/CT for the diagnosis of prostate cancer.
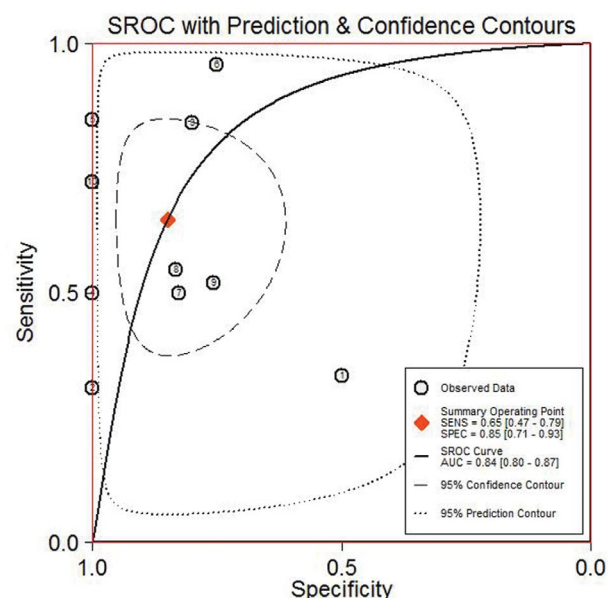

Figure 4: Hierarchical summary receiver-operating characteristic curve plot of the sensitivity and specificity of 18F-FDG-PET/CT for the diagnosis of prostate cancer.

Heterogeneity assessment

The test of homogeneity indicated the present of statistical heterogeneity (Q value=19.51, P=0.000, I^2=90% (95% CI, 80-100). Besides, the proportion of heterogeneity likely due to threshold effect is 0.00. Thus, it is unnecessary that meta-regression and subgroup analysis to be carried out to finding the potential sources of homogeneity.

From the forest plot (Figure 2), the included studies showed statistical heterogeneity in their estimate of sensitivity [(Q value=95.74, P=0.00; I^2=90.60.95% CI(86.12-95.08)] and specificity [(Q value=25.09, P=0.00; I^2=64.12,95% CI(39.77-88.47)] of 18F-FDG PET/CT on prostatic cancer, respectively. The pooled sensitivity and specificity of 18-F PET-CT in prostatic cancer were 0.65 (95% CI, 0.47-0.79) and

Figure 5: Deek's funnel plots for assessing the publication bias.
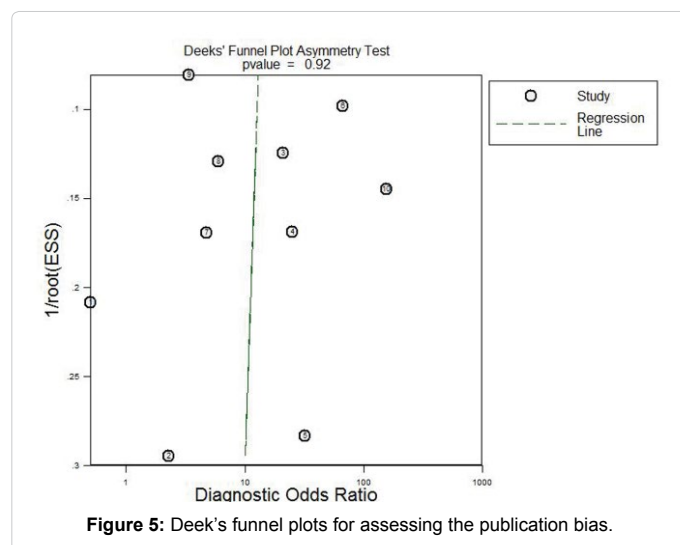
	Coef.	Std. Err.	t	P>|t|	95% CI
Bias	-1.18	10.76	0.11	0.92	26.00-23.62
Intercept	2.66	1.46	1.82	0.105	0.70-6.010

CI: Confidence Interval.

Table 3: Statistical tests for small study effects/publication bias.

0.85 (95% CI, 0.71-0.93), respectively (Figure 1).The overall PLR, NLR and DOR were 4.3 (95% CI, 2.0-9.2), 0.41 (95% CI, 0.25-0.68) and 10 (95% CI, 3-32), respectively. The area under the summary ROC curve was 0.84(95% CI，0.8-0.87) with a hierarchical SROC graph showed Figures 3 and 4. The more the curve approaches to the upper left corner, the higher the diagnostic efficacy is.

Publication Bias

In this meta-analysis, there is not exist publication bias in the included studies according to the Deek's test and the bias of test is 1.18(P=0.92) (Table 3). Besides, the Deek's funnel plots a symmetric test showed symmetric (P=0.92), also indicating the publication bias is absent (Figure 5).

Discussion

To the best of our knowledge, this meta-analysis is the first to evaluate the diagnostic accuracy of 18F-FDG-PET or PET/CT in the evaluation of primary tumor in patients with prostatic cancer [20]. Several trails have applied the 18F-FDG PET/CT reporting different values of sensitivity, specificity and accuracy in this setting. However, the different study results are huge so that there are not inconsistent conclusion because of the diversity of research population, different design method，and various regions. In order to derive more robust estimates of the diagnostic accuracy of 18F-FDG PET/CT in this setting we pooled published studies. A systematic review process was adopted in ascertaining studies, thereby avoiding selection bias.

In our study, a meta-analysis was carried for published literatures and suggested that diagnostic efficacy of 18F-FDG PET/CT was moderate in the prostate cancer, and the pooled sensitivity and specificity was 65% and 86%, respectively. Some authors [19] prospectively evaluated the 18F-FDG PET/CT in patients with prostate cancers, and compared the results to 99mTc MDP bone scintigraphy (BS) and whole-body MRI, and they reported that 18F-FDG PET/CT showed significantly higher sensitivity and accuracy than WBMRI (96.2% *vs.* 81.4%, P<0.001, 89.8% *vs.* 74.7%, P=0.01) and BS (96.2% *vs.* 64.6%, P<0.001, 89.8% *vs.* 65.9%, P<0.001) for the detection of skeletal lesions in prostate cancers. Meanwhile, the pooled diagnostic of ratio is 4.3, which indicates that the differential effect of the diagnostic test is better. Furthermore, the value of the AUC (0.84) demonstrates that 18F-FDG-PET or PET/CT is accurate diagnostic methods under such circumstances.

However, the sensitivity of 18F-FDG PET/CT in diagnosing prostate cancer is slightly low, that is, the false positive rate is obvious. It is the reason that both prostatitis and prostate tumor can cause the prostate gland tissue taking in 18F-FDG and the gland had higher levels of glucose metabolism than normal tissue. In addition, the diagnostic efficacy of 18F-FDG PET/CT was higher than that of no metastasis in distant metastasis, such as bone, soft tissue or lymph nodes metastasis [13,15]. From the results of meta-analysis, the pooled specificity of 18F-FDG PET/CT is very high. In other words, the patients have great possibility anosis if the prostate gland has not obvious glucose metabolism increasing in the PET/CT imaging. Liu's [5] results indicated that the sensitivity of 18F-FDG PET−CT in identifying untreated primary lesions was only 33% (3/9), and got the conclusion that 18F-FDG PET−CT is not useful for the diagnosis of prostate cancer, but may aid with the detection of metastatic disease in appropriately selected patients.

To evaluate the heterogeneity of this study, our carried out the test of heterogeneity and the result indicated the present of statistical heterogeneity. Meanwhile, the threshold effect is the source of the heterogeneity, we have not carried out the meta-regression and subgroup analysis to be to finding the potential sources of homogeneity and using sROC curve and calculating the AUC of ROC is the best method to pooling data information.

The quality of this study is limited by statistical heterogeneity. But, the methodological quality was considered as high level by using the QUADAS tool in this study. Additionally, the current study reveals a symmetric funnel plots', indicating the publication bias is not exist.

Conclusions

The results of our meta-analysis suggested that 18F-FDG PET-CT were imaging methods with high accuracy in differential diagnosis of prostate cancer patients.

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