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A Meta-Analysis on the Diagnostic Performance of ^{18}F-FDG and ^{11}C-Methionine PET for Differentiating Brain Tumors

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ABSTRACT

SUMMARY: ^{18}F-FDG-PET has been widely used in patients with brain tumors. However, the reported sensitivity and specificity of ^{18}F-FDG-PET for brain tumor differentiation varied greatly. We performed this meta-analysis to systematically assess the diagnostic performance of ^{18}F-FDG-PET in differentiating brain tumors. The diagnostic performance of ^{11}C-methionine PET was assessed for comparison. Relevant studies were searched in PubMed/MEDLINE, Scopus, and China National Knowledge Infrastructure (until February 2013). The methodologic quality of eligible studies was evaluated, and a meta-analysis was performed to obtain the combined diagnostic performance of ^{18}F-FDG and ^{11}C-methionine PET with a bivariate model. Thirty eligible studies, including 5 studies with both ^{18}F-FDG and ^{11}C-methionine PET data were enrolled. Pooled sensitivity, pooled specificity, and area under the receiver operating characteristic curve of ^{18}F-FDG-PET ($n = 24$) for differentiating brain tumors were 0.71 (95% CI, 0.63–0.78), 0.77 (95% CI, 0.67–0.85), and 0.80. Heterogeneity was found among ^{18}F-FDG studies. Subsequent subgroup analysis revealed that the disease status was a statistically significant source of the heterogeneity and that the sensitivity in the patients with recurrent brain tumor was markedly higher than those with suspected primary brain tumors. Pooled sensitivity, pooled specificity, and area under the receiver operating characteristic of ^{11}C-methionine PET ($n = 11$) were 0.91 (95% CI, 0.85–0.94), 0.86 (95% CI, 0.78–0.92), and 0.94. No significant statistical heterogeneity was found among ^{11}C-methionine studies. This meta-analysis suggested that ^{18}F-FDG-PET has limited diagnostic performance in brain tumor differentiation, though its performance may vary according to the status of brain tumor, whereas ^{11}C-methionine PET has excellent diagnostic accuracy in brain tumor differentiation.

ABBREVIATIONS: AUC = area under receiver operating characteristic curve; ^{18}F-FDOPA = 3,4-dihydroxy-6-^{18}F-fluoro-L-phenylalanine; ^{18}F-FET = O-(2-[^{18}F]fluoro-ethyl)-L-tyrosine; ^{18}F-FLT = 3′-deoxy-3′-^{18}F-fluorothymidine; HSROC = hierarchic summary receiver operating characteristics; LR = likelihood ratio; MET = methionine; SPBT = suspected primary brain tumor; SRBT = suspected recurrence of brain tumor after treatment

^{18}F-FDG-PET has been widely used in brain tumor differentiation. Commonly the glucose use in malignant brain tumors is increased, and ^{18}F-FDG-PET performs well in identifying high-grade gliomas.[1] However, because of the high physiologic glucose metabolism in normal brain tissue, the diagnostic accuracy of ^{18}F-FDG-PET in brain tumors is reduced, especially in low-grade brain tumors, which typically have lower levels of glucose metabolism.[2,3] Moreover, ^{18}F-FDG uptake in brain tumors demonstrates great variety and might not be closely associated with the

malignant grade,[3] making ^{18}F-FDG-PET unreliable in differentiating brain tumors.[4]

A number of ^{18}F-FDG-PET studies for differentiating brain tumors, including suspected primary brain tumor (SPBT) and/or suspected recurrence of brain tumors after treatment (SRBT), have shown a wide range of sensitivity and specificity, from 0.25 to 1.00 and 0.22 to 1.00, respectively.[1,2,5-27] This great disparity of diagnostic values causes confusion on the application of ^{18}F-FDG-PET for brain tumor differentiation. Therefore, although ^{18}F-FDG-PET remains the dominant approach for brain tumor imaging, a systematic assessment of the diagnostic performance of ^{18}F-FDG-PET for brain tumor differentiation is imperative.

In view of the limitation of ^{18}F-FDG, amino acid and amino acid analog PET tracers have been developed. PET imaging with these tracers improved the ability to differentiate brain tumors due to high tumor uptake and low uptake in normal brain tissue.[28] Among these tracers, ^{11}C-methionine (MET) is one of the most extensively investigated. ^{11}C-MET accumulates extensively in proliferating tumors by the mechanism of increased amino acid

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transport and protein synthesis. Several reports confirmed that ^{11}C-MET PET differentiated brain tumors with high sensitivity and specificity.[29,30]

A recent meta-analysis concluded that ^{18}F-FDG and ^{11}C-MET PET have moderately good overall accuracy for diagnosing recurrent glioma.[31] However, other types of brain tumors with high clinical incidence, such as SPBTs and nongliomas, have not been well studied so far. A thorough understanding of the diagnostic effectiveness of ^{18}F-FDG and ^{11}C-MET PET for differentiating brain tumors could be highly referential in clinical practice. Therefore, we performed a meta-analysis to comprehensively investigate the diagnostic performance of ^{18}F-FDG and ^{11}C-MET PET for differentiating brain tumors with various statuses and histologic types.

MATERIALS AND METHODS

Identification and Eligibility of Studies

A systematic search was performed in MEDLINE, Scopus, and the China National Knowledge Infrastructure data bases from January 1991 to February 2013, restricted to human studies in English and Chinese. The detailed search strategies are presented in the On-line Appendix. To search for more potential studies, we also screened references of the retrieved studies.

Studies using ^{18}F-FDG or/and ^{11}C-MET for the assessment of SPBT or SRBT were enrolled. Inclusion criteria were the following: 1) the purpose of the study was to differentiate SPBT or SRBT, 2) the study population consisted of a minimum of 10 patients, 3) histology or clinical follow-up was used as a reference standard, and 4) the reported primary data were sufficient to calculate both sensitivity and specificity. Exclusion criteria were the following: 1) the PET tracer not being ^{18}F-FDG or ^{11}C-MET; 2) animal or in vitro studies; 3) abstracts, systematic reviews, editorials, letters, comments, and case reports; and 4) studies for staging, searching for metastasis, and evaluating the therapeutic response of definitely diagnosed brain tumors.

Data Extraction and Study Quality

Two experienced nuclear medicine physicians (C.Z., Y.Z.) screened titles, abstracts, and full texts of eligible studies independently. Characteristics of eligible studies were extracted to 2 predefined forms, including the first author's name, year of publication, study country of origin, study design, sample size, mean or median age of patients, male to female ratio, type of brain tumor, disease status, PET tracers, prior imaging tests, reference standard, clinical or radiologic follow-up after PET, PET scanner type, injected dose, time of scanning after injection, scan time, analysis method for diagnostic performance, positive criteria of visual assessment, and cutoff value of quantitative parameters. After data extraction, discrepancies were resolved by consensus and discussion.

The methodologic quality of eligible studies was assessed by using 14 items of the Quality Assessment of Diagnostic Accuracy Studies.[32] Each item of the Quality Assessment of Diagnostic Accuracy Studies was described as yes (score = 2), unclear (score = 1), and no (score = 0). The total score was summarized from all the items with a range of 0–28. Two experienced reviewers (C.Z., Y.Z.) independently evaluated

the quality of selected studies, and disagreements were resolved by discussion.

True-positive, false-positive, true-negative, and false-negative values for ^{18}F-FDG or ^{11}C-MET PET in differentiating brain tumors were extracted for each eligible study to construct a contingency table.
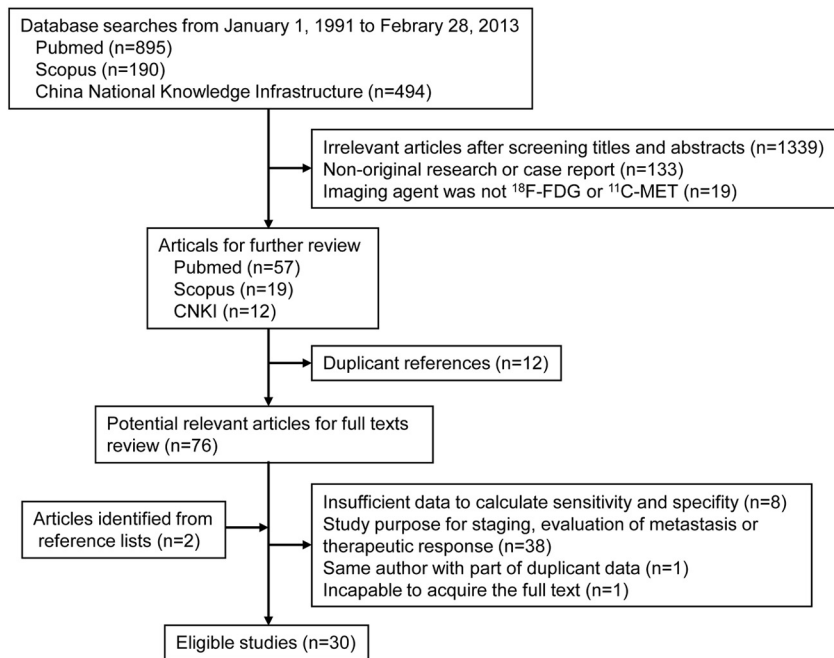
Data Analysis

Pooled estimates for sensitivity, specificity, likelihood ratios (LRs) with corresponding 95% confidence intervals, and area under receiver operating characteristic curve (AUC) for ^{18}F-FDG and ^{11}C-MET PET were analyzed for the primary meta-analysis on the basis of the bivariate mixed-effects regression model.[33] The bivariate model uses a random effects approach for both sensitivity and specificity, which allows heterogeneity beyond chance as a result of clinical and methodologic differences between studies, and the bivariate model is a more valid statistical model for a diagnostic meta-analysis.[34] The LRs indicate by how much a given test would raise or lower the probability of having a disease. Generally, a good diagnostic test may have LR+ above 5 and LR− below 0.2. The AUC is the average true-positive rate over the entire range of false-positive rate values and serves as a global measure of test performance. The guidelines for the interpretation of intermediate AUC values are the following: low accuracy, $0.5 \leq AUC \leq 0.7$; moderate accuracy, $0.7 < AUC \leq 0.9$; or high accuracy, $0.9 < AUC \leq 1$.[35]

To graphically describe the results, we plotted the hierarchic summary receiver operating characteristic (HSROC) curves. The HSROC curve is a recommended standard method for diagnostic meta-analysis.[36] Heterogeneity among the studies was checked by using the χ^2-based Q-test and the I^2 statistic.[37,38] The existence of significant heterogeneity was assumed with a P value $< .05$ for the Q-test and/or an I^2 statistic $\geq 50\%$. If significant heterogeneity was observed, subgroup analysis by using meta-regression was adopted to explore a potential source of heterogeneity by calculating the I^2 statistics. The covariates investigated included study design, imaging method, analysis method for diagnostic performance, malignant grade of brain tumor, disease status, and histology. The malignant grades of brain tumors in the studies were assigned according to the classification of World Health Organization.[39] The stability of our analysis model was tested by 1-way sensitivity analysis if heterogeneity existed. We excluded each study in turn and checked how the new summary diagnostic values could be influenced by the removed one.

We also performed direct comparison of the diagnostic values of ^{18}F-FDG and ^{11}C-MET PET from the 5 studies with the same population of the patients[22-26] to diminish the potential bias induced by pooling data from all the studies, though the data subset was smaller.

Publication bias was tested by using the linear regression method and funnel plot of Deeks et al.[40] A P value $< .05$ in this linear regression indicates potential publication bias.

Statistical analyses were performed with STATA 12.0 (StataCorp, College Station, Texas). The commands used are presented in the On-line Appendix. A P value $< .05$ was considered statistically significant. All P values were 2-sided.

FIG 1. Flow chart of identification of eligible studies.

The flow chart contains the following text:

Database searches from January 1, 1991 to Febrary 28, 2013
Pubmed (n=895)
Scopus (n=190)
China National Knowledge Infrastructure (n=494)

Irrelevant articles after screening titles and abstracts (n=1339)
Non-original research or case report (n=133)
Imaging agent was not ^{18}F-FDG or ^{11}C-MET (n=19)

Articals for further review
Pubmed (n=57)
Scopus (n=19)
CNKI (n=12)

Duplicant references (n=12)

Potential relevant articles for full texts review (n=76)

Articles identified from reference lists (n=2)

Insufficient data to calculate sensitivity and specifity (n=8)
Study purpose for staging, evaluation of metastasis or therapeutic response (n=38)
Same author with part of duplicant data (n=1)
Incapable to acquire the full text (n=1)

Eligible studies (n=30)

RESULTS

Study Characteristics, Quality, and Publication Bias

According to the search strategies, the electronic search yielded 1579 articles: 895 from PubMed, 190 from Scopus, and 494 from the China National Knowledge Infrastructure. After we screened article types, titles, and abstracts, 76 studies remained and the full-text versions were reviewed. After we reviewed full texts, 48 studies were excluded and 2 studies identified from the reference lists of other eligible studies were included (Fig 1). Finally 30 eligible studies were enrolled, including 19 for ^{18}F-FDG-PET,[1,2,5-21] 6 for ^{11}C-MET PET,[29,30,41-44] and 5 for both.[22-26] The characteristics of the studies are summarized in On-line Tables 1 and 2.

The quality of included studies was assessed on the basis of the Quality Assessment of Diagnostic Accuracy Studies (On-line Table 3). The overall quality of the included studies was considered acceptable for most of the items. The total score varied from 13 to 24 in ^{18}F-FDG studies and from 18 to 22 in ^{11}C-MET studies. The proportion of studies with a total score of >20 in ^{18}F-FDG studies (11/24) was apparently lower than that in ^{11}C-MET studies (9/11); this difference indicated the overall higher quality of ^{11}C-MET studies. A common poor-quality item (item 6) in most studies was the failure to use the same reference standard.

We found no significant evidence of publication bias in both ^{18}F-FDG ($P = .07$, On-line Fig 1) and ^{11}C-MET ($P = .26$, On-line Fig 2) studies by using the linear regression method of Deeks et al.[40]

Heterogeneity of ^{18}F-FDG-PET Studies and Sensitivity Analysis

The sensitivity and specificity of ^{18}F-FDG-PET for brain tumor differentiating across 24 eligible studies ranged from 0.25 to 1.00 and 0.22 to 1.00, respectively. The test of heterogeneity revealed significant statistical heterogeneity (Q-value for sensitivity = 83.23, $P = .00$, $I^2 = 72.37\%$; Q-value for specificity = 57.11, $P = .00$, $I^2 = 59.73\%$).

We excluded 1 study from the overall pooled analysis each time to check the influence of the removed dataset on the summary estimates. When a single study was excluded, the new pooled sensitivity and specificity remained close to those obtained with all eligible studies (On-line Table 4).

Diagnostic Values and HSROC Curve of ^{18}F-FDG-PET Studies

When all twenty-four ^{18}F-FDG studies were pooled, the sensitivity, specificity, and AUC for differentiating brain tumors were 0.71 (95% CI, 0.63–0.78), 0.77 (95% CI, 0.67–0.85), and 0.8. The overall LR+ and LR– were 3.13 (95% CI, 2.11–4.64) and 0.37 (95% CI, 0.29–0.48). The HSROC curve is shown in Fig 2.

In 5 studies with the same population of the patients for both ^{18}F-FDG and ^{11}C-MET PET, the pooled sensitivity, pooled specificity, and AUC for ^{18}F-FDG-PET were 0.70 (95% CI, 0.50–0.85), 0.78 (95% CI, 0.59–0.90), and 0.81. The overall LR+ and LR– of ^{18}F-FDG-PET were 3.17 (95% CI, 1.73–5.82) and 0.38 (95% CI, 0.22–0.65).

Heterogeneity of ^{11}C-MET PET Studies

The sensitivity and specificity of ^{11}C-MET PET for brain tumor differentiation across 11 eligible studies ranged from 0.75 to 1.00 and 0.6 to 1.00, respectively. The test of heterogeneity indicated no significant statistical heterogeneity (Q-value for sensitivity = 12.81, $P = .23$, $I^2 = 21.92\%$; Q-value for specificity = 10.98, $P = .36$, $I^2 = 8.89\%$).

Diagnostic Values and HSROC Curve of ^{11}C-MET PET Studies

When all eleven ^{11}C-MET studies were pooled, the sensitivity, specificity, and AUC for differentiating brain tumors were 0.91 (95% CI, 0.85–0.94), 0.86 (95% CI, 0.78–0.92), and 0.94. The overall LR+ and LR– were 6.60 (95% CI, 3.93–11.07) and 0.11 (95% CI, 0.07–0.18). The HSROC curve is shown in Fig 3.

In 5 studies with the same population of the patients for both ^{18}F-FDG and ^{11}C-MET PET, the pooled sensitivity, pooled specificity, and AUC for ^{11}C-MET PET were 0.94 (95% CI, 0.88–0.97), 0.87 (95% CI, 0.76–0.93), and 0.96. The overall LR+ and LR– of ^{11}C-MET PET were 7.28 (95% CI, 3.81–13.92) and 0.07 (95% CI, 0.04–0.14).

Subgroup Analyses of ^{18}F-FDG and ^{11}C-MET PET Studies

Metaregression was performed for ^{18}F-FDG-PET studies to explore the potential source of heterogeneity. The results of subgroup meta-analyses are shown in Table 1. The source of the heterogeneity among ^{18}F-FDG-PET studies was not observed with respect to study design, imaging method, malignant grade of brain tumor, and histology ($P > .05$). However, the disease status had a statistically significant influence on the heterogeneity ($I^2 =$
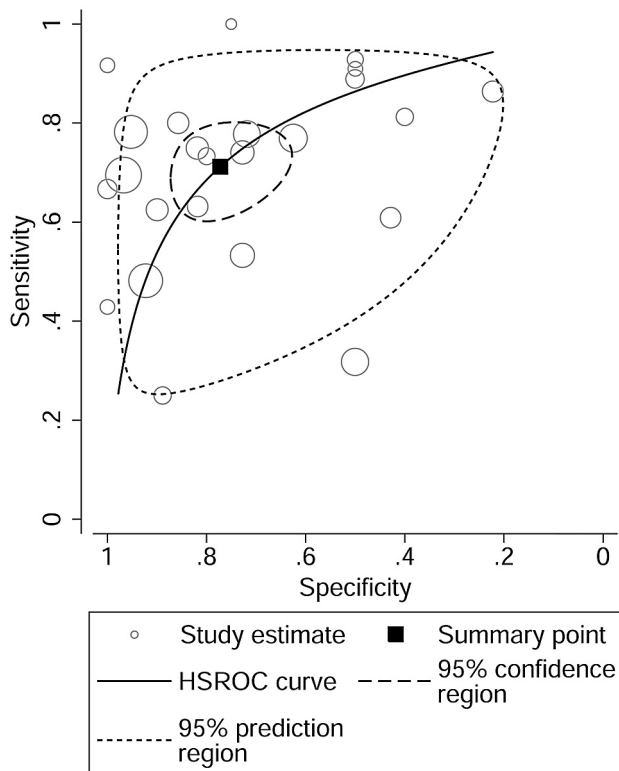
FIG 2. HSROC curve of ^{18}F-FDG-PET for differentiating brain tumors.
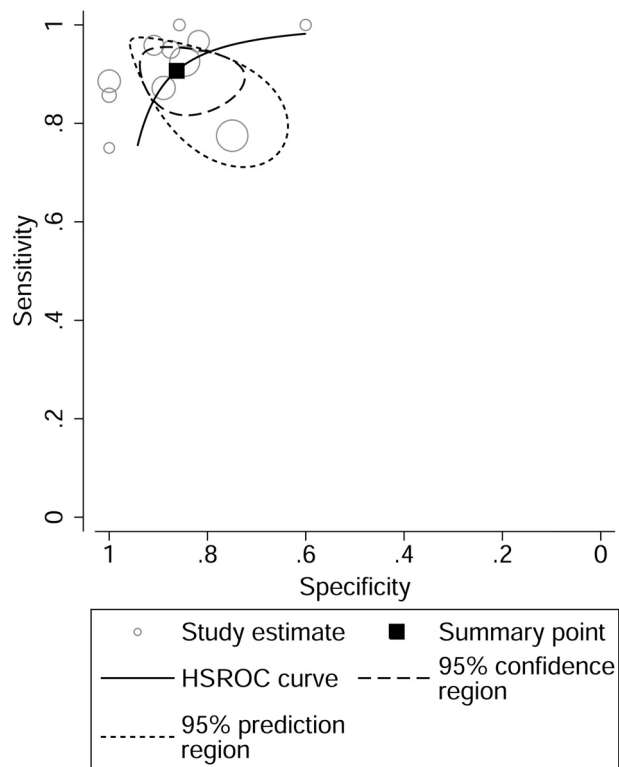
FIG 3. HSROC curve of ^{11}C-MET PET for differentiating brain tumors.

77.72; $P = .01$). The sensitivity in SPBT (0.43; 95% CI, 0.28 – 0.59) was markedly lower than that in SRBT (0.75; 95% CI, 0.67 – 0.81).

Metaregression was not performed for ^{11}C-MET PET studies

because no statistically significant heterogeneity was found. However, the sensitivity, specificity, and LRs in subgroups by study design, PET measurement, imaging method, malignant grade, disease status, and histologic finding were also calculated and are listed in Table 2. No apparent difference was observed among the subgroups.

DISCUSSION

We analyzed 24 ^{18}F-FDG-PET studies with an accumulated population of 857 patients for differentiating brain tumors, including SPBT and/or SRBT. The meta-analysis showed that ^{18}F-FDG-PET has moderately good pooled sensitivity (0.71; 95% CI, 0.63–0.78) and specificity (0.77; 95% CI, 0.67–0.85) for differentiating brain tumors. In the assessment of intracranial masses and the recurrence of brain tumors with ^{18}F-FDG-PET, a positive ^{18}F-FDG lesion without the presence of tumor (false-positive) often indicates inflammatory tissue or other nontumor tissues and thus limits the specificity.[3,45] On the other hand, absent or decreased ^{18}F-FDG uptake in pathologically identified brain tumors (false-negative) reflects the lower levels of glucose metabolism and is usually highly influenced by the high physiologic glucose metabolism in surrounding normal brain tissue, leading to a decrease of sensitivity.[11] The relatively low pooled sensitivity and specificity of ^{18}F-FDG-PET for differentiating brain tumors demonstrated in our meta-analysis indicates a considerably high incidence of both false-positives and false-negatives.

In the subgroup analyses of ^{18}F-FDG studies, the disease status was identified as the only possible source of heterogeneity. We found that the sensitivity of ^{18}F-FDG-PET was the worst (0.43; 95% CI, 0.3–0.58) when applied to the patients with SPBT. However, because no study on only SPBT was found, the SPBT data were extracted from 3 eligible studies on brain tumors with various statuses. As a result, the number of patients with SPBTs in subgroup analysis was limited, and the reliability of the subgroup analysis might be impaired to some extent. In subgroup analysis by malignant grade, low-grade brain tumors showed slightly less sensitivity (0.60; 95% CI, 0.35–0.81) compared with high-grade ones (0.74; 95% CI, 0.68–0.80). These results were consistent with those in previous reports by other investigators indicating that ^{18}F-FDG-PET was less effective in low-grade brain tumors,[2,29] though this difference was not a statistically significant source of heterogeneity ($P = .46$) in our analysis. In subgroup analysis by histology, the patients with glioma showed sensitivity and specificity similar to that of pooled data, suggesting that the type of brain tumor has no apparent influence on the diagnostic performance of ^{18}F-FDG-PET in brain tumor differentiation, regardless of the grading of glioma.

Qualitative assessment was used for image interpretation in most of the eligible ^{18}F-FDG studies, but there were various criteria for visual assessment as shown in On-line Table 2. These different criteria for visual assessment in ^{18}F-FDG studies may inevitably bring bias to our pooled data. Moreover, Tripathi et al[24] reported that even within the same ^{18}F-FDG study, interobserver agreement for visual interpretation was not good. The difficulty in discriminating the lesion and surrounding normal brain tissue in some patients and the subjectivity of visual assessment of the interpreter may together contribute to the low diagnostic ac-

Table 1: Metaregression analyses and diagnostic performance of ^{18}F-FDG-PET in subgroups of brain tumors

Analysis	No. of Studies (pts)	I² of Metaregression (95% CI, P Value)	Independent Estimates (95% CI)		LR (95% CI)	
			Sensitivity	Specificity	LR+	LR−
Design						
Retrospective	9 (333)	0.00 (0–100, .86)	0.71 (0.58–0.81)	0.73 (0.57–0.85)	2.63 (1.68–4.13)	0.40 (0.29–0.55)
Prospective	15 (524)		0.71 (0.60–0.79)	0.80 (0.66–0.89)	3.45 (1.96–6.07)	0.37 (0.26–0.52)
PET or PET/CT						
PET	17 (511)	0.00 (0–100, .38)	0.74 (0.64–0.81)	0.74 (0.60–0.84)	2.82 (1.74–4.55)	0.36 (0.25–0.51)
PET/CT	7 (346)		0.65 (0.50–0.78)	0.84 (0.68–0.92)	3.97 (2.09–7.54)	0.42 (0.29–0.59)
PET measurement						
Qualitative	19 (757)	57.87 (4.96–100, .09)	0.69 (0.60–0.76)	0.79 (0.67–0.87)	3.24 (2.00–5.24)	0.40 (0.30–0.52)
Quantitative	4 (85)		0.86 (0.71–0.94)	0.67 (0.43–0.84)	2.59 (1.40–4.81)	0.21 (0.09–0.45)
Malignant grade						
Low	14 (330)[a]	0.00 (0–100, .46)	0.60 (0.35–0.81)	0.79 (0.64–0.89)	2.87 (1.52–5.41)	0.50 (0.27–0.92)
High	17 (473)[a]		0.74 (0.68–0.80)	0.78 (0.65–0.87)	3.35 (2.09–5.38)	0.33 (0.26–0.42)
NS	7 (192)		0.70 (0.50–0.84)	0.70 (0.54–0.82)	2.33 (1.47–3.67)	0.44 (0.26–0.74)
Disease status						
SPBT	3 (127)[b]	77.72 (51.54–100, .01)	0.43 (0.28–0.59)	0.74 (0.49–0.90)	1.67 (0.59–4.76)	0.77 (0.48–1.24)
SRBT	20 (643)[b]		0.75 (0.67–0.81)	0.79 (0.66–0.88)	3.51 (2.17–5.66)	0.32 (0.25–0.41)
Histology						
Glioma	17 (609)[c,d]	0.00 (0–100, .47)	0.75 (0.64–0.83)	0.78 (0.64–0.87)	3.36 (2.02–5.59)	0.33 (0.23–0.47)
Nonglioma or NS	8 (250)[c]		0.64 (0.52–0.75)	0.75 (0.63–0.84)	2.58 (1.69–3.94)	0.48 (0.35–0.65)

Note:—NS indicates not separable; pts, patients.
[a] Patients with nonneoplastic lesions in 14 studies[2,6–8,11,12,15,16,18,19,21,23–25] were used for both low- and high-grade subgroups.
[b] Patients with nonneoplastic lesions in 2 studies[8,25] were used for both SPBT and SRBT subgroups.
[c] Five patients with nonneoplastic lesions from Hong et al 2011[16] were used for both glioma and nonglioma subgroups.
[d] One patient with lymphoma in Pauleit et al 2009[8] and 2 patients with esthesioblastoma and renal cell metastasis in Kahn et al 1994[12] were excluded from subgroup analysis.

Table 2: Diagnostic performance of ^{11}C-MET PET in subgroups of brain tumors

Analysis	No. of Studies (pts)	Independent Estimates (95% CI)		LR (95% CI)	
		Sensitivity	Specificity	LR+	LR−
Design					
Prospective	4 (156)	0.91 (0.84–0.95)	0.92 (0.78–0.97)	11.49 (3.87–34.08)	0.10 (0.06–0.18)
Retrospective	7 (260)	0.91 (0.81–0.96)	0.84 (0.73–0.90)	5.50 (3.18–9.51)	0.11 (0.05–0.24)
PET measurement					
Qualitative	5 (189)	0.93 (0.87–0.96)	0.85 (0.73–0.92)	6.10 (3.34–11.15)	0.08 (0.04–0.16)
Quantitative	6 (227)	0.89 (0.79–0.94)	0.89 (0.74–0.96)	8.38 (3.07–22.88)	0.13 (0.07–0.25)
PET or PET/CT					
PET	7 (232)	0.86 (0.78–0.91)	0.89 (0.72–0.96)	7.96 (2.75–23.00)	0.16 (0.10–0.26)
PET/CT	4 (184)	0.95 (0.89–0.97)	0.86 (0.74–0.93)	6.62 (3.48–12.59)	0.06 (0.03–0.13)
Malignant grade					
Low	5 (97)[a]	0.90 (0.76–0.96)	0.88 (0.77–0.94)	7.44 (3.68–15.02)	0.12 (0.05–0.30)
High	7 (132)[a]	0.98 (0.75–1.00)	0.88 (0.75–0.95)	8.51 (3.78–19.17)	0.02 (0.00–0.34)
NS	4 (153)	0.87 (0.79–0.93)	0.87 (0.69–0.96)	6.93 (2.52–19.04)	0.15 (0.08–0.26)
Disease status					
SPBT	2 (85)	0.95 (0.85–0.98)	0.83 (0.65–0.93)	5.49 (2.47–12.21)	0.07 (0.02–0.20)
SRBT	8 (238)	0.92 (0.83–0.97)	0.87 (0.75–0.93)	6.81 (3.39–13.69)	0.09 (0.04–0.21)
NS	2 (93)	0.88 (0.78–0.94)	0.95 (0.71–0.99)	16.69 (2.47–112.66)	0.13 (0.07–0.24)
Histology					
Glioma	9 (292)[b]	0.92 (0.85–0.95)	0.87 (0.76–0.93)	7.01 (3.67–13.38)	0.10 (0.05–0.18)
Nonglioma and NS	4 (182)[b]	0.88 (0.79–0.93)	0.83 (0.66–0.92)	5.07 (2.39–10.79)	0.14 (0.08–0.28)

Note:—NS indicates not separable; pts, patients.
[a] Patients with non-neoplastic lesions in 5 studies[23–25,30,43] were used for both low and high grade subgroups.
[b] Patients with non-neoplastic lesions in 2 studies[29,41] were used for both glioma and non-glioma subgroups.

curacy and require us to explain the pooled results prudently when using qualitative evaluation in ^{18}F-FDG-PET. Quantitative assessments were adopted in four ^{18}F-FDG-PET studies[20,22,24,26] that used a lesion-to–normal tissue ratio or standard uptake value as the criterion and showed better sensitivity but worse specificity than qualitative assessment. However, this difference was not a statistically significant source of heterogeneity ($P = .09$) in our analysis. The setting of the cutoff value in quantitative assessment may greatly influence the results of diagnostic estimates and consequently affect the reliability of direct comparison of the diag-

nostic values by quantitative and qualitative assessment. The limited number of patients analyzed with quantitative methods may also bring bias to the subgroup analysis by the method of assessment. In addition, due to the lack of the ability to distinguish lesion and normal brain tissue in ^{18}F-FDG-PET, the veracity of quantitative or semiquantitative methods for the interpretation of ^{18}F-FDG-PET images for evaluating brain tumor was also unreliable and could not provide additional information compared with visual assessment.[1,10,27] On the basis of the results of our meta-analysis, ^{18}F-FDG-PET does not appear to be an ideal ap-

proach for differentiating brain tumors, and we do not recommend its routine use for this purpose because a rather large number of diseases would be missed.

On the other hand, the meta-analysis in 11 ^{11}C-MET PET studies demonstrated excellent pooled sensitivity (0.91; 95% CI, 0.85–0.94) and specificity (0.86; 95% CI, 0.78–0.92) for differentiating brain tumors. The overall high diagnostic accuracy of ^{11}C-MET PET (AUC = 0.94) over ^{18}F-FDG-PET (AUC = 0.80) for brain tumor differentiation is likely due to the high uptake in tumor and low accumulation in normal brain tissue.[25,41] The sensitivity and specificity of ^{11}C-MET PET for differentiating brain tumors in the subgroups by various conditions showed higher values than those in pooled and subgroup ^{18}F-FDG-PET analyses, indicating the superiority of ^{11}C-MET PET over ^{18}F-FDG-PET and the stability of the diagnostic effectiveness of ^{11}C-MET PET in patients with various tumor types. This result was further verified by the direct comparison of the diagnostic values of ^{18}F-FDG and ^{11}C-MET PET from the 5 studies.[22-26] After removing the potential bias caused by pooling all the data, the overall diagnostic accuracy of ^{11}C-MET PET (AUC = 0.96) in the pooled data of the 5 studies was much higher than that of ^{18}F-FDG-PET (AUC = 0.81). Although there were 4 eligible ^{11}C-MET PET studies that included patients with different types of brain tumors,[23,29,41,42] no heterogeneity was observed. Therefore, the results of meta-analysis in ^{11}C-MET PET studies are more convincing, though there were fewer patients in ^{11}C-MET PET studies than in ^{18}F-FDG-PET studies. On the basis of our meta-analysis, it is always preferable to use ^{11}C-MET PET instead of ^{18}F-FDG-PET for differentiating brain tumors if possible.

However, although ^{11}C-MET PET appears to be a promising tracer for brain tumor differentiation, the use of ^{11}C-MET PET is restricted to the PET centers with a cyclotron due to the short half-life of [11]C (20 minutes) and the rapid catabolism of ^{11}C-MET.[25] As substitutes for ^{11}C-MET and ^{18}F-FDG, [18]F (half-life = 110 minutes) labeled PET tracers such as O-(2-[^{18}F]fluoroethyl)-L-tyrosine (^{18}F-FET),[8] 3,4-dihydroxy-6-^{18}F-fluoro-L-phenylalanine (^{18}F-FDOPA),[46] and 3′-deoxy-3′-^{18}F-fluorothymidine (^{18}F-FLT)[18,20] have been developed and applied in brain tumor imaging. Among these ^{18}F-labeled tracers, ^{18}F-FET and ^{18}F-FDOPA show superiority over ^{18}F-FDG in brain tumor differentiation, especially in low-grade brain tumors,[1,47] on the basis of the advantage of their high uptake in tumor tissue and low uptake in normal brain tissue. A meta-analysis with ^{18}F-FET PET studies in patients with SPBT has demonstrated the high performance of ^{18}F-FET PET with a pooled sensitivity and specificity of 0.82 and 0.76, respectively.[48] However, these values were not as good as our results for ^{11}C-MET PET. As for the ^{18}F-FLT PET, Choi et al[7] reported that although ^{18}F-FLT PET is useful for evaluating tumor grade and cellular proliferation in brain tumors, it is not useful enough for differentiating tumors from nontumorous lesions. Because the PET studies using ^{18}F-FDOPA for brain tumor differentiation are still insufficient, further systematic evaluation using this tracer is expected in the future.

The recent meta-analysis by Nihashi et al[31] on the diagnostic accuracy of PET for recurrent glioma reported that ^{18}F-FDG-PET had moderately good sensitivity and specificity in either pooled glioma with different grades (sensitivity = 0.77, specificity = 0.78) or high-grade glioma (sensitivity = 0.79, specificity = 0.70).

The subgroup analysis in our study showed similar sensitivity and specificity of ^{18}F-FDG-PET in the glioma group. However, Nihashi et al reported a pooled sensitivity as low as 0.7 for ^{11}C-MET PET for high-grade gliomas, which is considerably different from our results. We believe our results are more reliable because we enrolled more eligible studies with more abundant data and investigated more brain tumor types.

However, a few limitations should be addressed in this study. First, although the overall sample size was as much as 857 in ^{18}F-FDG-PET and 416 in ^{11}C-MET PET settings, there was still incomplete data collection as reflected by the failure to access the full text of an eligible study.[49] In addition, the insufficient data in certain subtypes of brain tumors may impair the reliability of the analysis. We searched potential sources for heterogeneity in ^{18}F-FDG-PET studies and found that disease status was a significant source. Although the use of the bivariate model could at least correct this issue to some extent, the results should be interpreted cautiously. Second, methodologic quality might be a source of heterogeneity in ^{18}F-FDG-PET studies. We found that some included studies had low methodologic quality with few Y scores (≤6 items) in the Quality Assessment of Diagnostic Accuracy Studies.[5,10,13] In addition, a number of eligible studies included patients with various types of brain tumors.[1,7,9,10,14,16,17,23] Because the characteristics of different brain tumors may vary greatly (eg, brain lymphoma usually presents with higher ^{18}F-FDG uptake than normal brain tissue),[50] the composition of different brain tumors might bring bias by a nonrepresentative patient spectrum in ^{18}F-FDG-PET studies. Third, some characteristics of the eligible studies were not in good agreement. For example, the starting time of PET imaging after tracer injection differed widely, especially in the ^{18}F-FDG-PET studies. The differences of study characteristics may also contribute to the heterogeneity of our meta-analysis.

CONCLUSIONS

Our meta-analysis shows that ^{18}F-FDG-PET has limited diagnostic performance in brain tumor differentiation. However, ^{11}C-MET PET has excellent diagnostic performance in brain tumor differentiation and should be considered as a preferential approach for this purpose if available. Due to the inconvenience of the supply of ^{11}C, other ^{18}F-labeled tracers such as ^{18}F-FDOPA could be considered as potential alternatives for brain tumor differentiation and deserve future systematic evaluation after accumulating relevant studies in the future.

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