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Performance of ^{18}F-FET versus ^{18}F-FDG-PET for the diagnosis and grading of brain tumors: Systematic review and meta-analysis

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Running title: Meta-analysis on FET vs. FDG-PET in brain tumors

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ABSTRACT (241 words)

Background: For the past decade ^{18}F-Fluoro-ethyl-L-tyrosine (FET) and ^{18}F-fluoro-deoxy-glucose (FDG) positron emitting tomography (PET) have been used for the assessment of patients with brain tumor. However, direct comparison studies only reported limited number of patients. Our purpose was to compare the diagnostic performance of FET and FDG-PET.

Methods: We examined studies published between January 1995 and January 2015 in the PUBMED database. To be included the study should: 1) use FET and FDG-PET for the assessment of patients with isolated brain lesion 2) use histology as the gold standard. Analysis was performed on a per patient basis. Study quality was assessed with STARD and QUADAS criteria.

Results: Five studies (119 patients) were included. For the diagnosis of brain tumor, FET-PET demonstrated a pooled sensitivity of 0.94 (95% confidence interval [CI]: 0.79-0.98) and pooled specificity of 0.88 (95%CI:0.37-0.99), with an area under the curve (AUC) of 0.96 (95%CI:0.94-0.97), a positive likelihood ratio (LR+) of 8.1 (95%CI:0.8-80.6) and negative likelihood ratio (LR–) of 0.07 (95%CI: 0.02-0.30) while FDG-PET demonstrated a sensitivity of 0.38 (95%CI:0.27-0.50) and specificity of 0.86 (95%CI:0.31-0.99), with an AUC of 0.40 (95%CI:0.36-0.44), a LR+ of 2.7 (95%CI:0.3-27.8) and LR– of 0.72 (95%CI:0.47-1.11). Target-to-background ratios of either FDG or FET however allow distinction between low and high-grade gliomas ($p>0.11$).

Conclusions:

For brain tumor diagnosis, FET-PET performed much better than FDG and should be preferred when assessing a new isolated brain tumor. For glioma grading, both tracers however showed similar performances.

Keywords: PET, brain tumor, meta-analysis, ^{18}F-Fluoro-ethyl-tyrosine, ^{18}F-Fluoro-deoxy-glucose

INTRODUCTION

Primary brain tumors have an annual age-adjusted incidence rate of 28 per 100'000 in adults. Gliomas represent 28% of all tumors but 80% of malignant tumors [1]. The World Health Organization (WHO) currently divides gliomas in four grades. Grade I and II tumors are considered as low-grade tumors that have a prolonged clinical course. Grade III (anaplastic glioma) or grade IV (glioblastoma) tumors are considered as high-grade lesions rapidely leading to death when left untreated [2]. Adequate tumor diagnosis and grading is thus crucial to initiate proper treatment and improve patient's outcome.

Molecular imaging with positron-emission tomography (PET) helps to identify and delineate areas of tumor with increased growth activity [3]. PET with ^{18}F-fluoro-deoxy-glucose (FDG) was first used to detect and distinguish between low and high-grade tumors [4]. However, FDG-PET is limited by high uptake in normal brain and unspecific uptake in inflammatory benign lesions [5]. ^{18}F-fluoro-ethyl-L-tyrosine (FET) is an artificial amino acid, which provides well-contrasted images in both high- and low-grade tumors while decreasing effective dose as compared to FDG [6]. FET-PET demonstrated value for guiding biopsy [7,8], for diagnosing primary brain tumor [9,10], for directing radiotherapy [11] and for distinguishing between tumor recurrence and radionecrosis after initial therapy [12,13]. Moreover, dynamic FET-PET analysis helps in differentiating low- from high-grade tumors [9,14,15] and in predicting patient's outcome [16-18].

Since FDG-PET is poorly reliable in predicting the neoplasic nature of a lesion due to uptake by inflammatory lesions, amino acid tracers such as FET have been developed in the past decades to increase specificity. However, to date, only a few studies limited to small patient populations directly compared FDG and FET diagnostic value.

The purpose of this report is firstly to systematically review studies of the literature and perform a meta-analysis on diagnostic performance of FDG and FET-PET in patients

with brain tumors, and secondly to assess whether tracer uptake may allow distinction between non-tumor and tumor lesions.

MATERIALS AND METHODS

Data Sources and Search

As the first reported study about FET synthesis was published in 1999 by Wester et al. [19], we performed a systematic search in the medical database PUBMED for English publications from January 1995 to January 2015 using the following search: "("O-(2-fluoroethyl)tyrosine" [all fields] OR "(18F)fluoroethyltyrosine" [all fields] OR "Fluorodeoxyglucose F18" [Mesh]) AND ("PET" [all fields]) AND ("Glioma" [Mesh]) AND ("Humans" [Mesh])". Errata, reviews, preclinical, animal, and nonradiopharmaceutical studies were excluded.

Study Selection

We considered studies using FET and FDG-PET for the assessment of patients with suspected brain tumors. Inclusion criteria were: 1) FET and FDG-PET used in the same patients with a newly diagnosed brain lesion or patients with suspicion of recurrence of a brain tumor; 2) patients who underwent or did not undergo radiotherapy, surgery, or chemotherapy before the PET studies; 3) use of histology as the gold standard to assess diagnostic performance. Studies in abstract form, case reports and studies including fewer than 10 patients were excluded.

Data Extraction and Quality Assessment

For each selected publication we extracted the following information: first author, year of publication, study population (number of patients who underwent FET and FDG for the assessment of brain tumor, sex, age, and histology), FET and FDG results (positive or negative, and target-to-background [TBR] ratio when reported). When possible, data were

recorded at the patient level. We used both checklists of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS, scale 0–14) and Standards for Reporting Studies of Diagnostic Accuracy (STARD, scale 0–25) to assess study quality and applicability [20,21].

Statistical Analysis

All analyses were performed at the patient level with Stata 13.1 software (StataCorp LP, College Station, TX). A p-value less than 0.05 was considered statistically significant. Continuous variables are presented as mean± standard deviation (SD) or median (interquartile range [IQR]). Dichotomized histologic diagnosis (tumor or not, glioma or not) according to the classification of tumors of the central nervous system of the WHO [2] and the third edition of the International Classification of Diseases for Oncology (ICD-O-3) was used as the gold standard. Gliomas were defined by ICD-O-3 codes 9380-9384, 9391-9460, and 9480. Each study had its own criteria for defining FET and FDG-PET positivity. The bivariate mixed-effects regression model was applied for data synthesis. Average sensitivity, specificity, positive and negative likelihood ratio (LR), diagnostic odds ratio (OR) and the respective 95% confidence intervals (95%CI) were calculated from the maximum likelihood estimates and graphically assessed by summarized receiver-operating-characteristic (SROC) curves. Forest plots, X^2 test and Cochran Q were used to graphically and statistically assess heterogeneity of the results between studies. To statistically quantify inconsistency of the results between the studies we used the I^2 statistic, which describes the percentage of total variation across studies attributable to heterogeneity rather than chance. The Funnel plot asymmetry test was used to assess publication bias. Finally after pooling all the patients, a ROC curve comparison between FDG and FET-PET performance for the diagnostic of either brain tumor versus non-tumor lesions and brain glioma versus non-glioma lesions was performed. By convention, the small letter n and the capital letter N were used in the figures and text when describing the

number of studies (n) and the number of patients (N).

Secondary analyses were performed at the patient level to compare quantitative FDG and FET uptake values. Patients were classified in three groups according to histological diagnosis (non-glioma tumor, glioma or non-tumor lesion). We then compared, among the groups, mean TBR (mean activity of the lesion divided by mean activity of the contralateral brain) or maximum TBR (maximum activity of the lesion divided by mean activity of the contralateral brain) measured on FDG and FET-PET images by Kruskall-Wallis test. We also compared mean TBR and maximum TBR values in glioma according to WHO grade to assess the ability of FDG and FET-PET to distinguish between low and high-grade gliomas.

RESULTS

Study Characteristics

In total, 253 papers were identified in the PUBMED database. After exclusion of review articles (n [studies]= 16), case reports (n= 31), preclinical and animal studies (n= 25), errata and comments (n=5), 176 studies about the use of PET in humans with brain tumors were found. After applying the inclusion criteria, 3 studies remained, excluding reports using FDG-PET alone (n=56), FET-PET alone (n=45) or other tracers alone or in combination with FDG-PET (n=72). Two additional studies were found through reference screening of the papers (Figure 1).

Overall, five studies including 190 patients (Table 1) respected the inclusion criteria and were included [22-26]. In one study [26] all patients did not have both FDG and FET-PET for evaluation, only patients who underwent both imaging modalities (N=23) were thus included in the analysis. In one study [24], the histological diagnosis could not be established in three patients, and therefore only the remaining 18 patients were included in the analysis. Finally, in the study by Floeth et al. [22], we included 11 of 14 reported patients who had both FDG and

FET-PET examinations. Thus 119 patients remained (median age: 45[37-57] years, mean age: 46±14 years, sex ratio: 2.2 M:F). Of these patients, 90 patients had a brain tumor, of whom 43 had a low-grade glioma and 39 a high-grade glioma. Low-grade gliomas included pilocytic astrocytoma (N=1), ganglioglioma (N=1), astrocytomas (N=20), oligoastrocytomas (N=7), oligodendrogliomas (N=10) and four unspecified low-grade gliomas. High-grade gliomas included anaplastic astrocytomas (N=14), anaplastic oligoastrocytomas (N=5), anaplastic oligodendroglioma (N=1) and glioblastomas (N=19). Eight patients had a non-glioma brain tumor: metastasis (N=3), lymphoma (N=2), invasive adenoma (N=1), ganglioneuroblastoma (N=1) and meningioma (N=1). Twenty-nine patients had non-tumoral lesions including 9 abscesses or empyemas, 4 hemorrhages, 2 encephalitis, 1 cortical dysplasia and 13 unspecified lesions.

Performances of FDG and FET-PET

From the five selected studies, four with a total of 104 patients were used in the bivariate mixed-effects regression model. The fifth one [25] could not be included because it did not report any true-negative or false-positive case to compute specificity. However, the pooled results of the five studies (N=119 patients) were used to compare area under the curve of FDG and FET-PET. Criteria for FET and FDG-PET positivity varied between studies. Positivity definition was based on qualitative visual analysis as compared to non-tumor brain background in four studies [23-26] or on quantitative assessment of TBR using defined threshold in one study [22].

Including four of the five selected studies, FDG-PET demonstrated an overall sensitivity of 0.38 (95%CI: 0.27–0.50) and specificity of 0.86 (95%CI: 0.31–0.99), with an area under the curve of 0.40 (95%CI: 0.36–0.44), positive LR of 2.7 (95%CI: 0.3–27.8), negative LR of 0.72 (95%CI: 0.47–1.11) and diagnostic OR of 4 (95%CI: 0–58) for the

diagnosis of brain tumoral versus non-tumoral lesions. FET-PET demonstrated a sensitivity of 0.94 (95%CI: 0.79–0.98) and specificity of 0.88 (95%CI: 0.37–0.99), with an area under the curve of 0.96 (95%CI: 0.94–0.97), positive LR of 8.1 (95%CI: 0.8–80.6), negative LR of 0.07 (95%CI: 0.02–0.30) and diagnostic OR of 113 (95%CI: 4–2975).

For the diagnosis of glioma versus non-glioma lesions, FDG-PET demonstrated an overall sensitivity of 0.35 (95%CI: 0.11–0.71) and specificity of 0.65 (95%CI: 0.48–0.79), with an area under the curve of 0.60 (95%CI: 0.56–0.65), positive LR of 1.0 (95%CI: 0.4–2.7) negative LR of 1.0 (95%CI: 0.58–1.73) and diagnostic OR of 1.0 (95%CI: 0–5) whilst FET-PET demonstrated an overall sensitivity of 0.92 (95%CI: 0.75–0.98) and specificity of 0.62 (95%CI: 0.43–0.79), with an area under the curve of 0.89 (95%CI: 0.86–0.91), positive LR of 2.4 (95%CI: 1.4–4.1), negative LR of 0.13 (95%CI: 0.04–0.48) and diagnostic OR of 18 (95%CI: 4–92).

By pooling patients' results of the five selected studies (N=119), FET-PET's area under the curve (0.85 [95%CI: 0.77–0.93]) was significantly higher than FDG-PET's area under the curve (0.56 [95%CI: 0.47–0.66], $p<0.0001$) for the diagnosis of brain tumor (Figure 2). For the diagnosis of glioma, FET-PET's area under the curve (0.76 [95%CI: 0.67–0.84]) was also significantly higher than FDG-PET's area under the curve (0.49 [95%CI: 0.40–0.58], $p<0.0001$).

Assessment of Heterogeneity, Inconsistency and Quality Studies

For the differentiation between brain tumoral and non-tumoral lesions, a Forest plot did not show any significant performance heterogeneity (Cochran Q=3.4, p=0.092) but mild inconsistency between studies (I^2 41% attributable to heterogeneity rather than chance) for FDG-PET. There was neither performance heterogeneity (Cochran Q=1.3, p=0.27) nor inconsistency (I^2 0%) between studies for FET-PET. For the diagnosis of brain glioma versus

non-glioma lesions, a Forest plot showed major inconsistency between studies for FDG-PET (I^2 100%) but not for FET-PET (I^2 0%). This was mainly due to heterogeneity and inconsistency of sensitivity (Cochran Q=9.10, p=0.03 and I^2 67%) due to the high sensitivity value of FDG-PET in the study by Floeth et al. [22] that includes only high grade gliomas with no false negative case (Figure 3). Funnel plots did not demonstrate publication bias for FDG (p>0.051) or FET (p>0.18) PET analysis. QUADAS and STARD scores for the assessment of study quality are reported in Figure 4.

Quantitative analysis

Among the five studies selected, only two (N=63) reported mean and maximum TBR values of the lesions for both FDG and FET-PET. Among these 63 cases, 47 gliomas, 2 non-glioma tumors and 14 non-tumoral lesions were included. Of the 47 gliomas, 22 were low-grade and 25 high-grade lesions. Neither mean TBR (1.3±0.5 vs. 1.1±0.5, p=0.14) nor maximum TBR (2.0±1.0 vs. 1.8±0.9, p=0.32) on FDG-PET were significantly different between tumoral and non-tumoral lesions. On FET-PET images, both mean TBR (2.1±0.8 vs. 1.4±0.3, p=0.0015) and maximum TBR (2.9±1.2 vs. 1.9±0.5, p=0.0007) were significantly higher in tumoral than in non-tumoral lesions.

There was no statistically significant difference of mean TBR (2.1±0.9 vs. 2.0±0.1, p =0.69) and maximum TBR values (3.0±1.2 vs. 2.6±0.1, p=0.40) on FET-PET images between glial and non-glial tumors. FDG mean TBR (1.3±0.5 vs. 1.7±1.3, p=0.88) and maximum TBR values (2.0±0.9 vs. 2.5±1.9, p=0.88) were also not significantly different between glial and non-glial tumors.

Taking into account all gliomas (N=47), while mean TBR (2.1±0.9 vs. 1.4±0.3, p =0.003) and maximum TBR values (3.0±1.2 vs. 1.9±0.5, p=0.0009) on FET-PET images were significantly higher than in non-tumoral lesions, neither mean TBR (1.3±0.5 vs. 1.1±0.6,

p=0.15) nor maximum TBR values (2.0±0.9 vs. 1.8±0.9, p=0.33) on FDG-PET images were significantly different. However, both mean TBR and maximum TBR on FDG and FET-PET images were significantly higher in high-grade lesion (N=25) when compared to low-grade lesions (N=22) (Figure 5). ROC curve analysis showed that a mean TBR of at least 1.4 and a maximum TBR of at least 1.8 had the best value to distinguish between low and high-grade glioma with FDG-PET reaching a sensitivity, specificity and accuracy of 0.60, 0.91, 0.74 and 0.72, 0.73, 0.72 respectively. For FET-PET we observed that a mean TBR of at least 2.0 and a maximum TBR of at least 3.0 reached a sensitivity, specificity and accuracy of 0.88, 0.73, 0.81 and 0.80, 0.82, 0.81 respectively. Performances of these thresholds for glioma grading were not different between FDG and FET-PET using mean TBR (p=0.22) or maximum TBR (p=0.11).

DISCUSSION

The main results of this meta-analysis may be summarized as follows: (1) FET-PET demonstrated significantly higher diagnostic performance for the diagnosis of brain tumor (AUC of 0.96 vs. 0.40, p<0.0001) and glioma (AUC of 0.89 vs. 0.60, p<0.0001) as compared to FDG-PET; (2) Mean and maximum TBR values on FET-PET can distinguish between tumoral and non-tumoral lesions in the brain while mean and maximum TBR values on FDG-PET cannot; and (3) Both FDG and FET quantitative parameters allow distinction between low and high-grade gliomas.

Due to the known lack of specificity of conventional MRI to non-invasively characterize brain lesions, metabolic imaging using PET tracers has been increasingly studied. FDG-PET being limited by high uptake in normal brain and unspecific uptake in inflammatory benign lesions, radiolabeled amino acids tracers such as ^{11}C-methionine (MET) and ^{18}F-fluoro-ethyl-tyrosine have been developed to overcome these limitations. FET-PET

has demonstrated its value for the diagnosis [9,10] and grading [9,14,15] of newly identified brain tumor, for the diagnosis [27] and grading [28] of tumor recurrence, for the differentiation between brain tumor recurrence and radiation necrosis [12,13] and for the assessment of treatment response [29] with lower radiation burden than FDG-PET [6]. However, only few studies with small patient populations report direct comparison of FET and FDG-PET for the qualitative and quantitative characterization of brain lesions in humans. In the presented meta-analysis, we demonstrated the strong advantage of FET-PET over FDG-PET for the diagnosis of brain tumors (AUC of 0.96 vs. 0.40, $p<0.0001$) and gliomas (AUC of 0.89 vs. 0.60, $p<0.0001$). This is in line with a recent meta-analysis reporting the good performance of FET-PET with an area under the curve of 0.84 (95%CI: 0.80-0.87) for the initial assessment of patients with new isolated brain lesions [9]. Regarding clinical applications, due to positive and negative likelihood ratios of 2.7 (95%CI: 0.3-27.8) and 0.72 (95%CI: 0.47-1.11) respectively, FDG-PET qualitative analysis has very small informational value for the differentiation of brain tumors versus non-tumoral lesions. In contrast, FET-PET positive and negative likelihood ratios (8.1 [95%CI: 0.8-80.6] and 0.07 [95%CI: 0.02-0.30], respectively) indicate that FET-PET may help to exclude and to confirm the diagnosis of brain tumor. The higher accuracy for brain tumor diagnosis was also demonstrated with other radiolabeled amino acid tracers as compared to FDG-PET [30-33], especially in a recent meta-analysis by Zhao et al. [33] who argued for the excellent diagnostic performance of MET while conceding the major inconvenience of tracer supply.

Regarding quantitative analysis, only mean and maximum TBR values on FET-PET images had the ability to distinguish between tumoral and non-tumoral brain lesions, mainly due to high FDG uptake in inflammatory lesions such as abscess, as previously demonstrated[5]. Based on the small number of cases where uptake quantification of the two tracers was performed, respective values for the differentiation of non-glioma versus glioma

tumors could not reliably be assessed in our study. However, both tracers were able to distinguish between low grade and high-grade gliomas, which is consistent with previously published studies on FET-PET [9,14,15,28,34] and FDG-PET [4,35-38]. Though mean and maximum TBR cut-off values were different between FDG and FET-PET, performances were similar with both tracers ($p>0.11$) and close to those reported in the literature [4,14,15]. Similar performance for distinguishing low and high-grade gliomas has also been reported for FDG-PET and MET-PET [35,37]. Among current amino acid tracers, the performance of FET-PET for glioma grading seems however to be better than 18F-fluoro-dihydroxy-phenalalanine (FDOPA) [39] and MET [40], the use of time-activity curve parameters from dynamic FET-PET acquisition [14,28,34,40] even improving tumor characterization. It is however important to take into account that glioma is a heterogeneous histological family. Oligodendroglial component may have a singular behavior both on FET-PET [41] and FDG-PET [35] that may impair diagnostic accuracy for both examination types. In a recent study, Manabe et al. [35] thus concluded that the results of PET imaging should be revised after obtaining histology report to better classify patient recurrence risk.

Substantial data in the literature also demonstrated the value of FET-PET for guiding and evaluating response to therapy, and for the prediction of patient outcome. FET-PET may help to delineate tumoral volume before radiotherapy [11,42], to monitor the effects of radiotherapy [43,44] and chemotherapy [45,46]. The prognostic value of FET-PET has also been demonstrated for the assessment of low-grade and high-grade gliomas. Floeth et al. [17] first found that low-grade gliomas exhibiting a diffuse tumoral pattern with positive uptake on baseline FET-PET have a significant lower progression-free survival. Two recent studies reported that dynamic FET-PET analysis could also help in identifying low-grade gliomas at high-risk of progression [47,48]. FET-PET is also useful to evaluate patient prognosis in the preoperative, postoperative and pre-radiative phases of high-grade gliomas management

[16,29,49-53]. Untreated gliomas with high TBR on baseline static FET-PET images have a lower overall survival [49], while grade III astrocytoma tumors with an early minimal time-to-peak on dynamic FET-PET images exhibit similar survival than glioblastoma [50]. Higher postoperative residual tumor volume on FET-PET and decreasing time-activity-curve [51,52] as well as decreasing time-activity-curve prior re-irradiation of recurrent glioblastoma [53] were also related to impaired patient survival. In contrast, early TBR decrease on serial static FET-PET examinations [16,29,54] but not dynamic FET-PET parameters changes [54] after radiochemotherapy in glioblastoma was associated with a better patient survival. Though the prognostic value of FDG-PET has also been reported in newly diagnosed and recurrent gliomas prior therapy [55-57] and for response assessment [58], it seems to be lower than for amino acid tracers PET [37,59].

Regarding the development of hybrid PET/MR imaging, it is furthermore worthy to mention that the respective value of combining FDG and FET-PET with MRI techniques cannot be deduced from this meta-analysis. FET-PET increases MRI accuracy [7,8] to guide biopsies, and notably helps in determining the outcome of patients with low-grade glioma [17]. However, only few studies report combination of multiparametric MRI with quantitative analysis of FDG [38] or FET-PET [41,60,61]. Yoon et al. [38] concluded that in case of concordant results of multiparametric MR techniques for high-grade lesions, the additive value of FDG PET may be limited. In contrast, combination of dynamic FET-PET with diffusion MRI improves glioma grading [41] and improves presurgical biopsy guidance [61] as compared to a single modality approach. Furthermore, spatial congruence of increased FET or FDOPA uptake area and abnormal area on enhanced MRI [62] or perfusion weighted MRI [60,63] are different, highlighting that practical guidelines for interpreting multimodal imaging have to be developed to ensure accurate glioma classification. The diagnostic superiority of combined FET-PET/MRI over FDG-PET/MRI in a same patient population also remains to be

demonstrated. Finally, although Heinzel et al. [64] demonstrated that the combined use of FET-PET and conventional MRI was cost-effective in the planning of biopsies of glioma, the cost-effectiveness of multiparametric MRI associated or not with FDG or FET-PET remains to be determined.

Our systematic review of the literature only found five studies that directly compare FDG and FET-PET for assessing patients with suspected brain tumor. While all achieved a good quality (QUADAS scores >10 and STARD scores >18), the small number of studies resulted in substantial inconsistency between study results for FDG-PET but not for FET-PET. No publication bias was observed for both tracers. There were however some limitations. First, only 4 studies were included in the meta-analysis because of the absence of true negative and false negative cases in one study. Second, due to the small number of pooled patients, a definitive conclusion about the value of FDG and FET TBR to differentiate gliomas (N= 47) versus non-glioma tumors (N= 2) cannot be reliably made. Though we did not observe patients characteristics overlap, the two studies that gave TBR values both on FDG and FET-PET came from the same institution, emphasizing the need of multicenter prospective studies to overcome limitations of single center multiple retrospective reports. Multicenter prospective studies could also assess the comparative value of parameters extracted from dynamic PET acquisition (i.e time-activity-curve for FET or cerebral metabolic rate of glucose for FDG) and from multiparametric MRI for the diagnostic and prognostic assessment of patients with brain tumors, which could not be performed hereby.

On the basis of our systematic review and meta-analysis we could recommend that though FET-PET should be preferred to FDG-PET for the diagnosis of brain tumor and glioma. Moreover, FET and FDG TBR may be used indifferently to distinguish between low and high-grade gliomas. Multicentric multitracer studies should be developed to assess the respective values of dynamic PET parameters notably to distinguish between gliomas and

non-glioma tumors. Regarding the emergence of hybrid PET/MR imaging, development of integrated interpretation guidelines and evaluation of diagnostic performance and cost-effectiveness of multiparametric MRI in comparison or in combination with PET is also mandatory in order to avoid wasting time and funds.

CONCLUSION

This systematic review and meta-analysis indicate that FET-PET has significant higher diagnostic performance for the diagnosis of brain tumor and glioma than FDG-PET. Although both FDG and FET quantitative parameters allow distinction between low and high-grade tumors, only TBR values on FET-PET can distinguish between tumoral and non-tumoral lesions, confirming FET-PET superiority over FDG-PET for brain lesion characterization. Additive value and cost-effectiveness of the use of FDG and FET-PET in combination with multiparametric MRI in the same population have to be assessed considering the development of hybrid PET/MR imaging and should provide new insights to reduce diagnostic time and cost.

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Figure and captions

Figure 1. Flowchart of study selection

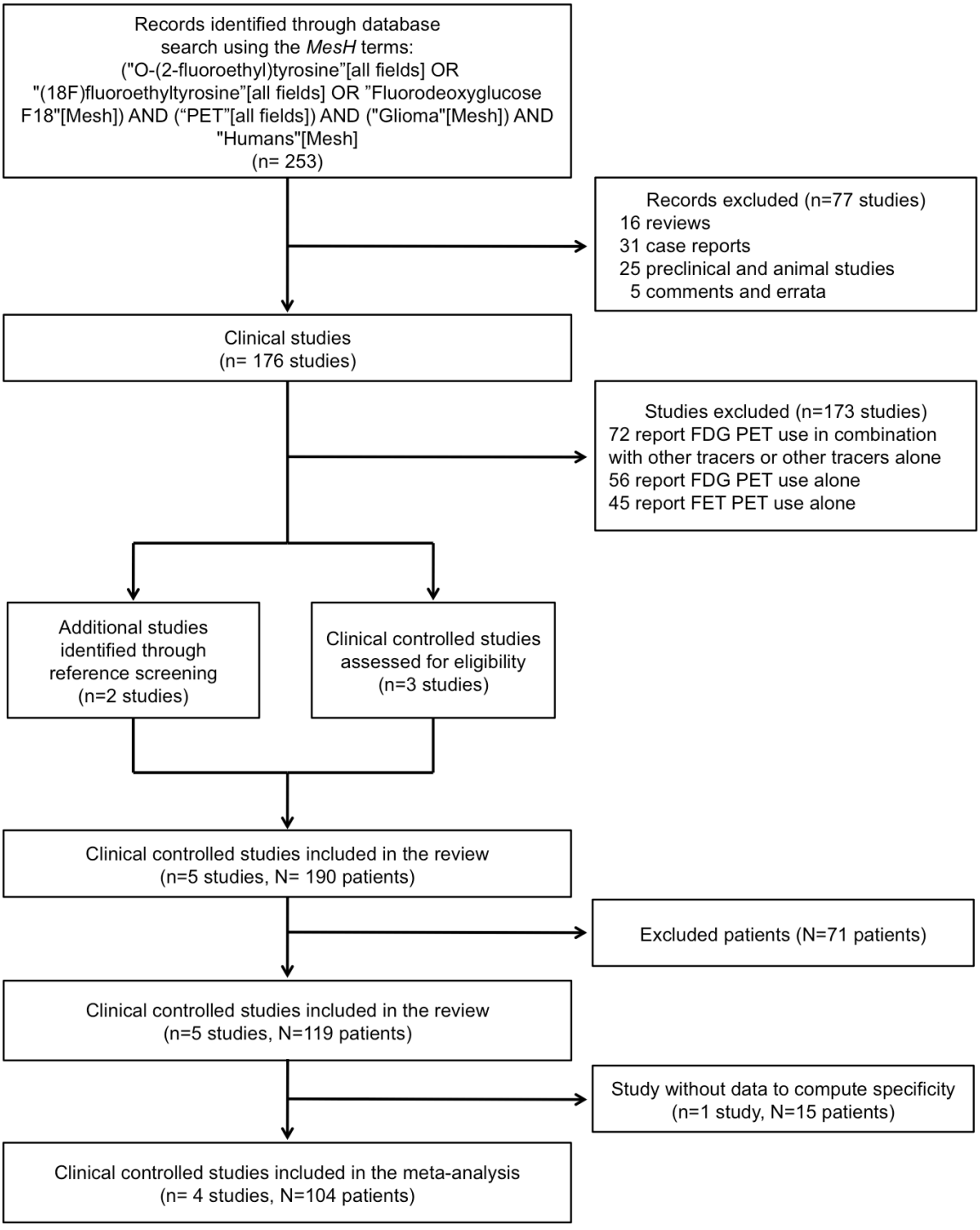

Figure 2. Receiver Operating Characteristics curves for discrimination between brain tumoral and non-tumoral lesion for FDG-PET and FET-PET (N= 119 patients). Dashed line indicates FDG-PET; solid line indicates FET-PET; fine dashed line indicates chance.

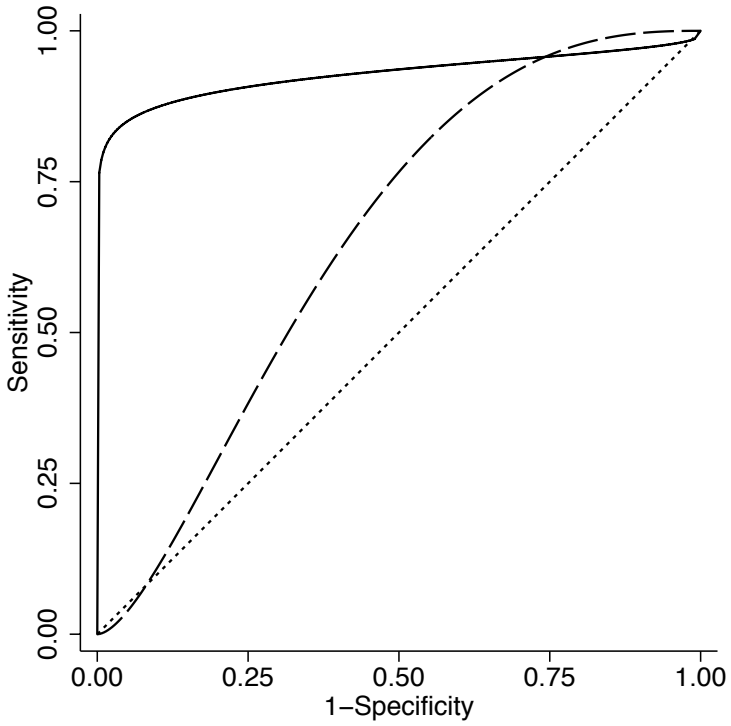

Figure 3. Forest plot of studies included in the meta-analysis for discrimination between glioma versus non-glioma lesions with FDG-PET.

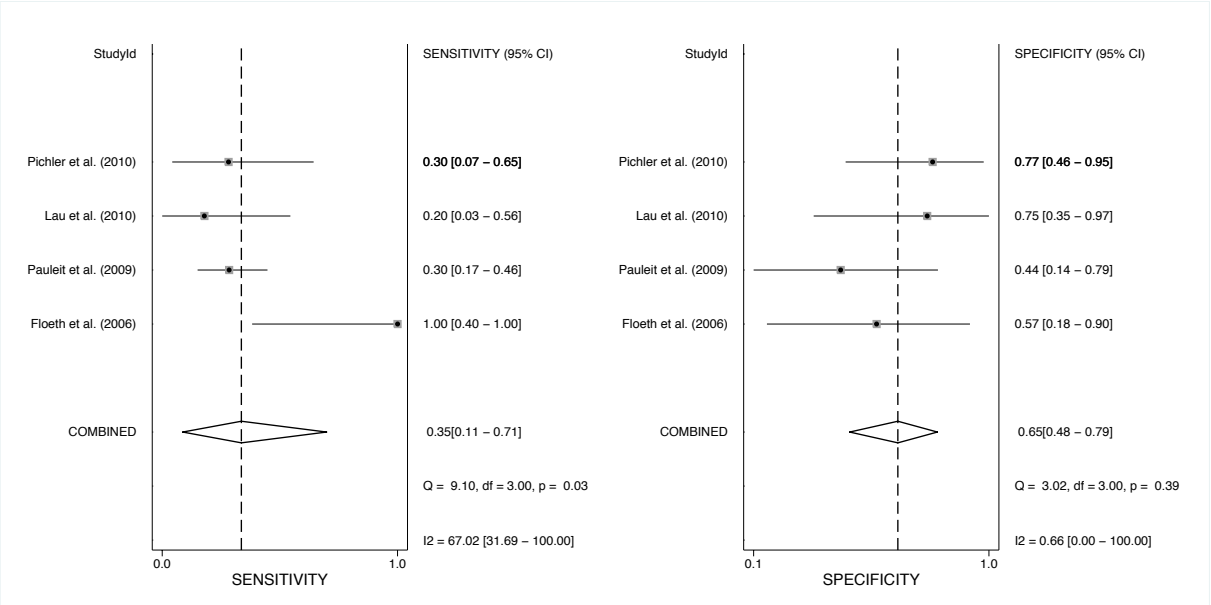

Figure 4. Study quality grading using QUADAS scores (range 0-14) and STARD scores (range 0-25). *Studies included in the meta-analysis. Dashed line indicates maximal score for QUADAS.

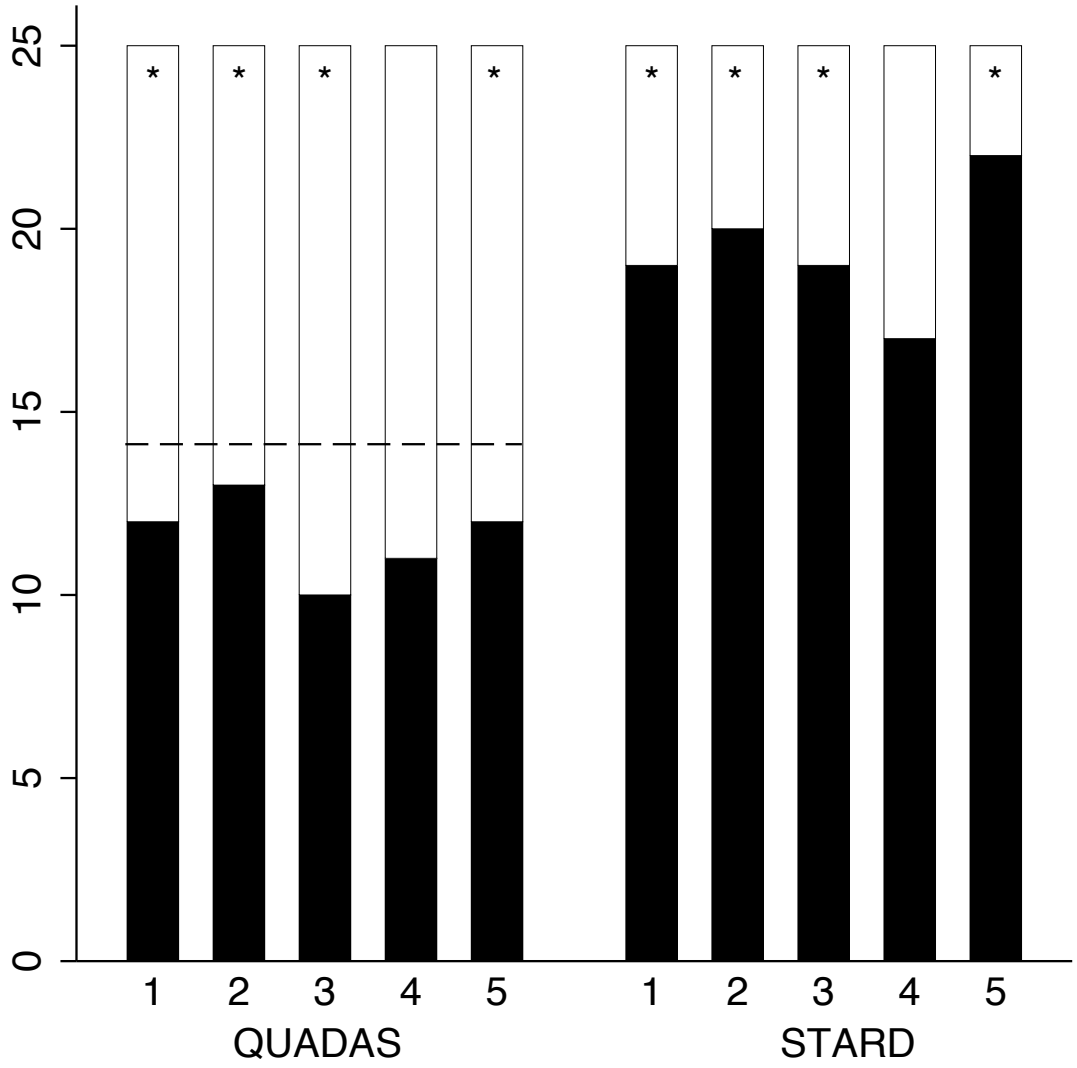

Figure 5. TBR comparison according to histologic WHO grading. Light gray and medium light gray indicate mean TBR and maximum TBR from FDG-PET, medium dark and dark grey indicate mean TBR and maximum TBR from FET-PET. *p=0.0028 versus WHO grade I–II; **p=0.0065 versus WHO grade I–II, ‖p=0.0001 versus WHO grade I–II. For comparison between non-tumoral lesions and WHO grade I–II gliomas, all p-values>0.44.