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Diagnostic accuracy of positron emission tomography tracers for the differentiation of tumor progression from treatment-related changes in high-grade glioma: a systematic review and meta-analysis

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ABSTRACT

Background: Post-treatment high-grade gliomas are usually monitored with contrast-enhanced MRI, but its diagnostic accuracy is limited as it cannot adequately distinguish between true tumor progression and treatment-related changes. According to recent response assessment in neuro-oncology (RANO) recommendations PET overcomes this limitation. However, it is currently unknown which tracer yields the best results. Therefore, a systematic review and meta-analysis were performed to compare the diagnostic accuracy of the different PET tracers in differentiating tumor progression from treatment-related changes in high-grade glioma patients.

Method: Pubmed, Web of Science and Embase were searched systematically. Study selection, data extraction and quality assessment were performed independently by two authors. Meta-analysis was performed using a bivariate random effects model when ≥ 5 studies were included.

Results: 39 studies (11 tracers) were included in the systematic review. ^{18}F-FDG (12 studies, 171 lesions) showed a pooled sensitivity and specificity of 84% (95%CI 72-92) and 84% (69-93), respectively. ^{18}F-FET (7 studies, 172 lesions) demonstrated a sensitivity of 90% (81-95) and specificity of 85% (71-93). ^{11}C-MET (8 studies, 151 lesions) sensitivity was 93% (80-98) and specificity was 82% (68-91). The number of included studies for the other tracers were too low to combine, but sensitivity and specificity ranged between 93-100% and 0-100% for ^{18}F-FLT, 85-100% and 72-100% for ^{18}F-FDOPA and 100% and 70-88% for ^{11}C-CHO, respectively.

Conclusions: ^{18}F-FET and ^{11}C-MET, both amino-acid tracers, showed a comparable higher sensitivity than ^{18}F-FDG in the differentiation between tumor progression and treatment-related changes in high-grade glioma patients. The evidence for other tracers is limited, thus ^{18}F-FET and ^{11}C-MET are preferred when available. Our results support the incorporation of amino-acid PET tracers for the treatment evaluation of high-grade gliomas.

KEYWORDS

- High grade glioma
- Positron Emission Tomography
- Meta-analysis
- Diagnostic accuracy

INTRODUCTION

Positron emission tomography (PET) was recently recommended by the response assessment in neuro-oncology (RANO) working group in the follow-up during and after treatment of high-grade gliomas as conventional magnetic resonance imaging (MRI) is not able to reliably differentiate tumor progression from treatment-related changes (*1*). This differentiation is of utmost importance for making adequate treatment decisions and determining prognosis. Contrast enhancement on conventional MRI has been classically used to identify tumor progression (*2*,*3*). However, treatment effects such as pseudoprogression or radiation necrosis occur in about one third of the high-grade glioma patients (*4*). These treatment effects result in blood-brain barrier disruption with similar appearances on post-contrast MRI as tumor progression (*5*–*8*). This hinders a reliable differentiation of tumor progression from treatment changes.

PET was thus recently incorporated in the RANO guidelines in addition to MRI as PET adds metabolic information regarding tracer accumulation to the anatomical information of MRI. The most frequently-used PET tracer, 2-^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG), is glucose-based. However, in brain tumors, the use of ^{18}F-FDG is considered to be limited due to the relatively high glucose metabolism in normal brain tissue (*9*). Therefore, the RANO group recommend the use of amino-acid PET for the differentiation between treatment-related changes and true tumor progression if PET is used (*1*). In particular, the tracers (S-^{11}C-methyl)-L-methionine (^{11}C-MET), O-(2-^{18}F-fluoroethyl)-L-tyrosine (^{18}F-FET) and 3,4-dihydroxy-6-^{18}F-fluoro-L-phenylalanine (^{18}F-FDOPA) were suggested to have a higher diagnostic accuracy than MRI for this purpose (*1*).

Although PET might be beneficial for the differentiation of tumor progression from treatment changes in patients with high-grade glioma, until now it is unclear which of the PET tracers can be best used to differentiate tumor progression from treatment changes. This systematic review and meta-analysis aims to provide this overview of the diagnostic accuracy of all studied PET tracers for distinguishing true tumor progression from treatment-related changes in high-grade glioma patients.

METHODS

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria (*10*). See electronic Supplementary Table 1 for the full PRISMA checklist. Additionally, the AMSTAR 2 guidelines and the Cochrane handbook for systematic reviews of diagnostic test accuracy were used (*11*).

Search Strategy

We searched PubMed, Embase and Web of Science using a search strategy consisting of database keywords and text words, with the latest search on 2018-03-29. The search term was composed to describe glioma, PET and treatment evaluation and variations of these words. See electronic Supplementary Text 1 for the full search strategy. No filters were used. Studies in English, French and German were included. Studies in other languages were excluded. Grey literature was also included in the search as Embase contains conference proceedings.

Selection Criteria

Studies were included if;

i) they included adult high-grade glioma patients that received first line standard therapy according to the Stupp protocol (*12*)

ii) patients underwent PET imaging after treatment

iii) definite diagnosis, either tumor progression or treatment-related changes, was established by histological-, imaging-, or clinical follow-up, or a combination of these

iv) 2x2 tables could be extracted.

Brain stem or optic gliomas were excluded. Studies were also excluded if their results were not described separately for the patient population of interest in our analysis (e.g. if the resulting 2x2 table included patients with other tumors than high-grade gliomas, children or patients not treated according to the Stupp

protocol). Case reports and studies with <5 eligible patients per PET tracer were also excluded. Studies that were conducted before 2005 were excluded as temozolomide, which is known to increase the occurrence of treatment-related changes (*5*,*13*), was not yet routinely incorporated in standard therapy following the Stupp protocol. Studies in which the relevant patient group happened to include exclusively patients with tumor progression (and no patients with treatment-related changes) were included in the systematic review, but excluded from the meta-analysis as specificity cannot be calculated for these studies.

Study Selection, Data Extraction and Quality Assessment

After duplicates were eliminated, studies were independently screened for eligibility based on title, abstract, and subsequently on full text by two authors (P.Z., B.D.). Reference checks have been performed for all included articles, as well as for all obtained reviews on the topic of interest.

Data from the included studies were extracted with the use of a data extraction form. Extracted data contained true positives, false positives, true negatives, false negatives, and general characteristics. General characteristics included total number of patients, study design, mean age and range, gender, tumor histology, used reference standard, and PET characteristics. If multiple methods of examining the PET were described that led to different 2x2-tables, then only the method with the highest accuracy was used for the forest plots and meta-analysis. However, all methods and 2x2-tables were extracted and provided in the results section. Study quality was assessed according to the quality assessment of diagnostic accuracy studies (QUADAS-2) (*14*).

Statistical Analysis

Sensitivity and specificity with 95% confidence interval (CI) were calculated for all PET tracers in RevMan 5.3 (Cochrane collaboration, Copenhagen, Denmark). Visual inspection of the generated forest plots was done to assess heterogeneity. We evaluated whether the following factors could explain heterogeneity: study type, mean age of patients, WHO type, cut-off value of the index test, and type of

follow-up. We performed sub-group analysis (≥5 studies) to explore and explain heterogeneity in test characteristics. Moreover, we evaluated whether outliers could be explained by study or patient characteristics, and we performed sensitivity analysis without small studies (≤10 patients) to evaluate how robust the results are.

Bivariate random effects models are used, because heterogeneity is to be expected in diagnostic test accuracy studies (*15*). Pooled estimates of sensitivity, specificity, positive likelihood ratios and negative likelihood ratios with 95%CI were calculated for each index test consisting of five or more studies, using the MIDAS module for meta-analysis of diagnostic test accuracy studies in STATA/SE 12.1 (College Station, TX, USA).

To provide insight in the potential clinical consequences, we established a hypothetical cohort of 100 high-grade glioma patients suggestive of progression for each PET tracer. We calculated 2x2 tables by using the mean tumor prevalence (based on the reference standard of the cohort studies included in this meta-analysis), pooled sensitivities and specificities of each PET tracer, and we present the number of misclassifications, false positives and false negatives.

RESULTS

A total of 2957 unduplicated studies were identified through our electronic database search (Fig. 1 for the flow chart). Four of these studies were excluded due to language restrictions. After screening based on title and abstract, the 137 remaining studies underwent full-text eligibility assessment, which resulted in the identification of 38 relevant studies (see Supplementary Table 2 for an overview of why excluded studies were rejected). Reference checks of the included studies yielded one additional study that was included (*16*), thus giving a total inclusion of 39 studies in this systematic review (*7*,*16*–*53*). These studies covered a total of 11 different tracers (Supplementary Table 3). Six studies did not include patients with treatment-related changes (*16*,*25*,*36*,*47*,*48*,*52*), making them non-eligible for the meta-analysis as specificity cannot be calculated. Tracers for which ≥5 studies remained, and thus for which meta-analysis was performed, were ^{18}F-FDG (12 studies), ^{11}C-MET (8 studies) and ^{18}F-FET (7 studies). The study characteristics of the included studies are shown in Supplementary Table 4.

The included studies consisted of 771 patients with 832 lesions (either tumor progression or treatment-related changes). The mean age of the patients was 50.2 years with 65% being male (Supplementary Table 5). The initial lesion was proven to be WHO III in 17.4% (*N*=145) and WHO IV in 57.5% (*N*=478). The remaining 25.1% (*N*=209) were unspecified WHO III or IV gliomas. Mean tumor prevalence was 73.4% (range 33.3-100%). As far as documented in the included studies, histological follow-up was used in 30.9% (N=257) of lesions, imaging in 14.4% (N=120) of lesions, clinical follow-up in 1.3% (N=11) of lesions, and a combination was used in 26.8% (N=223) of lesions. In 26.6% (N=221) of lesions, follow-up was not specified on the individual lesion level. Several of the included studies analyzed two PET tracers per lesion (*21*,*29*,*33*–*35*,*41*,*46*,*52*,*53*); a total of 951 PETs (see Supplementary Table 5 for the tracer distribution) were included.

Methodological Quality of Included Studies

See Supplementary Text 2 and Supplementary Table 6.

Main Findings

The forest plots and pooled results are demonstrated in Tables 1 and 2, respectively. The ^{18}F-FDG PET forest plot (12 studies, 171 PET scans) shows a substantial variation in both sensitivity and specificity, with relatively wide confidence intervals for the specificity in particular. This can be explained by the relatively large number of six small studies (*19*,*21*,*24*,*33*,*41*,*53*) (*N*≤10 patients) for ^{18}F-FDG PET in general and a small number of included patients with treatment-related changes in particular. ^{18}F-FDG PET showed a pooled sensitivity and specificity of 84% (95%CI 72-92) and 84% (95%CI 69-93), respectively. A sensitivity analysis with the exclusion of all small studies with ≤10 patients leads to a slightly lower pooled sensitivity and specificity of 82% (95%CI 64-92) and 79% (95%CI 61-90), respectively.

The ^{18}F-FET PET forest plot (10 studies, 207 PET scans) shows more uniformity in the sensitivity and specificity between the different studies. Outliers on the low end of sensitivity (*47*) and of specificity (*39*) can be explained by their low patient numbers. Pooled sensitivity and specificity for ^{18}F-FET PET (excluding the three studies that did not include patients without tumor progression (*36*,*47*,*52*) are 90% (95%CI 81-95) and 85% (95%CI 71-93), respectively. A sensitivity analysis with the exclusion of one small study (*39*) (*N*=8) showed a very similar pooled sensitivity and specificity of 90% (95%CI 80-96) and 86% (95%CI 72-94), respectively.

The forest plot for ^{11}C-MET PET (9 studies, 164 PET scans) shows a consistently high sensitivity without any major outliers. Two outliers on the low end of specificity (*7*,*30*) can again be explained by their low number of patients with treatment-related changes and have broad confidence intervals. Pooled sensitivity and specificity for ^{11}C-MET PET (excluding one study that did not include patients without tumor progression (*48*) are 93% (95%CI 80-98) and 82% (95%CI 68-91), respectively. A sensitivity analysis with the exclusion of the two small studies (*21*,*30*) leads to a pooled sensitivity and specificity of 91% (95%CI 78-97) and 83% (95%CI 68-92), respectively.

Eight alternative PET tracers (3′-deoxy-3′-^{18}F-fluorothymidine (^{18}F-FLT), ^{18}F-FDOPA, ^{11}C-choline (^{11}C-CHO), ^{18}F-fluorocholine (^{18}F-FCH), ^{13}N-ammonia (^{13}N-NH_3), modified ^{11}C-MET, α-^{11}C-methyl-L-tryptophan (^{11}C-AMT) and ^{18}F-FPPRGD2; see Supplementary Table 3 for an overview of the included PET tracers and their abbreviations) have been studied for their ability to differentiate high-grade glioma tumor progression from treatment-related changes. They have, however, insufficient independent reports to be taken into account in the pooled meta-analysis. Individual study data is, however, shown in Table 1.

Particularly noteworthy are ^{18}F-FLT and ^{18}F-FDOPA, the most thoroughly-studied alternative tracers. ^{18}F-FLT (five studies, 59 PET scans) has a sensitivity range of 93-100% and a specificity range of 0-100%, the latter due to the low number of included patients with treatment-related changes and thus broad confidence intervals. ^{18}F-FDOPA (four studies, 217 PET scans) has a sensitivity range of 85-100% and a specificity range of 72-100%.

Of the other included tracers, ^{11}C-CHO (two studies, 28 PET scans) has a sensitivity of 100% in both studies and a specificity range of 70-88%. ^{18}F-FCH (two studies, 20 PET scans) has a sensitivity of 100% in both studies and a specificity of 100% in the one study in which it could be determined. ^{13}N-NH_3 (one study, 18 PET scans) showed a sensitivity of 78% and a specificity of 67%. Modified ^{11}C-MET (one study, 49 PET scans) showed a sensitivity of 79% and a specificity of 94%. ^{11}C-AMT (one study, 10 PET scans) showed a sensitivity and specificity of 100%, as did ^{18}F-FPPRGD2 (one study, 8 PET scans).

Study type, mean age, WHO type, cut-off value of the index test and follow-up method (Supplementary Table 4) were evaluated as covariates but were unable to explain differences in sensitivity and specificity for all the studies and PET tracers.

To provide insight into the clinical implication of these results, the missed number of patients with true progression and total number of misclassifications in a hypothetical cohort of 100 high-grade glioma patients was calculated for each PET tracer included in the meta-analysis. The average tumor prevalence of 73% (found in this systematic review) and the pooled sensitivity and specificity of each PET tracer were used in this analysis. With ^{18}F-FDG PET, 12 cases of tumor progression would be missed. For ^{18}F-

FET and ^{11}C-MET, this would be 7 and 5 missed tumors, respectively. ^{18}F-FDG PET would show a total of 16 misclassified patients, which would be 11 for ^{18}F-FET. ^{11}C-MET would induce the lowest number of misclassifications, with 10 out of the 100 patients being misclassified.

DISCUSSION

This systematic review and meta-analysis, including 39 studies, is the first to pool the results of all PET tracers for distinguishing tumor progression from treatment-related changes in high-grade glioma patients. This meta-analysis shows that PET can reliably differentiate tumor progression from treatment-related changes, with the highest diagnostic accuracy being reached among amino-acid tracers.

A substantial variety of PET tracers has been empirically studied for this purpose, including (among others) tracers that demonstrate glucose metabolism (^{18}F-FDG) or amino acid uptake (^{11}C-MET, ^{18}F-FET, ^{18}F-FDOPA), or are markers of cell proliferation (^{18}F-FLT) or membrane phospholipids (^{18}F-FCH, ^{11}C-CHO). It is demonstrated that ^{18}F-FET and ^{11}C-MET showed a higher sensitivity than ^{18}F-FDG in the differentiation between treatment-related changes and true progression.

^{18}F-FDG is currently the most commonly used PET-tracer in oncology (*9*), and therefore the most readily available. However, ^{18}F-FDG PET showed the lowest accuracy of all repeatedly-studied tracers, which is due to its relatively low sensitivity of 84%; this can be explained by the high physiological uptake of glucose in the brain, making it more difficult to detect true tumor progression when a glucose-based tracer is used (*9*).

^{11}C-MET and ^{18}F-FET are, when available, preferred over ^{18}F-FDG due to their higher sensitivity. Combining all the gathered evidence, there does not seem to be one particular PET tracer that should be recommended over other tracers. Although ^{11}C-MET showed the highest sensitivity for tumor progression in the pooled analysis, its availability is limited to hospitals with an on-site cyclotron due to its short half-life of approximately 20 min (*9*). When it is not available, ^{18}F-FET is a good alternative with similar diagnostic accuracy. Compared to ^{11}C, ^{18}F-based tracers (with a half-life of approximately 110 min) have

the logistical advantage of not requiring the on-site cyclotron and allow the usage of the existing ^{18}F-FDG-based infrastructure for their deliverance, thus facilitating their availability.

^{18}F-FLT and ^{18}F-FDOPA, as well as some other less common tracers, have shown promising results in a small amount of studies and could be comparable or competitive to ^{18}F-FET and ^{11}C-MET in terms of diagnostic accuracy. However, these tracers need to be studied more.

Previously, a systematic review and meta-analysis has been performed for a similar patient population, in which different advanced MRI techniques are compared (*54*). When comparing these PET results to those MRI results, it is apparent that magnetic resonance spectroscopy (MRS; the advanced MRI technique with the best results) seems to have a higher specificity (95%) than ^{11}C-MET and ^{18}F-FET PET. However, their sensitivities are comparable and diagnostic accuracies of these amino-acid PET tracers are at least similar to those of all other studied MRI techniques, including perfusion and diffusion MRI. Recently it was demonstrated that ^{18}F-FET PET outperforms diffusion MRI in differentiating treatment-related changes from tumor progression (*55*). An additional consideration is that the advanced MRI methods suffer from limitations such as challenging interpretation and frequent impairment by susceptibility artifacts; in contrast, amino-acid PET scan reading is relatively easy due to high tumor-to-background contrast (*9*). Further limitations of advanced MRI techniques are the lack of standardization of acquisition protocols and post-processing methods, and the large variety of thresholds of quantitative parameters (*54,56*). Disadvantages of amino-acid PET relative to MRI include the necessity of additional scanning, its smaller availability, lower spatial resolution and higher expenses (*9*). Combining PET and MRI on hybrid devices might be able to circumvent some of the downsides of each individual imaging modality (*57*) and is more convenient for patients than separate investigations, but these systems are inherently costly.

Several limitations can be noted regarding this review. First, publication bias might have influenced the diagnostic accuracy of many of the tracers included in this review. This holds not only for tracers that were used in only a limited amount of studies, but publication bias might also have played a role for ^{18}F-FDG; its diagnostic accuracy is higher than we expected based on the apparent consensus that

this tracer is only of moderate additional value to MRI for differentiating true tumor progression and treatment-related changes in gliomas due to beforementioned higher background uptake (*1*).

Second, the review included nine abstracts (*24–26*,*31*,*33*,*36*,*37*,*42*,*47*). Although inclusion of abstracts (partially) prevents publication bias, quality and extend of information provided in abstracts is limited and they have not usually undergone the same peer review process as full articles.

Third, a substantial variation exists between the included studies in terms of reference standard (Supplementary Table 4). The vast majority of patients for which the reference standard is described, has undergone some form of histological or radiological confirmation of the diagnosis. The reliability of histological and radiological confirmation may, however, not be equivalent. Furthermore, the reliability of the reference standard may differ between the included studies depending on the follow-up duration. Although pseudoprogression is most prevalent within the first 12 weeks after completion of the concurrent chemoradiotherapy (CCRT), it has been suggested that around one third of the cases occurs after more than three months post-CCRT (*3,58*). However, no difference could be seen between early follow-up studies and studies that were conducted more than three months after CCRT.

Fourth, the method to judge PET positivity showed a large variation between the included studies (Supplementary Table 4). Many studies used a visual analysis, which is often unstandardized and may lead to clinician-dependent results. Moreover, semi-quantitative cut-offs were often based on a ROC-analysis that was itself partially based on patients that were not included in this review (e.g. low-grade glioma patients). In theory, the accuracy of all tracers would be better than reported here when the cut-offs would be optimized for the population of this review. Also, the different cut-offs in the semi-quantitative analyses might have led to artificial differences in the trade-off between sensitivity and specificity between studies and tracers. A well-justified recommendation regarding the optimal cut-off values for the different PET tracers in order to most precisely differentiate post-therapeutic changes from tumor progression is currently hindered by the high variability of the used cutoffs, even though it would be a valuable guideline for the clinician in daily practice. However, attempts are now being made to provide evidence-based recommendations for clinical use of PET imaging in glioma patients (*59*).

Fifth, the comparisons between different PET tracers in this review lack statistical support, as this meta-analysis contains largely non-comparative studies of the different PET tracers. Only two studies compared ^{18}F-FDG and ^{11}C-MET in the same patient population (*21*,*46*). We did not directly compare the PET tracers, because the differences in study design, patient groups and reference standard can confound the differences in diagnostic accuracy (*60*).

Finally, isocitrate dehydrogenase (IDH) mutation status of patients was not provided for most included studies. The occurrence of treatment-induced changes in relation to IDH mutation status should therefore be studied further.

In order to overcome some of the above-mentioned limitations, more large prospective studies are needed, especially on other PET tracers than ^{18}F-FDG, ideally testing more than one tracer in the same population such that results can be directly compared. These studies should use cut-off values that are predefined and are based on earlier studies (such as those included in this review) that study the same patient population. However, different post-processing protocols may have considerable influence on metabolic measurements and thus predefined cut-off values should, for now, be considered with caution (*61*).

CONCLUSION

This meta-analysis demonstrated a clear advantage of ^{11}C-MET and ^{18}F-FET over ^{18}F-FDG for differentiation between true progression and treatment-induced changes in patients with high-grade glioma, with ^{11}C-MET and ^{18}F-FET having the highest sensitivity and specificity, respectively. Diagnostic accuracy does not differ substantially between ^{11}C-MET and ^{18}F-FET. Hence, this meta-analysis supports the recommendations of the RANO group of implementing amino-acid PET in the treatment response evaluation of patients with high-grade glioma. A number of other PET tracers show promising results but have so far been insufficiently studied to warrant a direct comparison. Implication of the here-mentioned recommendations into clinical practice would be an important step in accurately differentiating true

progression from treatment-related changes in high-grade glioma patients presenting with possible progression after treatment, and is therefore highly relevant for making well-justified treatment decisions in this patient population.

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KEY POINTS

QUESTION: Which PET tracer can be best used to differentiate tumor progression from treatment changes in high-grade gliomas?

PERTINENT FINDINGS: This meta-analysis shows that ^{18}F-FET and ^{11}C-MET, both amino-acid tracers, showed a comparable higher sensitivity than ^{18}F-FDG in the differentiation between tumor progression and treatment-related changes in high-grade glioma patients.

IMPLICATIONS FOR PATIENT CARE: Amino PET should be implemented in treatment follow-up of patients with high-grade glioma.

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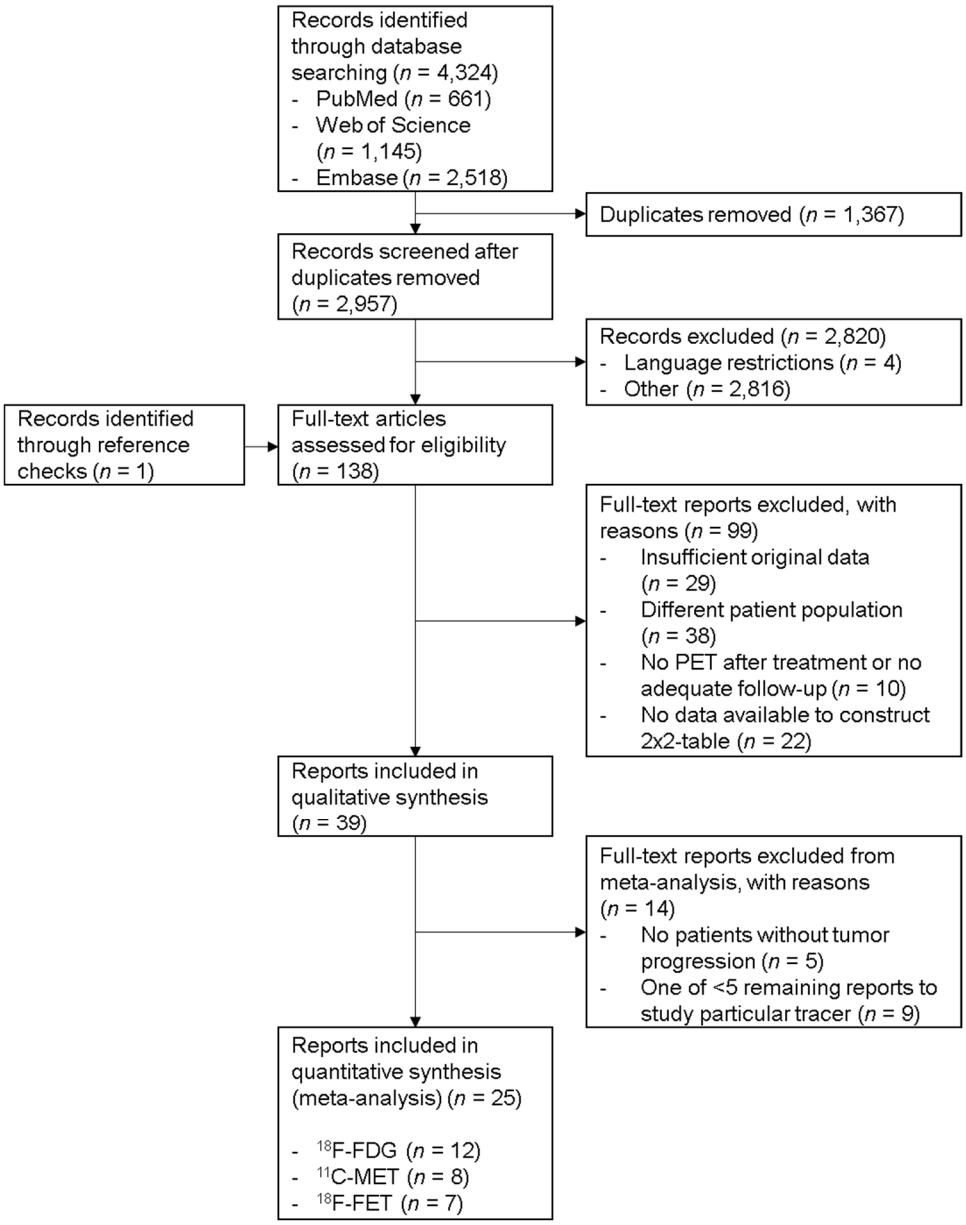
Figure 1: Flow chart of included studies



Abbreviations: PET = positron emission tomography. See Supplementary Table 3 for tracer abbreviations.

Table 1: Forest plots with 2x2 tables, sensitivity and specificity per study

^{18}F-FDG

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Imani et al. (19)	2	0	0	4	1.00 [0.16, 1.00]	1.00 [0.40, 1.00]
Sher et al. (24)	9	0	0	1	1.00 [0.66, 1.00]	1.00 [0.03, 1.00]
Hojjati et al. (51)	18	1	0	4	1.00 [0.81, 1.00]	0.80 [0.28, 0.99]
Sharma et al. (46)	9	0	1	2	0.90 [0.55, 1.00]	1.00 [0.16, 1.00]
Tripathi et al. (21)	7	0	1	1	0.88 [0.47, 1.00]	1.00 [0.03, 1.00]
Enslow et al. (41)	6	0	1	3	0.86 [0.42, 1.00]	1.00 [0.29, 1.00]
Hong et al. (53)	4	1	1	1	0.80 [0.28, 0.99]	0.50 [0.01, 0.99]
Arora et al. (27)	11	1	3	3	0.79 [0.49, 0.95]	0.75 [0.19, 0.99]
Khangembam et al. (34)	7	3	2	6	0.78 [0.40, 0.97]	0.67 [0.30, 0.93]
Karunanithi et al. (45)	10	0	3	5	0.77 [0.46, 0.95]	1.00 [0.48, 1.00]
Iagaru et al. (33)	3	0	2	3	0.60 [0.15, 0.95]	1.00 [0.29, 1.00]
Dankbaar et al. (17)	13	2	11	6	0.54 [0.33, 0.74]	0.75 [0.35, 0.97]

^{18}F-FET

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lapa et al. (52)	23	0	0	0	1.00 [0.85, 1.00]	Not estimable
Jena et al. (22)	25	2	0	4	1.00 [0.86, 1.00]	0.67 [0.22, 0.96]
Iravani et al. (36)	6	0	0	0	1.00 [0.54, 1.00]	Not estimable
Galldiks et al. (28)	11	1	0	10	1.00 [0.72, 1.00]	0.91 [0.59, 1.00]
Jeong et al. (35)	8	0	1	2	0.89 [0.52, 1.00]	1.00 [0.16, 1.00]
Hiob et al. (31)	39	2	6	13	0.87 [0.73, 0.95]	0.87 [0.60, 0.98]
Kebir et al. (40)	11	0	2	3	0.85 [0.55, 0.98]	1.00 [0.29, 1.00]
Kebir et al. (39)	5	1	1	1	0.83 [0.36, 1.00]	0.50 [0.01, 0.99]
Verger et al. (49)	14	1	4	5	0.78 [0.52, 0.94]	0.83 [0.36, 1.00]
Pyka et al. (47)	4	0	2	0	0.67 [0.22, 0.96]	Not estimable

^{11}C-MET

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kits et al. (30)	5	1	0	1	1.00 [0.48, 1.00]	0.50 [0.01, 0.99]
Garcia et al. (38)	21	2	0	7	1.00 [0.84, 1.00]	0.78 [0.40, 0.97]
Tripathi et al. (21)	8	0	0	1	1.00 [0.63, 1.00]	1.00 [0.03, 1.00]
Sharma et al. (46)	10	0	0	2	1.00 [0.69, 1.00]	1.00 [0.16, 1.00]
D'Souza et al. (20)	16	2	1	8	0.94 [0.71, 1.00]	0.80 [0.44, 0.97]
Park et al. (7)	21	2	5	3	0.81 [0.61, 0.93]	0.60 [0.15, 0.95]
Shishido et al. (29)	12	1	3	5	0.80 [0.52, 0.96]	0.83 [0.36, 1.00]
Nakajima et al. (43)	4	0	1	9	0.80 [0.28, 0.99]	1.00 [0.66, 1.00]
Martínez-Amador et al. (48)	10	0	3	0	0.77 [0.46, 0.95]	Not estimable

^{18}F-FLT

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Yamamoto et al. (16)	10	0	0	0	1.00 [0.69, 1.00]	Not estimable
Jeong et al. (35)	9	0	0	2	1.00 [0.66, 1.00]	1.00 [0.16, 1.00]
Enslow et al. (41)	7	0	0	3	1.00 [0.59, 1.00]	1.00 [0.29, 1.00]
Hong et al. (53)	5	2	0	0	1.00 [0.48, 1.00]	0.00 [0.00, 0.84]
Shishido et al. (29)	14	2	1	4	0.93 [0.68, 1.00]	0.67 [0.22, 0.96]

^{18}F-FDOPA

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lapa et al. (52)	23	0	0	0	1.00 [0.85, 1.00]	Not estimable
Karunanithi et al. (50)	18	0	0	6	1.00 [0.81, 1.00]	1.00 [0.54, 1.00]
Paquet et al. (37)	47	3	2	8	0.96 [0.86, 1.00]	0.73 [0.39, 0.94]
Herrmann et al. (32)	69	8	12	21	0.85 [0.76, 0.92]	0.72 [0.53, 0.87]

^{11}C-CHO

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hu et al. (26)	6	3	0	7	1.00 [0.54, 1.00]	0.70 [0.35, 0.93]
Li et al. (23)	4	1	0	7	1.00 [0.40, 1.00]	0.88 [0.47, 1.00]

^{18}F-FCH

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Testart et al. (25)	9	0	0	0	1.00 [0.66, 1.00]	Not estimable
Montes et al. (44)	9	0	0	2	1.00 [0.66, 1.00]	1.00 [0.16, 1.00]

^{13}N-NH$_3$

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Khangembam et al. (34)	7	3	2	6	0.78 [0.40, 0.97]	0.67 [0.30, 0.93]

mod-MET

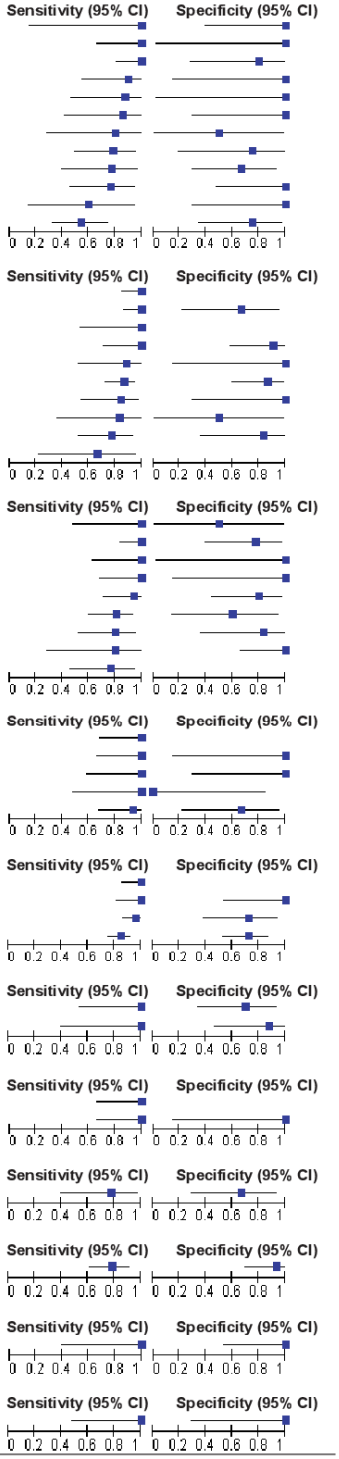
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Takenaka et al. (42)	26	1	7	15	0.79 [0.61, 0.91]	0.94 [0.70, 1.00]

^{11}C-AMT

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Alkonyi et al. (18)	4	0	0	6	1.00 [0.40, 1.00]	1.00 [0.54, 1.00]

^{18}F-FPPRGD2

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Iagaru et al. (33)	5	0	0	3	1.00 [0.48, 1.00]	1.00 [0.29, 1.00]



Abbreviations: CI = confidence interval; FN = false negatives; FP = false positives; TN = true negatives; TP = true positives. See Supplementary Table 3 for tracer abbreviations.

Table 2: Pooled analyses of PET tracers.

Analysis	**Studies**	***N***	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Positive LR (95% CI)**	**Negative LR (95% CI)**
^{18}F-FDG	12	171	84 (72-92)	84 (69-93)	5.29 (2.45-11.39)	0.19 (0.10-0.36)
^{18}F-FET	7	172	90 (81-95)	85 (71-93)	5.80 (2.89-11.66)	0.12 (0.06-0.24)
^{11}C-MET	8	151	93 (80-98)	82 (68-91)	5.12 (2.71-9.69)	0.09 (0.03-0.26)
^{18}F-FDG (SA)	6	121	82 (64-92)	79 (61-90)	3.95 (1.90-8.21)	0.23 (0.10-0.51)
^{18}F-FET (SA)	6	164	90 (80-96)	86 (72-94)	6.56 (3.02-14.21)	0.11 (0.05-0.24)
^{11}C-MET (SA)	6	135	91 (78-97)	83 (68-92)	5.32 (2.68-10.55)	0.11 (0.04-0.28)

Abbreviations: CI = confidence interval; LR = likelihood ratio; N = number of PET scans; SA = sensitivity analysis without small studies. See Supplementary Table 3 for tracer abbreviations.

All searches were performed on 2018-03-29.

Pubmed:

("Glioma"[Mesh] OR glioma*[tiab] OR glioblastom*[tiab] OR astrocytom*[tiab] OR oligodendrogliom*[tiab] OR oligoastrocytom*[tiab] OR (glia*[tiab] AND (tumor[tiab] OR tumour[tiab]))) AND ("Positron-Emission Tomography"[Mesh] OR PET[tiab] OR Positron emission[tiab]) AND ("Disease Progression"[Mesh] OR "Treatment Outcome"[Mesh:NoExp] OR "Radiation Injuries"[Mesh] OR "Dose-Response Relationship, Radiation"[Mesh] OR "radiation effects" [Subheading] OR treatment-induc*[tiab] OR radiation induc*[tiab] OR radiation associat*[tiab] OR radiation chang*[tiab] OR radiation effect*[tiab] OR treatment effect*[tiab] OR post treat*[tiab] OR posttreat*[tiab] OR posttherap*[tiab] OR post therap*[tiab] OR postsurg*[tiab] OR post-surg*[tiab] OR post irradiat*[tiab] OR postirradiat*[tiab] OR after irradia*[tiab] OR after rad*[tiab] OR post radiat*[tiab] OR postradiat*[tiab] OR treatment outcome*[tiab] OR radiation injur*[tiab] OR pseudo progress*[tiab] OR true progress*[tiab] OR pseudoprogress*[tiab] OR pseudorespon*[tiab] OR radiation necro*[tiab] OR radio necro*[tiab] OR radionecros*[tiab] OR disease progress*[tiab] OR recurrent glio*[tiab] OR true tumo*[tiab] OR treatment-relat*[tiab] OR residu*[tiab] OR pseudo[tiab] OR ((recurr*[tiab] OR progress*[tiab]) AND (tumor*[tiab] OR tumour*[tiab]))) AND (("2005/01/01"[PDat] : "3000/12/31"[PDat]))

Results: 661

Web of Science:

You searched for: TS=(glioma* OR glioblastom* OR astrocytom* OR oligodendrogliom* OR oligoastrocytom* OR (glia* AND (tumor OR tumour))) AND TS=(PET OR "Positron emission") AND (TS=(necro* OR radionecro* OR true OR residu* OR pseudo* OR posttreat* OR posttherap* OR postsurg* OR postirradi* OR postradiat*) OR TS=(treatment NEAR/2 (induc* OR effect OR effects OR relat* OR outcome* OR post)) OR TS=(radiation NEAR/2 (induc* OR associat* OR chang* OR effect* OR injur*)) OR TS=((post OR after) NEAR/1 (treat* OR surg* OR therap* OR irradiat* OR radiat*)) OR TS=(true NEAR/5 progress*) OR TS=(disease NEAR/1 (course OR progress*)) OR TS=(recurr* NEAR/5 glio*) OR TS=((recurr* OR progress*) AND (tumor* OR tumour*)))

Refined by: PUBLICATION YEARS: (2014 OR 2010 OR 2018 OR 2017 OR 2008 OR 2015 OR 2007 OR 2013 OR 2006 OR 2016 OR 2012 OR 2005 OR 2009 OR 2011)

Timespan: All years. **Indexes:** SCI-EXPANDED, SSCI, A&HCI, ESCI.

Results: 1,145 (from Web of Science Core Collection)

Embase:

(('glioma'/exp OR 'glioma' OR glioma*:ab,ti OR glioblastom*:ab,ti OR astrocytom*:ab,ti OR oligodendrogliom*:ab,ti OR oligoastrocytom*:ab,ti OR (glia*:ab,ti AND (tumor:ab,ti OR tumour:ab,ti))) AND ('positron emission tomography'/exp OR 'positron emission tomography' OR pet:ab,ti OR 'positron emission':ab,ti) AND ('disease exacerbation'/exp OR 'disease exacerbation' OR 'disease course'/exp OR 'disease course' OR 'treatment outcome'/exp OR 'treatment outcome' OR 'clinical outcome'/exp OR 'clinical outcome' OR 'radiation injury'/exp OR 'radiation injury' OR 'radiation response'/exp OR 'radiation response' OR 'minimal residual disease'/exp OR 'minimal residual disease' OR ((treatment NEAR/2 (induc* OR effect OR effects OR relat* OR outcome* OR post)):ab,ti) OR ((radiation NEXT/2 (induc* OR associat* OR chang* OR effect* OR injur*)):ab,ti) OR (((post OR after) NEXT/1 (treat* OR surg* OR therap* OR irradiat* OR radiat*)):ab,ti) OR posttreat*:ab,ti OR posttherap*:ab,ti OR postsurg*:ab,ti OR postirradiat*:ab,ti OR postradiat*:ab,ti OR ((true NEAR/5 progress*):ab,ti) OR radionecros*:ab,ti OR ((disease NEXT/1 (course OR progress*)):ab,ti) OR ((recurr* NEAR/5 glio*):ab,ti) OR residu*:ab,ti OR pseudo*:ab,ti OR necro*:ab,ti OR ((recurr*:ab,ti OR progress*:ab,ti) AND (tumor*:ab,ti OR tumour*:ab,ti)))) AND (2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py)

Results: 2,518

Methodological Quality of Included Studies

In the first domain regarding patient selection, one out of 39 studies (3%) was considered to be of high risk of bias (*19*), since patients who demonstrated significant tumor growth were excluded from the analysis. This might have induced a selection bias. Furthermore, 17 studies (44%) were considered to be of unclear risk of bias since it was not specified whether their patient selection was random or consecutive (*18*,*21*,*24–26*,*31–33*,*37–39*,*41–43*,*46*,*47*,*51*). The remaining 21 studies (54%) were considered to be of low risk of bias (*7*,*16*,*17*,*20*,*22*,*23*,*27–30*,*34–36*,*40*,*44*,*45*,*48–50*,*52*,*53*).

In the index test domain 20 studies (51%) were considered to be of high risk of bias, 19 of which because they did not pre-specify the PET threshold or cut-off value (*7*,*17*,*18*,*21*,*22*,*28–32*,*35*,*38–43*,*46*,*51*), and one study due to awareness of the evaluating physician of the results of the reference test (*16*). In an additional 9 studies (23%) it was not assured that the results of the reviewed PET technique were interpreted without knowledge of the results of the reference standard (*23*,*25*,*26*,*33*,*36*,*47–49*,*53*). Hence, we considered them to be of unclear risk of bias. We considered the 10 remaining studies (26%) to be of low risk of bias (*19*,*20*,*24*,*27*,*34*,*37*,*44*,*45*,*50*,*52*).

In the domain of the reference standard, four studies (10%) were considered to be of high risk; one of these studies used a too high pathologic cut-off for tumor progression (20% viable tumor in the pathologic specimen) (*51*), whereas in the other three studies the reference standard results were interpreted without blinding to the PET results (*7*,*30*,*49*). All 35 other studies (90%) were considered to be of unclear risk of bias as it was not specified if the reference standard results were interpreted without knowledge of the PET results (*16–29*,*31–48*,*50*,*52*,*53*). Moreover, in four of these studies, the reference standard itself was too imprecisely described (*16*,*24*,*28*,*33*).

Finally, in the flow and timing domain, 30 studies (77%) were considered to be of high risk of bias, because not all patients received the same reference standard (*7*,*17–23*,*25–29*,*31*,*32*,*34–38*,*43–46*,*48–51*,*53*) or because not all patients were included in the analysis (*30*). Five other studies (13%) were considered to be of unclear risk of bias, as it was unknown if all patients received the same reference

standard (*16*,*24*,*33*) or the interval between the PET and the reference standard was not specified (*42*,*47*). The remaining four studies (10%) were considered to be of low risk of bias (*39–41*,*52*).

All studies showed high risk of bias in at least one of the four domains with the exception of four studies (*24*,*33*,*47*,*52*). However, none of the studies showed low risk of bias in all domains. Overall, study quality can be regarded as moderate.

Regarding the applicability assessment, we had concerns that the included patients and setting matched our review question in one study (3%), as not all high-grade glioma patients received treatment according to Stupp (*49*). In 19 other studies (49%), there were limited patient applicability concerns (*16*,*21*,*22*,*24–27*,*31–34*,*36*,*37*,*41*,*42*,*44*,*45*,*47*,*50*); in 18 of these studies, there were limited concerns if all patients were treated according to the Stupp protocol (*16*,*21*,*25–27*,*31–34*,*36*,*41*,*42*,*44*,*45*,*47*,*50*) and/or if there were no patients <18 years included (*24–26*,*31*,*34*,*37*,*45*,*47*,*50*). In one study, it was not explicitly stated that all patients were high-grade glioma patients (*22*). In the 19 remaining studies, there were no concerns regarding patient applicability (*7*,*17–20*,*23*,*28–30*,*35*,*38–40*,*43*,*46*,*48*,*51–53*). In two studies (5%), there were applicability concerns regarding the PET conduct and interpretation (*39*,*42*) that might not be feasible in clinical practice. In one study, a relatively complicated cluster analysis was performed (*39*). In the other study, a modified ^{11}C-MET PET was used (exclusion of vascular factors from a normal ^{11}C-MET PET) (*42*). There were no concerns in any of the other studies regarding applicability of index test. Moreover, there were no concerns that the reference standard did not match our review question in any of the studies. In conclusion, we had no applicability concern for 18 out of the 39 included studies (*7*,*17–20*,*23*,*28–30*,*35*,*38*,*40*,*43*,*46*,*48*,*51–53*).

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page # (page numbers refer to the original manuscript, which may differ from those in the published article)
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary material
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6

PRISMA 2009 Checklist

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not possible to specify, as no formal assessment was performed. A reflection on the possibility of publication bias is provided in the discussion on page 14.
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6-7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supplementary table 3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8-10, and table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	As this is a review of diagnostic studies, there is no intervention. Equivalent information (i.e. 2x2-tables) is presented in table 2 and forest plots are shown in table 4.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-12, and table 5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	See discussion on page 14 for a reflection regarding publication bias.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-12, and table 5
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15-16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Supplementary Table 3: PET tracers, their abbreviations and their (suggested) working mechanism.

Abbreviation	**Full name or explanation**	**Indicator of**
^{18}F-FDG	2-^{18}F-fluoro-2-deoxy-D-glucose	Glucose metabolism
^{18}F-FET	O-(2-^{18}F-fluoroethyl)-L-tyrosine	Amino acid uptake
^{18}F-FLT	3′-deoxy-3′-^{18}F-fluorothymidine	Cell proliferation
^{18}F-FDOPA	3,4-dihydroxy-6-^{18}F-fluoro-L-phenylalanine	Amino acid uptake
^{18}F-FCH	^{18}F-fluorocholine	Membrane phospholipid
^{11}C-MET	(S-^{11}C-methyl)-L-methionine	Amino acid uptake
^{11}C-CHO	^{11}C-choline	Membrane phospholipid
^{11}C-AMT	α-^{11}C-methyl-L-tryptophan	Amino acid uptake
^{13}N-NH_3	^{13}N-ammonia	Perfusion
^{18}F-FPPRGD2	^{18}F-FPPRGD2 (FDA eIND 104150)	Angiogenesis
mod-MET	^{11}C-MET without vascular factors	Amino acid uptake

Abbreviations: eIND = exploratory investigative new drug; FDA = Food and Drug Administration; mod = modified.

Supplementary Table 4: Study characteristics.

Reference	Number of patients (tumors)†	% Male	Age (years) mean ± SD (range)	Histology	Study type	Selection	Reference standard	Tracer; dose (mean ± SD (range)); time of acquiring after tracer injection; additional scan	Method of analysis	TP	FP	TN	FN
Alkonyi et al. (*18*)	10	80.0	45.0 (30-61)	WHO III: 4; WHO IV: 6	Unknown	HGG with potential tumor recurrence or radiation injury based on MRI lesion after treatment	Histology (*N* = 7), radioclinical (*N* = 3)	^{11}C-AMT; 3.7 MBq/kg; 25-60 min (dynamic);	Lesion-to-cortex K-ratio > 1.5-1.7	4	0	6	0
Arora et al. (*27*)	18	71.7*	38.0 ± 9.7 (18-58)*	WHO III: 15; WHO IV: 3	Pros	HGG with clinical/radiological suspicion of recurrence after treatment	Histology and/or radioclinical (*N* = 18)	^{18}F-FDG; (296-370 MBq)*; 45-60 min; CT	Visual inspection	11	1	3	3
D'Souza et al. (*20*)	27	74.1	42.6 (18-61)	WHO III: 16; WHO IV: 11	Unknown	HGG patients who underwent PET after treatment	Histology (*N* = 20), radioclinical (*N* = 7)	^{11}C-MET; 7 mBq/kg (authors most likely meant MBq);	L/N tissue ratio > 1.58	16	2	8	1

								15-35 min; CT					
Dankbaar et al. (*17*)	25 (32)	Unknown	56.4 (41-68)	WHO III: 4; WHO IV: 28º	Retro	HGG with new or progressive enhancement on MRI after treatment	Histology (*N* = 12), imaging (*N* = 18), clinical (*N* = 2)º	^{18}F-FDG; 2MBq/kg; 30-40 min; CT	Relative SUVpeak > 2.26	13	2	6	11
Enslow et al. (*41*)	10	60.0*	(22-75)*	WHO IV: 10	Unknown	GBM patients who underwent PET for differentiating between radiation necrosis and recurrent tumor for a new enhancing lesion on Gd-MRI, after treatment	Imaging (*N* = 10)	^{18}F-FDG; 370 MBq; 45-75 min;					
									Ratio Lesion-White Matter > 1.83	6	0	3	1
									SUV_{max} ≥ 6.20	6	0	3	1
								^{18}F-FLT; 370 MBq; up to 70 min (dynamic) or 60-70 min (static);	Visual inspection	6	1	2	1

									Ki_{max} ≥ 0.0165	7	0	3	0
									SUV_{max} ≥1.34	6	0	3	1
Galldiks et al. (*28*)	22	63.6	56 (34-76)	WHO IV: 22	Retro	GBM with new lesions or an enlargement of constrast-enhancing lesions on standard MRI (gadolinium-based contrast agent) within the first 12 w after completion of radiotherapy with concomitant temozolomide	Histology (*N* = 11), radioclinical based on neccessity of change of treatment (*N* = 11)	^{18}F-FET; 200 MBq; up to 50 min (dynamic);	TBR_{max} > 2.3	11	1	10	0
									TBR_{mean} > 2.0	9	2	9	2
	21			WHO IV: 21					TBR_{max} > 2.3 and kinetic pattern II or III	8	1	10	2
									TBR_{mean} > 2.0 and kinetic pattern II or III	6	1	10	4
Garcia et al. (*38*)	30	53.3	55 ± 13	WHO III + IV: 30	Retro	HGG with indeterminate MRI findings 5-18 mo after treatment	Histology (*N* = 3), radioclinical (*N* = 27)	^{11}C-MET; 6 MBq/kg; 20-30 min; CT	Visual inspection	21	2	7	0
									Lesion/background SUV ratio > 2.35	19	0	9	2
Herrmann et	110	65.5	51.7 ±	WHO IV:	Retro	GBM with suspected	Histology (*N*	^{18}F-FDOPA;	Visual inspection	69	8	21	12

al. (*32*)			12.1 (23-80)	110		glioblastoma recurrence based on contrast enhancement on MRI scans	= 41), radioclinical (*N* = 69)	133.94 ± 30.34 MBq; 10-30 min; CT					
									max L/S ≥ 1.0	68	11	18	13
Hiob et al. (*31*)	45 (60)	Unknown	Unknown	WHO III + WHO IV: 60º	Unknown	HGG with contrast-enhancing lesion(s) suggestive of recurrence on follow-up MRI after therapy	Histology (*N* = 16), imaging (*N* = 44)º	FET; unknown; 0-40 min (dynamic); MRI	Exact decision rule not provided, using both static and dynamic imaging	39	2	13	6
									Using exclusively static imaging	37	2	13	8
Hojjati et al. (*51*)	19 (23)	66.7*	57.5 (34-81)*	WHO IV: 23º	Retro	GBM with new and/or increasing enhancement on follow-up MRI after treatment	Histology (70.8%), radioclinical (29.2%)*	^{18}F-FDG; median 444 MBq (333-555 MBq)*; 45-55 min; CT	Relative mean ≥ 1.47	15	1	4	3
									Relative median ≥ 1.48	15	1	4	3
									Relative max ≥ 1.86	14	1	4	4
								57-67 min; MRI	Relative mean ≥ 1.31	18	1	4	0
									Relative median ≥ 1.35	17	1	4	1

									Relative max ≥ 1.90	15	0	5	3
Hong et al. (*53*)	7	42.9	39.6 (25-53)	WHO III: 3; WHO IV: 4	Unknown	HGG with suspected recurrence on brain MRI after treatment	Histology (25%), radioclinical (75%)*	^{18}F-FLT; 370 MBq; 65-80 min;	Visual inspection	5	2	0	0
									T/N ratio > 1.18	5	2	0	0
								^{18}F-FDG; 370 MBq; 65-80 min;	Visual inspection	4	1	1	1
Hu et al. (*26*)	16	Unknown	Unknown	WHO III + WHO IV: 16	Unknown	HGG patients who underwent PET after treatment	Histology and/or radioclinical (*N* = 16)	^{11}C-choline; unknown; unknown; CT	Visual inspection	6	3	7	0
Iagaru et al. (*33*)	8	50.0	47.9 ± 10.8 (25-64)	WHO IV: 8	Unknown	GBM patients with suspected recurrence	Imaging (*N* = 1), unknown reference (*N* = 7)	^{18}F-FPPRGD2; 351.5 ± 125.8 MBq; up to 3 hours (dynamic); CT	Unknown	5	0	3	0
								^{18}F-FDG; unknown; unknown;	Unknown	3	0	3	2

								CT					
Imani et al. (*19*)	6	66.7	40.8 (29-60)	WHO III: 6	Retro	HGG with MRI and clinical symptoms suggestive but not conclusive of progression after treatment	Radioclinical (*N* = 6)	^{18}F-FDG; (353-532 MBq); unknown;	Visual inspection	2	0	4	0
Iravani et al. (*36*)	6	Unknown	Unknown	WHO III + WHO IV: 6	Retro	HGG patients referred for FET-PET with suspected tumor recurrence on MRI after treatment	Histology (*N* = 3), radioclinical (*N* = 3)	FET; 185 MBq; 30-60 min;	TBR_{max} > 2.5	6	0	0	0
Jena et al. (*22*)	25 (31)	84.0	52.9 (27-79)	Likely WHO III and WHO IV only	Pros	Glioma patients with high index of suspicion of recurrence clinically and/or in the follow-up contrast-enhanced MRI after treatment	Histology (*N* = 12), radioclinical (*N* = 19)º	^{18}F-FET; 222 ± 30 MBq; 0-25 min; MRI	TBR_{max} > 2.11	25	2	4	0
									TBR_{mean} ≥ 1.437	24	4	2	1
Jeong et al. (*35*)	11	45.5	44.9 (32-57)	WHO III: 4; WHO IV: 7	Retro	HGG with abnormal enhanced lesion on follow-up MRI after treatment	Histology (12.5%), radioclinical (87.5%)*	FLT; 370 MBq; 30-50 min; CT	SUVmax > 0.8	9	0	2	0
	10	50.0	44.7 (32-57)	WHO III: 4; WHO IV: 6					LNR > 3.00	9	0	1	0

	11	45.5	44.9 (32-57)	WHO III: 4; WHO IV: 7				FET; 370 MBq; 30-50 min; CT	SUVmax > 1.66	8	0	2	1
	10	50.0	44.7 (32-57)	WHO III: 4; WHO IV: 6					LNR > 2.46	7	0	1	2
Karunanithi et al. (*45*)	24	80.0*	38.6 (11-62)*	WHO III: 8; WHO IV: 16	Pros	HGG with clinical suspicion of recurrence after treatment	Histology (17.1%), radioclinical (82.9%)*	^{18}F-FDOPA; 3.5 MBq/kg; start after 20-30 min; CT	Visual inspection	18	0	6	0
Karunanithi et al. (*50*)	18	85.7*	38.82 (11-62)*	WHO III: 5; WHO IV: 13	Pros	HGG with clinical/imaging suspicion of recurrence after treatment	Histology (*N* = 2), radioclinical (*N* = 16)	^{18}F-FDG; 370 MBq; start after 45-60 min, scan for 3-10 min*; CT	Visual	10	0	5	3
Kebir et al. (*40*)	16	87.5	55.2 (23-76)	WHO IV: 16	Retro	GBM patients experiencing increasing contrast-enhancing lesions on MRI after treatment	Imaging (*N* = 16)	^{18}F-FET; 200 MBq; up to 50 min (dynamic);	TBR_{max} > 1.9	11	0	3	2
									TBR_{mean} > 1.9	10	0	3	3
Kebir et al.	8	50.0	55.4 (29-	WHO III: 2; WHO	Retro	HGG with increasing constrast-enhancing	Imaging (*N* =	^{18}F-FET; 200 MBq;	Cluster (based mainly on	5	1	1	1

(*39*)			70)	IV: 6		lesions on MRI and/or any new lesion more than 4 w after end of treatment	8)	20-40 min; CT	textural PET features) < 3				
Khangembam et al. (*34*)	18	62.5*	38.8 ± 12.1 (7-63)*	WHO III: 12; WHO IV: 6	Pros	HGG with clinical suspicion of recurrence after treatment	Histology (23.2%), radioclinical (76.8%)*	^{13}N-NH_3; (444-592 MBq)*; 3-10 min; CT	Visual inspection	7	3	6	2
								^{18}F-FDG; 185 MBq; start after 45-60 min, duration 10 min; CT	Visual inspection	7	3	6	2
Kits et al. (*30*)	7	71.4	50.3 (40-65)	WHO III: 3; WHO IV: 4	Retro	HGG patients who received MET PET to differentiate between tumor recurrence and radiation injury after treatment	Histology (*N* = 7)	^{11}C MET; 6 MBq/kg; 10-40 min (dynamic);	SUR_{max}mirror > 1.62	5	1	1	0
Lapa et al. (*52*)	20 (23)	75.0	53.8 (33-75)	WHO III: 2; WHO IV: 21º	Pros	HGG with suspected recurrence after treatment	Histology (*N* = 23)º	^{18}F-DOPA; 175 ± 39 MBq*; 15-35 min; CT	Visual inspection	23	0	0	0
								^{18}F-FET; 217 ± 13	Visual inspection	23	0	0	0

								MBq*; 10-20 min; CT					
Li et al. (*23*)	12	66.7	48.2	WHO III: 4; WHO IV: 8	Unknown	HGG with suspicion of recurrence by clinical or contrast-enhanced MRI after treatment	Histology (*N* = 3), radioclinical (*N* = 9)	^{11}C-choline; 370 MBq; 5-9 min; CT	Visual inspection	4	2	6	0
									T/N > 1.42	4	1	7	0
Martínez-Amador et al. (*48*)	(13)	30.8	56.2 (41-67)	WHO III: 6; WHO IV: 7	Retro	HGG with MRI suspicion of recurrent tumor after therapy	Histology (29.3%), radioclinical (70.7%)*	^{11}C-MET; (555-740 MBq); 20-50 min; CT	Visual inspection	10	0	0	3
									L/CP SUV_{max} ≥ 1.21	9	0	0	4
Montes et al. (*44*)	11	72.7	50.5 (32-76)	WHO III: 7; WHO IV: 4	Pros	HGG with clinical and/or radiological suspicion of recurrence and doubtful MR findings	Histology (*N* = 3), radioclinical (*N* = 8)	^{18}F-FCH; 370 MBq; start after 50 min	Visual inspection	9	0	2	0
Nakajima et al. (*43*)	14	71.4	45.4 (23-67)	WHO III: 6; WHO IV: 8	Retro	HGG patients who developed recurrent lesions on MRI suspected to be recurrent tumor or radiation necrosis after treatment	Histology (*N* = 11), radioclinical (*N* = 3)	^{11}C-MET; (200-550 MBq)*; 20-30 min;	L/R > 2.00	4	0	9	1
Paquet et al.	35 (60)	Unknown	60	WHO III:	Pros	HGG patients who	Histology (*N*	^{18}F-FDOPA;	Visual	47	3	8	2

(*37*)				1; WHO IV: 34		underwent PET after treatment	= 15), imaging (*N* = 20)	2 MBq/kg; 20-30 + 90-100 min; CT				
Park et al. (*7*)	31	48.4	50.3	WHO III: 4; WHO IV: 27	Retro	HGG with clinical indication of suspected recurrence after treatment	Histology (72.1%), radioclinical (27.9%)*	^{11}C-MET; 555 MBq; 20-40 min; CT	TNR_{max} > 1.40	21	2	3	5
Pyka et al. (*47*)	6	54.2*	52*	WHO III + WHO IV: 6	Unknown	HGG patients who had received PET/MRI for suspected recurrence	Histology (*N* = 6)	^{18}F-FET; 185 MBq; unknown; MR	Unknown	4	0	0	2
Sharma et al. (*46*)	12	83.3	46.9 (23-65)	WHO III: 4; WHO IV: 8	Retro	HGG patients investigated with PET for detection of recurrent disease after treatment	Clinical (*N* = 9), imaging (*N* = 3)	^{11}C-MET; 370 MBq; unknown; CT	Visual inspection	10	0	2	0
									TBR ≥ 1.47	10	0	2	0
								^{18}F-FDG; 370 MBq; start after 60 min, 15-20 min per bed position; CT	Visual inspection	9	0	2	1
Sher et al.	10	Unknown	Unknown	WHO III + WHO IV:	Unknown	HGG with MR evidence of progressive disease per	Unknown	^{18}F-FDG; unknown;	Visual inspection	7	0	1	2

(*24*)				10		RANO criteria after treatment		unknown; CT						
							Unknown	^{18}F-FDG; unknown; unknown; MR attenuation correction		9	0	1	0
							Unknown	^{18}F-FDG; unknown; unknown; conventional diagnostic MR		9	0	1	0
Shishido et al. (*29*)	21	52.4	54.0 ± 13.6 (22-71)	WHO III: 7; WHO IV: 14	Retro	HGG patients with first radiological suspicion of recurrence during follow-up after treatment	Histology (*N* = 13), radioclinical (*N* = 8)	^{11}C-MET; 215 ± 58 MBq (126-318 MBq); 10-15 min;	L/N ratio ≥2.69	12	1	5	3
									Visual inspection	15	5	1	0
								^{18}F-FLT; 204 ± 79 MBq (91-337 MBq); 40-50	L/N ratio ≥4.94	14	2	4	1

								min;					
									Visual inspection	15	6	0	0
Takenaka et al. (*42*)	49	Unknown	Unknown	WHO III: 16; WHO IV: 17‡	Unknown	Unknown, but results suggest that exclusively HGG patients for which a differentiation between tumor reccurence and radiation necrosis was needed were included.	Histology (*N* = 49)	mod-MET (combination of ^{11}C-CHO and ^{11}C-MET); unknown; unknown;	L/N ratio > 4.75	26	1	15	7
Testart et al. (*25*)	9	43*	46.9 ± 6.2*	Unknown	Pros	HGG under suspicion of tumor growth after treatment	Histology (42.9%), radioclinical (57.1%)*	^{18}F-FCH; unknown; unknown	Unknown	9	0	0	0
Tripathi et al. (*21*)	9	66.7	48.8 (35-65)	WHO III: 4; WHO IV: 5	Pros	HGG patients evaluated for recurrent disease after treatment	Histology (40%), radioclinical (60%)*	C-11 methionine; (550-740 MBq)*; 20-40 min; CT	T/N ratio >1.9	8	0	1	0
								F-18 FDG; (222-296 MBq)*; 60-80 min; CT	T/N ratio >0.75	7	0	1	1
Verger et al.	23 (24)	50º	51.8 (29-	WHO III: 2; WHO	Retro	HGG with standard MRI suggestive of progression	Histology (78%),	^{18}F-FET; 3 MBq/kg; up	Visual inspection	14	3	3	4

(*49*)			69)º	IV: 22º		or recurrence after treatment	radioclinical (22%)*º	to 50 min (dynamic); MRI					
									TBR_{max} >2.61	14	1	5	4
Yamamoto et al. (*16*)	10	70.0	49.7 (32-65)	WHO IV: 10	Retro	GBM with signs of tumor recurrence based on clinical and/or radiologic examination after treatment	Unknown, no histology	^{18}F-FLT; 150 MBq (104-202 MBq); 5-60 min;	Visual inspection	10	0	0	0

† Note that this is the number of patients/tumors that is included in this review. In general, this is not necessarily the same as the number of patients/tumors in the referred article.

‡ Histology not provided for primary diagnoses but for recurrences. Thus, the 16 patients without tumor progression are not taken into account in these numbers.

* = based on a larger patient group

º = based on number of tumours, not on number of patients

Abbreviations: Bq = becquerel; CT = computed tomography; FN = false negatives; FP = false positives; GBM = glioblastoma multiforme; Gd = Gadolinium; HGG = high-grade glioma; kg = kilogram; Ki_{max} = Patlak-derived metabolic flux parameter; L/CP = lesion/contralateral parenchyma; L/N = lesion-to-normal ratio; L/S = lesion-to-striatum ratio; LNR = lesion-to-normal ratio; max = maximal; min = minute; mo = months; mod = modified; MR = magnetic resonance; MRI = magnetic resonance imaging; PET = positron emission tomography; Pros = prospective; RANO = Response assessment in neuro-oncology; Retro = retrospective; SD = standard deviation; SUR = lesion-to-background SUV ratio; SUV = standard uptake value; T/N = tumor-to-normal ratio; TBR = tumor-to-background ratio; TN = true negatives; TNR = tumor-to-normal ratio; TP = true positives; w = weeks; WHO = World Health Organization. See Supplementary Table 3 for a list of PET tracer abbreviations.

Supplementary Table 5: General characteristics of included patients, lesions and scans.

Patients (number)		771*
Lesions (number)		832
Scans (number)		951
	^{18}F-FDG	171
	^{18}F-FET	207
	^{11}C-MET	164
	^{18}F-FLT	54
	^{18}F-FDOPA	192
	^{11}C-CHO	24
	^{18}F-FCH	20
	^{13}N-NH_3	18
	mod-MET	49
	^{11}C-AMT	10
	^{18}F-FPPRGD2	8
Mean age (years)		50.2†
% Male		65.0‡
Histology (number)	WHO III	145
	WHO IV	478
	WHO III or IV (not specified)	209
Follow-up (number)	Histology	257
	Imaging	120
	Clinical	11
	Combination or unknown on the individual lesion level	444
% True progression		73.4§

* For one study (*48*), only a number of 13 PET scans is known. For this study, the number of patients is assumed to be the same as the number of scans. † Calculated using studies for which mean age is known only. ‡ Calculated using studies for which the percentage of males is known only. § Based on the number of lesions

Abbreviations: WHO = World Health Organization. See Supplementary Table 3 for a list of PET tracer abbreviations.

Supplementary Table 6: Quality assessment of included studies.

	Risk of bias				Applicability concerns		
	Patient	Index test	Reference	Flow and timing	Patient	Index test	Reference
Alkonyi et al. (18)	?	-	?	-	+	+	+
Arora et al. (27)	+	+	?	-	?	+	+
D'Souza et al. (20)	+	+	?	-	+	+	+
Dankbaar et al. (17)	+	-	?	-	+	+	+
Enslow et al. (41)	?	-	?	+	?	+	+
Galldiks et al. (28)	+	-	?	-	+	+	+
Garcia et al. (38)	?	-	?	-	+	+	+
Herrmann et al. (32)	?	-	?	-	?	+	+
Hiob et al. (31)	?	-	?	-	?	+	+
Hojjati et al. (51)	?	-	-	-	+	+	+
Hong et al. (53)	+	?	?	-	+	+	+
Hu et al. (26)	?	?	?	-	?	+	+
Iagaru et al. (33)	?	?	?	?	?	+	+
Imani et al. (19)	-	+	?	-	+	+	+
Iravani et al. (36)	+	?	?	-	?	+	+
Jena et al. (22)	+	-	?	-	?	+	+
Jeong et al. (35)	+	-	?	-	+	+	+
Karunanithi et al. (45)	+	+	?	-	?	+	+
Karunanithi et al. (50)	+	+	?	-	?	+	+
Kebir et al. (40)	+	-	?	+	+	+	+
Kebir et al. (39)	?	-	?	+	+	-	+
Khangembam et al. (34)	+	+	?	-	?	+	+
Kits et al. (30)	+	-	-	-	+	+	+
Lapa et al. (52)	+	+	?	+	+	+	+
Li et al. (23)	+	?	?	-	+	+	+
Martínez-Amador et al. (48)	+	?	?	-	+	+	+
Montes et al. (44)	+	+	?	-	?	+	+
Nakajima et al. (43)	?	-	?	-	+	+	+
Paquet et al. (37)	?	+	?	-	?	+	+
Park et al. (7)	+	-	-	-	+	+	+
Pyka et al. (47)	?	?	?	?	?	+	+
Sharma et al. (46)	?	-	?	-	+	+	+
Sher et al. (24)	?	+	?	?	?	+	+
Shishido et al. (29)	+	-	?	-	+	+	+
Takenaka et al. (42)	?	-	?	?	?	-	+
Testart et al. (25)	?	?	?	-	?	+	+
Tripathi et al. (21)	?	-	?	-	?	+	+
Verger et al. (49)	+	?	-	-	-	+	+
Yamamoto et al. (16)	+	-	?	?	?	+	+

The risk of bias in four different domains and concerns about applicability are shown for the included studies. High risk/concern (-), unclear risk/concern (?) and low risk/concern (+).

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Diagnostic accuracy of positron emission tomography tracers for the differentiation of tumor progression from treatment-related changes in high-grade glioma: a systematic review and meta-analysis

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