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Evidence Summary PET 20

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Ontario Health (Cancer Care Ontario)

^{18}F-FET PET Imaging in Brain Tumours

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Evidence Summary

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Ontario Health (Cancer Care Ontario). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC is a provincial initiative of OH (CCO) supported by the Ontario Ministry of Health (OMH). All work produced by the PEBC is editorially independent from the OMH.

INTRODUCTION

Central nervous system (CNS) tumours are a heterogeneous group of neoplasms with wide variation in prognosis across histologic types and behaviour. They are comprised of primary CNS tumours (that arise from brain or spinal cord tissue) and secondary/metastatic tumours (malignant cells that spread hematogenously from a primary cancer outside the brain). In Ontario, 1110 people are expected to be diagnosed with primary brain and spinal cord malignancies in 2020, of which 540 men and 410 women will die from the disease [1]. Glioma, which originates from glial cells, is the most common primary brain tumour in adults, accounting for approximately 81% of all malignant brain tumours [2]. Specifically, high-grade gliomas including glioblastoma (grade IV), anaplastic astrocytoma (grade III), and anaplastic oligodendroglioma (grade III) are among the most aggressive forms of the disease, with five-year survival rates of 4%, 18.2%, and 41.5%, respectively [3]. Likewise, the prognosis of patients with brain metastases is generally poor, with median survival of 13 months following diagnosis [4]. Recent data from Ontario suggested that the incidence of brain metastases is 1.6 times greater than that of all primary brain tumours combined, affecting up to 24.2 per 100,000 persons per year. Brain metastases are most commonly seen in lung cancer (60%), breast cancer (11%), and melanoma (6%) [5].

Current first-line treatment of most high-grade gliomas involves maximally safe surgical resection followed by radiotherapy with concomitant and adjuvant temozolomide chemotherapy [6]. Outcomes in this population vary with the extent of resection as well as the intrinsic response of these molecularly heterogeneous tumours to radiation and chemotherapy. Minimizing toxicity by decreasing radiation exposure of normal-appearing brain is limited due to microscopic extension of malignant cells that leads to the majority of recurrences occurring within 4 cm of the original tumour [7]. In clinical practice, contrast-enhanced magnetic resonance imaging (MRI) remains the method of choice for anatomical delineation for radiotherapy planning; however, it can be limited in differentiating postoperative changes from residual tumour as well as not being able to distinguish peri-tumoural edema from microscopic tumour cells within the MRI T2-signal abnormality. Brain metastases are often treated with highly focal radiation called stereotactic radiosurgery (SRS) with local control rates approaching 90%. However, approximately 5% of brain metastases develop adverse radiation effect, also

called radiation necrosis (RN), after SRS [8]. Unfortunately, anatomical MRI scans cannot distinguish between recurrent tumour and RN after SRS, which limits clinical decision making. After radiation in gliomas, a phenomenon called pseudo-progression (a transient alteration in the blood-brain barrier) is seen in 20% to 30% of cases from six weeks to six months post therapy, which is also indistinguishable from true tumour progression with MRI [9,10]. To overcome these deficiencies with conventional MRI, positron emission tomography (PET) imaging using radiolabeled amino acids such as O-(2-^{18}F-fluoroethyl)-L-tyrosine (^{18}F-FET) has been increasingly proposed because uptake of this tracer is independent of blood-brain barrier disruption. Furthermore, increased ^{18}F-FET uptake has been observed in non-enhancing tumour subregions that are at higher risk of recurrence but are difficult to delineate using routine MRI [11]. It is in this context that the aim of the present review was to provide a summary of evidence demonstrating the complementary or additive value of ^{18}F-FET PET imaging in the management of patients with brain tumours. This review has been registered at International prospective register of systematic reviews (PROSPERO), registration number CRD42021227766.

OBJECTIVES

To provide a synthesis and summary of evidence surrounding the diagnostic performance and clinical impact of ^{18}F-FET PET imaging in brain tumours.

RESEARCH QUESTIONS

These research questions were developed to direct the search for available evidence on ^{18}F-FET PET imaging in brain tumours.

- What is the diagnostic performance and clinical impact of ^{18}F-FET PET or PET-computed tomography (PET/CT) or PET/MR as a potential replacement or add-on to conventional imaging in:
    - High-grade gliomas
        - Pre-treatment planning.
        - Prediction of post-treatment failure.
        - Recurrence versus post-treatment changes.
    - Brain metastases
        - Recurrence versus post-treatment changes.

TARGET POPULATION

Patients with high-grade gliomas or brain metastases.

INTENDED PURPOSE

To review emerging evidence for an amino acid tracer in neuro-oncology as per a request from a member of the Ontario PET Steering Committee.

INTENDED USERS

To guide the Ontario PET Steering Committee in their decision making with respect to the development of indications in the context of the patient management pathway. This evidence summary may also be useful to inform clinicians who are involved in the management of patients with gliomas or brain metastases.

METHODS

This evidence summary was developed by a Working Group consisting of a nuclear medicine physician, radiation oncologist, and health research methodologist at the request of the Ontario PET Steering Committee.

The Working Group was responsible for reviewing the identified evidence and drafting the summary. Conflict of interest declarations for all authors are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

Search for Systematic Reviews

A search for systematic reviews up to September 18, 2020 was carried out using the electronic databases MEDLINE, Embase, and Cochrane Database of Systematic reviews. Systematic reviews published as a component of practice guidelines were also considered eligible for inclusion. See Appendix 2 for the search strategies.

Search for Primary Literature

Literature Search Strategy

The primary literature was searched using MEDLINE and Embase online databases up to September 18, 2020.

Study Selection Criteria and Process

Inclusion Criteria

1. Published as a full-text article in the English language.
2. Evaluated the use of PET or PET/CT or PET/MR with tracer ^{18}F-FET.
3. Reported on diagnostic test parameters, such as sensitivity, specificity, positive predictive value, negative predictive value, and accuracy, or metrics representing impact on clinical management decisions and/or survival outcomes.
4. A composite reference standard consisting of post-surgical or post-biopsy histology, clinical or radiologic follow-up.
5. Included ≥12 patients for prospective studies or ≥20 patients for retrospective studies.

Exclusion Criteria

1. Literature or narrative reviews, letters, editorials, historical articles, commentaries, or case reports.
2. Studies that included >20% of patients with low-grade or unknown grade gliomas in which data for patients with high-grade glioma or brain metastases could not be separated.
3. Studies that specifically addressed radiomic features.

A review of the titles and abstract that resulted from the search was conducted by one reviewer, as were the items that warranted full-text review.

Data Extraction and Assessment of Risk of Bias

All included primary studies underwent data extraction by one reviewer with all extracted data and information audited subsequently by an independent auditor for accuracy and completeness. For each study, the principal author, publication year, country of origin, study design, number of lesions/patients, histology, reference standard criteria, age, sex, type of imaging modality, test parameter and cut-off, and the outcomes of interest were recorded.

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [12] was used to evaluate the risk of bias and applicability concerns for each eligible study.

Synthesizing the Evidence

Data were summarized in evidence tables and described in the text. When clinically and methodologically homogenous results from four or more studies and sufficient data were available, a bivariate, random-effects model was used to produce summary estimates of sensitivity and specificity with 95% confidence intervals (CIs) and to plot summary receiver operating characteristic (SROC) curves with 95% confidence regions. This model incorporates any correlation that might exist between sensitivity and specificity and accounts for the estimated variability among the studies [13]. The I^2 percentage was calculated as a measure of heterogeneity. Statistical analyses were performed with STATA version 11.2 using the midas command and the metaprop command with Freeman-Tukey double arcsine transformation.

Assessment of the Certainty of the Evidence

The certainty of the evidence per outcome for each research question, taking into account risk of bias, inconsistency, indirectness, imprecision, and publication bias was assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach [14].

RESULTS

Search for Systematic Reviews

The search for existing systematic reviews identified a number of publications that were considered relevant to the research questions. However, none of these systematic reviews focused primarily on ^{18}F-FET for all the clinical indications of interest and therefore were not discussed further.

Search for Primary Literature

A search for primary literature yielded a total of 1259 unique citations, of which 1192 were excluded after a review of titles and abstracts. Sixty-seven were considered candidates, but upon full-text review, 45 did not meet the inclusion criteria. The remaining 22 studies were included in this systematic review. See Appendix 3 for the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) flow diagram.

Study design and the Certainty of the Evidence

Five studies enrolled patients prospectively [15,17-19,35], while 17 studies collected data retrospectively [16,20-34,36]. Patients with high-grade glioma and brain metastases were examined in 17 [15-31] and five [32-36] studies, respectively. The number of lesions/patients included among these studies ranged from 19 to 168. Details of the study characteristics are reported in Table 1. Quality assessment for each study was performed according to the four QUADAS-2 domains (Appendix 4). All studies were judged to have low concerns regarding applicability. For the domains relating to risk of bias, three studies were judged to have high risk in patient selection. Two studies only included patients with suspected non-enhancing tumour [16] or residual tumour [17] seen on MRI. Such constraints may lead to an overestimation of the impact of ^{18}F-FET PET/CT. In the third study [24], ^{18}F-FET PET was often considered appropriate only if it was based on the recommendation of the multidisciplinary tumour board after equivocal MRI. This may carry a selection bias for particularly difficult cases and in turn could lead to an underestimation of the true accuracy. Despite these restrictions, the use of ^{18}F-FET PET imaging as a problem-solving tool has been used in many centres in Europe. Additionally, nine studies [15,19,22,23,26-28,32,33] lacked the information to permit a

judgement on whether a consecutive or random sample of patients were enrolled. In the same way, many studies had reference standard readings that were either not blinded to the results of the index test [23] or unclear as to whether they were interpreted without the knowledge of the index test [20-22,24-30,32-36]. Unclear risk of bias may be a consequence of incomplete reporting; however, it is uncertain if this would have a notable effect on test accuracy outcomes. No studies were judged as being at risk for the domains covering index test and flow and timing. With regard to the GRADE criteria, assessment for indirectness and imprecision was low across all studies and there is no suspicion of relevant publication bias since for-profit interests were not detected in any of the included studies. However, there are concerns with inconsistency due to substantial inter-study variability in terms of imaging protocols and cut-offs for the definition of vital tumour. This is expected as current usage of this technology differs among providers and institutions with lack of a standardized protocol. Overall, the aggregate quality of the evidence was rated as low to moderate.

Table 1: Characteristics of included studies.

Study, year	Country	Study design	No. of lesions or patients/ histology	Reference standard	Mean age	Sex (M/F)	Imaging modality	Parameter	Cut-off[£]	TP	FP	FN	TN
High-grade glioma													
Dissaux et al, 2020 [15]	France	P	Grade III: 5 Grade IV: 25	F-U	63*	20/10	PET/CT CE-MRI	TBR V	1.6 -	- -	- -	- -	- -
Hayes et al, 2018 [16]	Australia	R	Grade III: 5 Grade IV: 21	F-U	61*	17/9	PET/CT CE-MRI FLAIR-MRI	TBR V V	1.6 - -	- - -	- - -	- - -	- - -
Weber et al, 2008 [17]	Switzerland	P	Grade III: 5 Grade IV: 14	F-U	53.5*	9/10	PET/CT CE-MRI	SUV_{max} V	40% -	- -	- -	- -	- -
Galldiks et al, 2012 [18]	Germany	P	Grade IV: 25	F-U	54	15/10	PET CE-MRI	TBR_{max} V	Δ20%[π] Δ0%/Δ25%	- -	- -	- -	- -
Galldiks et al, 2018 [19]	Germany, Denmark	P	Grade IV: 21	F-U	55*	13/8	PET CE-MRI	TBR_{max} TBR_{mean} MTV_{rel} MTV_{abs} RANO	7% 16% 27% 5 ml PR/SD	12 12 10 11 5	3 3 3 1 4	1 1 3 2 3	5 5 5 7 9
Buchmann et al, 2019 [20]	Germany	R	Grade IV: 33	F-U	59	18/14	PET/CT CE-MRI	TBR_{max} V	1.3 -	28[μ] 14	0 0	4 18	1 1
Lohmeier et al, 2019 [21]	Germany	R	Grade I/II: 2 Grade III/IV: 40	Histology (36), F-U (6)	47	24/18	PET DWI-MRI PET/MRI	TBR_{max} ADC_{mean} TBR_{max} + ADC_{mean}	2.0 1254 × 10^{-6} mm^2/s -	26 20 31	4 0 4	6 12 1	6 10 6
Pyka et al, 2018 [22]	Germany	R	Grade II: 5 Grade III: 20 Grade IV: 38	Histology (23), F-U (40)	53	25/22	PET PWI-MRI DWI-MRI PET/MRI	TBR_{mean}[**] TBR_{mean}[β] TTP $rCBV_{uncor}$ $rCBV_{cor}$ ADC_{mean} $nADC_{mean}$ FA TBR_{max}[**] + TTP + $rCBV_{cor}$ + nADC	2.07 1.71 20 min 4.32 3.35 1610 × 10^{-6} mm^2/s 1.22 98.9 -	40 38 32 30 32 24 30 31 37	2 2 3 3 3 3 3 5 1	10 12 18 19 17 24 181 7 11	11 11 10 10 10 10 10 8 12

Verger et al, 2018 [23]	Germany	R	Grade II: 2 Grade III: 3 Grade IV: 27	Histology (25), F-U (7)	52	16/15	PET	V	-	19	3	6	4
								TBR_{max}	2.61	20	1	5	6
							PWI-MRI	V	-	13	3	12	4
Maurer et al, 2020 [24]	Germany	R	Unknown: 2 Grade II: 21 Grade III: 36 Grade IV: 68	Histology (40), F-U (87)	50	83/44	PET	TBR_{max}	1.95	66	10	28	23
								TBR_{mean}	1.95	53	7	41	26
								Slope	0.2 SUV/h	51	4	43	29
								TBR_{max} + Slope	-	81	11	13	22
Mihovilovic et al, 2019 [25]	Germany	R	Grade IV: 36	Histology (16), F-U (20)	54	22/14	PET/CT	TBR_{max}	3.52	25	2	3	6
								TBR_{mean}	2.98	23	1	5	7
Popperl et al, 2006 [26]	Germany	R	Grade III: 5 Grade IV: 19	Histology (9), F-U (15)	49	15/9	PET	V	-	16	2	1	5
								TU_{max}/BG	2.4***	14	0	3	7
Kebir et al, 2016 [27]	Germany	R	Grade IV: 26	Histology (6), F-U (20)	58*	21/5	PET	TBR_{max}	1.9	16	1	3	6
								TBR_{mean}	1.9	14	1	5	6
								TAC	II/III	16	0	3	7
Werner et al, 2019 [28]	Germany	R	Grade III: 8 Grade IV: 40	Histology (10), F-U (38)	50	29/19	PET	$TBR_{max/mean}$	1.95	30	0	8	10
								TTP	32.5 min	25	2	11	8
								Slope	0.32 SUV/h	27	3	9	7
								$TBR_{max/mean}$ + TTP	-	33	1	3	9
								$TBR_{max/mean}$ + Slope	-	35	2	1	8
							DWI-MRI	V	-	25	3	13	7
								ADC_{mean}	1.09×10^{-3} mm^2/s	27	4	11	6
							PET/MRI	$TBR_{max/mean}$ + ADC_{mean}	-	36	3	2	7
Kertels et al, 2019 [29]	Germany	R	Grade IV: 36	Histology (16), F-U (20)	54	22/14	PET/CT	TBR_{max}	3.69	22	1	6	7
								TBR_{max}	3.58	18	0	10	8
								TBR_{max}	3.44	24	1	4	7
								TBR_{mean}	2.31	17	0	11	8
								TBR_{mean}	2.19	20	1	8	7
								TBR_{16mm}	2.44	23	2	5	6
								TBR_{10mm}	2.86	24	2	4	6
								$TBR_{90\%}$	3.23	20	0	8	8
								$TBR_{80\%}$	3.08	23	1	5	7
								$TBR_{70\%}$	2.72	24	1	4	7

Galldiks et al, 2015 [30]	Germany	R	Grade IV: 22	Histology (11), F-U (11)	56	14/8	PET	TBR_{max}	2.3	11	1	0	10
								TBR_{mean}	2.0	9	2	2	9
								TAC	II/III	8	5	2	6
								TBR_{max} + TAC	-	8	1	2	10
								TBR_{mean} + TAC	-	6	1	4	10
Bashir et al, 2019 [31]	Denmark	R	Grade IV: 168	Histology (104), F-U (64)	59.5*	96/50	PET/CT	TBR_{max}	2.0	151	1	1	15
								TBR_{mean}	1.8	146	1	6	15
								BTV	0.55 cm^3	149	1	3	15
Brain metastases													
Galldiks et al, 2021 [32]	Germany, Switzerland	R	27	Histology (2), F-U (25)	53.9	24/3	PET	TBR_{mean}	1.95	7	1	3	16
								TTP	27.5 min	4	0	3	10
								TBR_{mean} + TTP	-	4	0	3	10
Romagna et al, 2016 [33]	Germany	R	50	Histology (20), F-U (30)	61.9*	11/11	PET	TBR_{max}	2.15	18	6	3	23
								TBR_{mean}	1.95	18	6	3	23
								TAC	Decrease	16	8	4	14
								$TBR_{max/mean}$ + TAC	-	19	4	1	18
Lohmann et al, 2017 [34]	Germany	R	54	Histology (21), F-U (33)	55	11/36	PET	TBR_{max}	3.11	24	3	6	21
								TBR_{mean}	1.99	25	5	5	19
								TAC	1.5	27	13	3	11
								TTP	32.5 min	18	7	12	17
								TBR_{max} + TBR_{mean}	-	24	2	6	22
								TBR_{max} + TAC	-	22	1	8	23
Galldiks et al, 2012 [35]	Germany	P	40	Histology (11), F-U (29)	53	5/26	PET	TBR_{max}	2.55	15	5	4	16
								TBR_{mean}	1.95	14	2	5	19
								TAC	II/III	16	0	3	21
								TBR_{mean} + TAC	-	18	2	1	19
Ceccon et al, 2017 [36]	Germany	R	76	Histology (26), F-U (50)	55	14/48	PET	TBR_{max}	2.55	30	6	6	34
								TBR_{mean}	1.95	31	5	5	35
								TTP	32.5 min	21	11	15	29
								Slope	0.125 SUV/h	22	13	14	27
								TBR_{max} + Slope	-	28	3	8	37

			TBR_{mean} + Slope	-	30	3	6	37

Abbreviations: abs, absolute; ADC, apparent diffusion coefficient; BG, ratio to background; BTV, biological tumour volume; CE, contrast-enhanced; cor, corrected; CT, computed tomography; DWI, diffusion-weighted imaging; F, female; FA, fractional anisotropy; FLAIR, fluid-attenuated inversion recovery; FN, false-negative; FP, false-positive; F-U, clinical/imaging follow-up; M, male; MRI, magnetic resonance imaging; MTV, metabolic tumour volume; n, normalized; P, prospective; PET, positron emission tomography; PR, partial response; PWI, perfusion-weighted imaging; R, retrospective; RANO, response assessment in neuro-oncology; rCBV, relative cerebral blood volume; rel, relative; SD, stable disease; SUV, standardized uptake value; TAC, time-activity curve; TBR, tumour-to-brain ratio; TN, true-negative; TP, true-positive; TTP, time-to-peak; TU, tumoural uptake; uncor, uncorrected; V, visual

*Median age

**Measurements acquired 30 to 40 minutes after injection

***Threshold value for best differentiation between tumour recurrence and reactive changes

[β]Measurements acquired 10 to 20 minutes after injection

[μ]Partially predictive cases were considered to be true positive

[π]Optimal cut-off point for prediction of overall survival

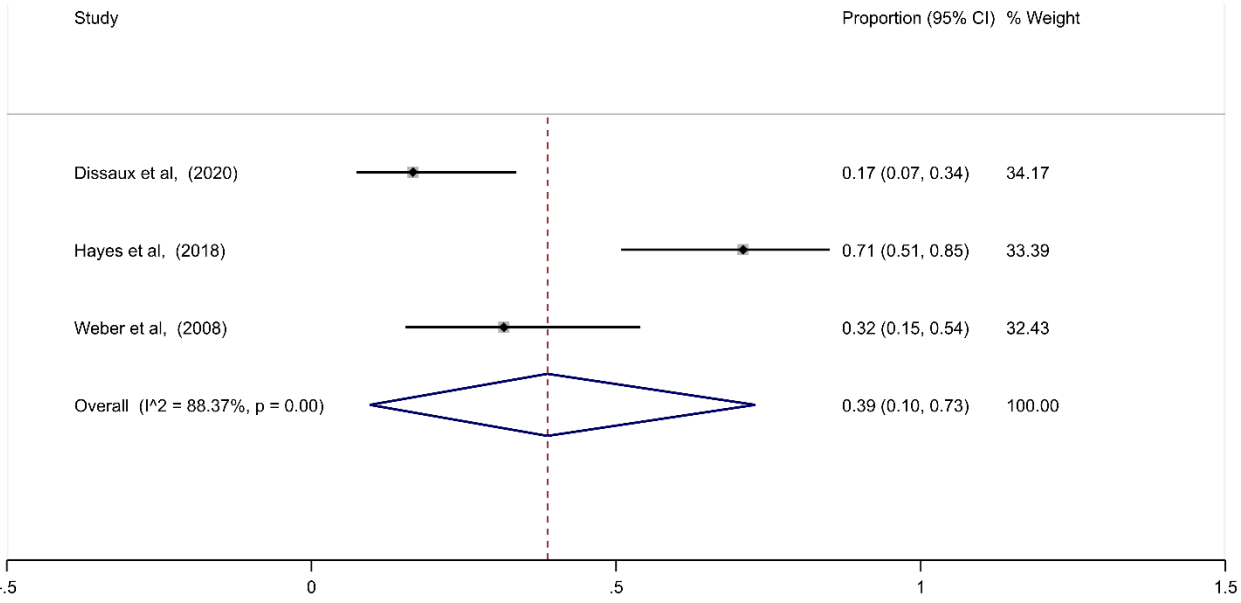
[£]Image-derived parameter indicating abnormal tissue

Radiotherapy Planning

High-grade glioma

Three studies evaluated the impact of ^{18}F-FET PET/CT on radiotherapy target volume delineation. A threshold value of 1.6 for the tumour-to-brain ratio (TBR) was used in two studies [15,16], while a threshold value of 40% of maximum standardized uptake value (SUV_{max}) was used in the other study [17]. Taken together, the pooled proportion of patients with FET uptake extending beyond the 20 mm margin from the gadolinium enhancement on standard MRI was 39% (95% CI, 10% to 73%) (Figure 1). Similarly, there was a significant difference in volumetric change between FET-avid disease and MRI T2-weighted-fluid-attenuated inversion recovery (T2 FLAIR) abnormalities (p<0.0001), where 83.3% (20/24) of patients had FET uptake outside the hyperintense region seen on MRI T2 FLAIR [16].

Figure 1: Forest plot of the overall impact of ^{18}F-FET PET/CT on radiotherapy target volume delineation in comparison to standard MRI.



Assessment of Treatment Response

High-grade glioma

Response evaluation was established with respect to survival time of the patients in two studies. Early ^{18}F-FET PET assessment (a decrease of TBR_{max} of more than 20%) at seven to 10 days after completion of adjuvant radiotherapy with concomitant temozolomide identified responders (progression-free survival/overall survival > median) with a sensitivity of 83% and a specificity of 67% (area under the curve [AUC], 0.75; p=0.04). Overall, early PET responders exhibited a significantly longer median overall survival than non-responders (16.1 months versus 9.3 months, p=0.02). Furthermore, various other parameters derived from ^{18}F-FET PET (TBR_{mean} and TBR greater than 1.6) remained significant in the multivariate analysis for predicting treatment response at an early stage of disease. In contrast, gadolinium contrast-enhancing volumes on MRI failed to show any significant prognostic value for patient survival [18]. Likewise, in patients with progressive glioblastoma, ^{18}F-FET PET was useful in identifying early responders (overall survival >9 months) to bevacizumab plus lomustine. The relative reductions of TBR_{max} (sensitivity, 92.3%; specificity, 62.5%; AUC, 0.78; p=0.036), TBR_{mean} (sensitivity, 92.3%; specificity, 62.5%; AUC, 0.81; p=0.02), and metabolic tumour volume (MTV) (sensitivity,

76.9%; specificity, 62.5%; AUC, 0.82; p=0.015) were all found to be significant predictors of superior overall survival, as was the absolute MTV threshold of 5 ml at follow-up (sensitivity, 84.6%; specificity, 87.5%; AUC, 0.92, p=0.001). The latter of which (absolute MTV at follow-up) remained significant in the multivariate analysis (hazard ratio, 0.158, 95% CI, 0.042 to 0.595, p=0.006). Contrast-enhanced MRI, on the other hand, was not predictive of early responders (sensitivity, 62.5%; specificity, 69.2%; p=0.203) [19].

One study compared the value of immediate postoperative (within 72 hours) ^{18}F-FET PET/CT to that of contrast-enhanced MRI in predicting the site of later tumour recurrence. Twenty patients underwent first-time surgery, whereas 13 patients had undergone reoperation for recurrent tumours. Both ^{18}F-FET PET/CT and contrast-enhanced MRI demonstrated 100% specificity for the prediction of tumour recurrence location. However, the sensitivity (87.5%) and accuracy (87.9%) of ^{18}F-FET PET/CT were greater than that of contrast-enhanced MRI (sensitivity, 43.8%; accuracy, 45.5%). In cases that were not predictable by contrast-enhanced MRI, 63.2% (12/19) could have been predicted using ^{18}F-FET PET/CT [20].

Recurrence versus Post-Treatment Changes

High-grade glioma

For the differentiation of tumour recurrence from treatment-related changes, 11 studies investigated the diagnostic performance of ^{18}F-FET PET or PET/CT using various approaches of image analysis. In most studies, patients were referred for ^{18}F-FET PET or PET/CT scanning due to suspicion of recurrence or disease progression based on conventional MRI [22-25,27-31]. One study only selected patients who had received a simultaneous ^{18}F-FET PET/MRI acquisition [21], while another study evaluated the utility of ^{18}F-FET PET for monitoring the effects of adjuvant intracavitary radioimmunotherapy [26].

For static ^{18}F-FET PET parameters, the pooled sensitivity and specificity from six studies [21,24,27,28,30,31] that expressed tumour uptake as TBR_{max} with a cut-off value of 1.9 to 2.3 were 91% (95% CI, 74% to 97%) and 84% (95% CI, 69% to 93%), respectively (Figure 2). Significant heterogeneity was observed among the studies for both sensitivity (I^2=91.7%, p<0.001) and specificity (I^2=73.8%, p<0.001). The area under the SROC curve was 0.92 (95% CI, 0.90 to 0.94) (Figure 3). Other TBR_{max} measures that used higher threshold values (2.61 to 3.69) showed a sensitivity that ranged from 64.3% to 89.3%, a specificity that ranged from 75.0% to 100%, and an accuracy that ranged from 72.2% to 86.1% [23,25,29].

Figure 2: Forest plots of the sensitivity and specificity for TBR_{max} with cut-off of 1.9 to 2.3 (glioma).

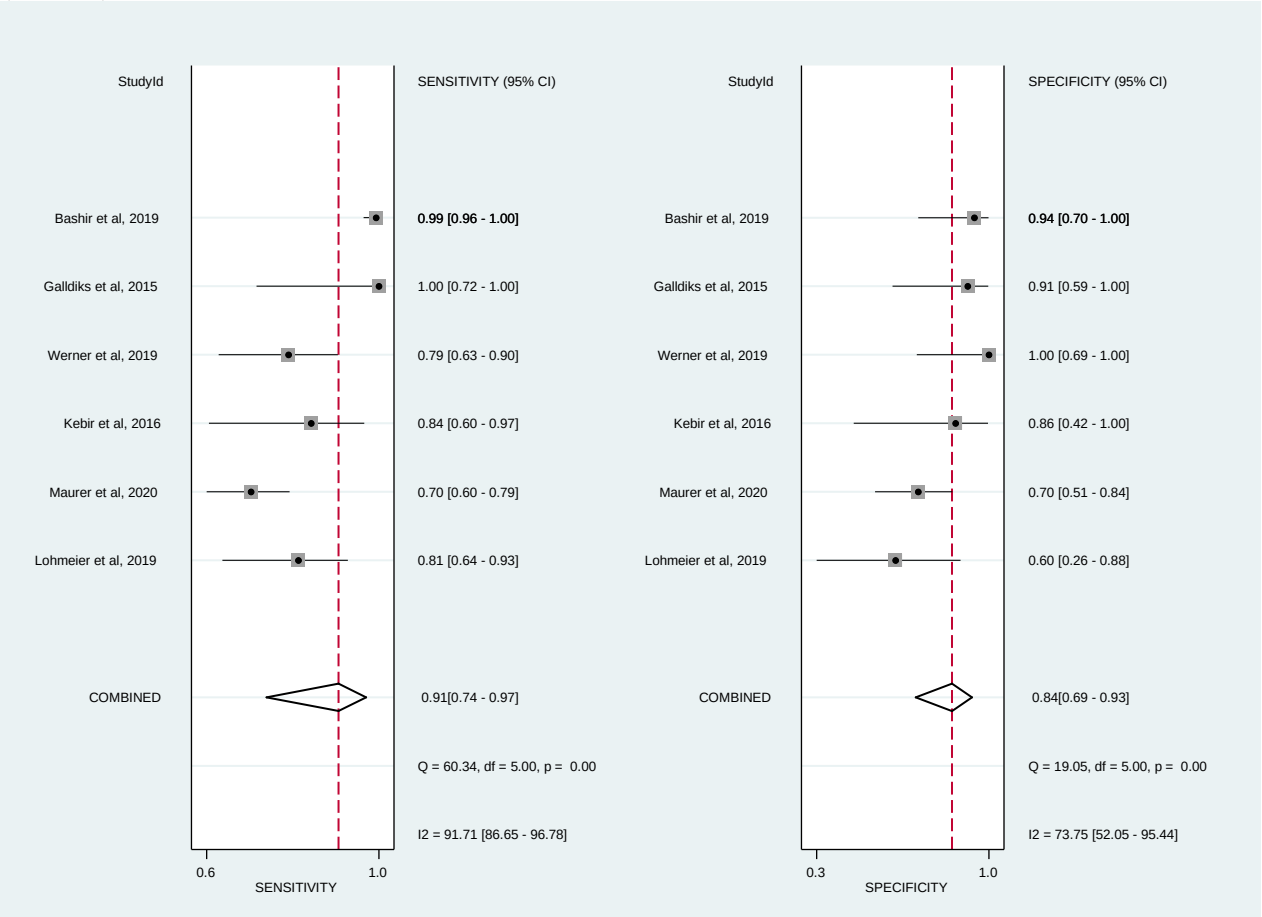
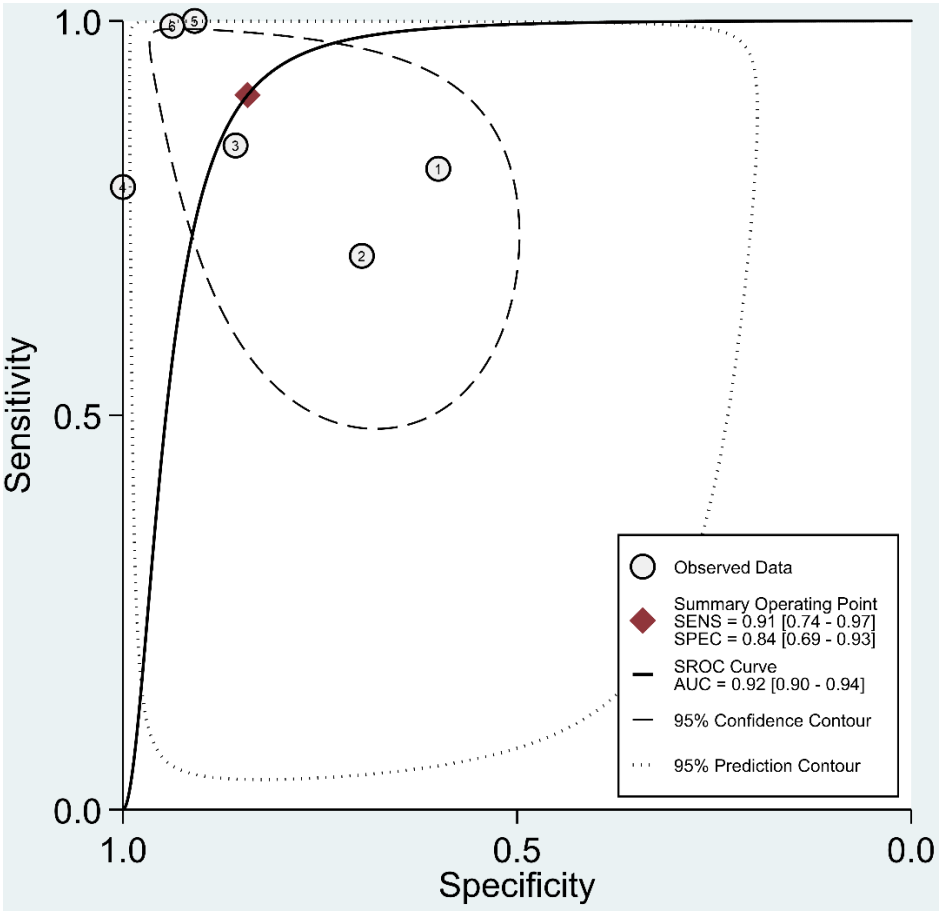


Figure 3: Summary receiver operating characteristic curve for TBR_{max} with cut-off of 1.9 to 2.3 (glioma).



Likewise, the pooled sensitivity and specificity from seven studies [22,24,27-31] that expressed tumour uptake as TBR_{mean} with a cut-off value of 1.8 to 2.3 were 80% (95% CI, 67% to 89%) and 87% (95% CI, 77% to 93%), respectively (Figure 4). Only a significant heterogeneity for sensitivity (I^2=89.6, p<0.001) was detected. The area under the SROC curve was 0.91 (95% CI, 0.88 to 0.93) (Figure 5). One of the studies also obtained early measurements at 10 to 20 minutes after ^{18}F-FET injection and demonstrated a sensitivity of 76.0%, a specificity of 84.6%, and an accuracy of 77.8% using a cut-off value of 1.71 [22]. In two studies that selected higher threshold values, Kertels et al [29] reported a sensitivity of 60.7%, a specificity of 100%, and an accuracy of 69.4% for TBR_{mean} >2.31 and Mihovilovic et al [25] reported a sensitivity of 82.1%, a specificity of 87.5%, and an accuracy of 83.3% for TBR_{mean} >2.98.

Figure 4: Forest plots of the sensitivity and specificity for TBR_{mean} with cut-off of 1.8 to 2.3 (glioma).

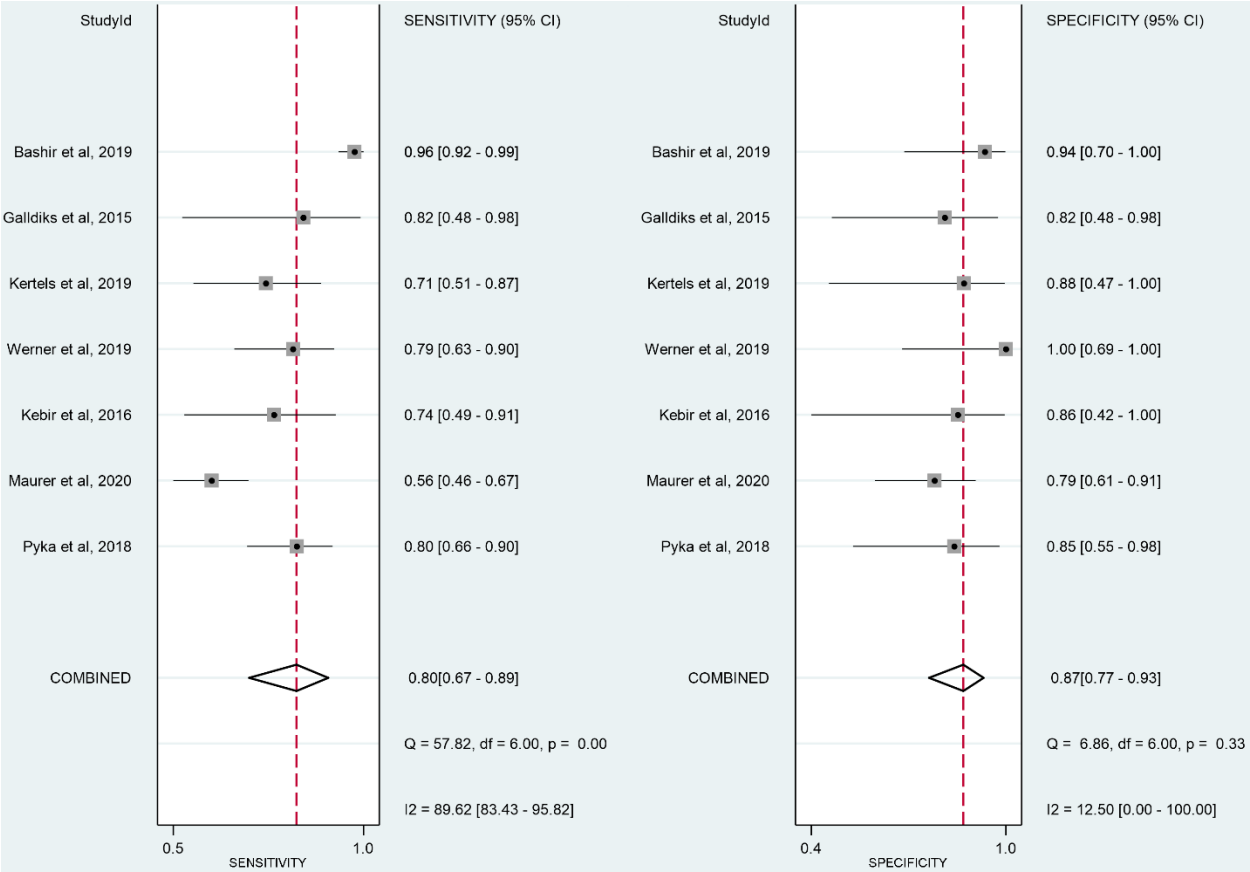
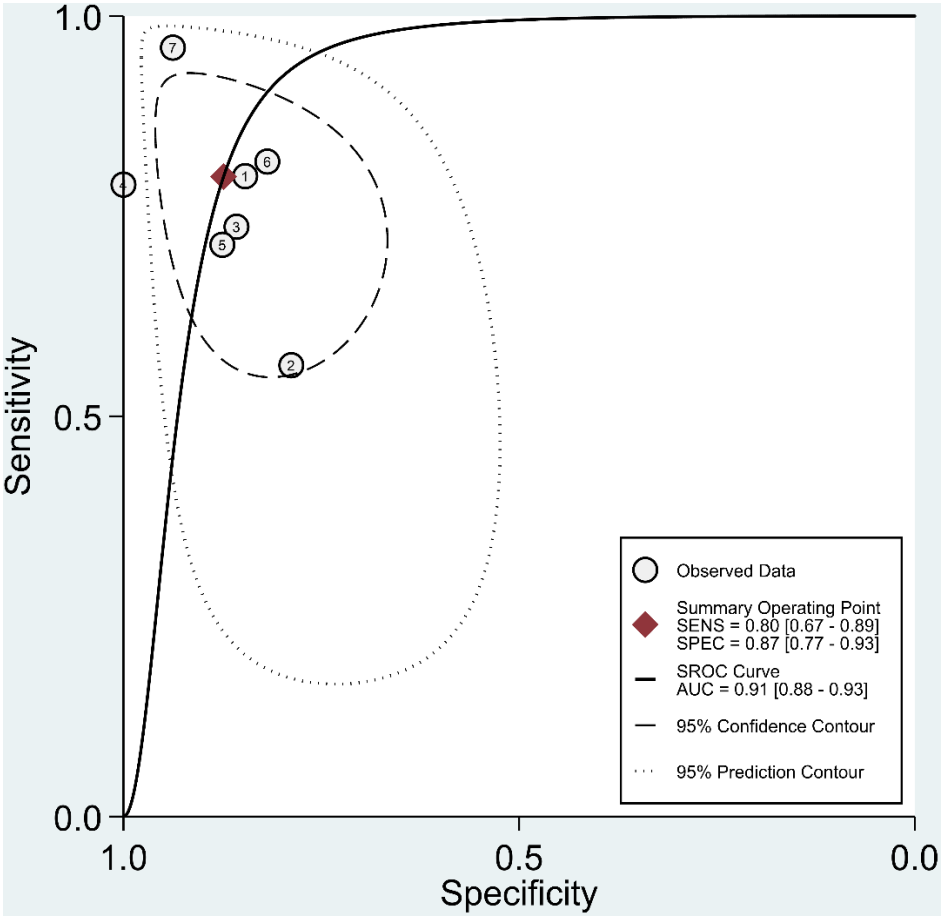


Figure 5: Summary receiver operating characteristic curve for TBR_{mean} with cut-off of 1.8 to 2.3 (glioma).



All additional semiquantitative analysis methods (TBR_{10mm}, TBR_{16mm}, $TBR_{70\%}$, $TBR_{80\%}$, $TBR_{90\%}$, maximum tumoural uptake/ratio to background, and biological tumour volume) yielded a sensitivity that ranged from 71.4% to 98.0%, a specificity that ranged from 75.0% to 100%, and an accuracy that ranged from 77.8% to 97.6% [26,29,31]. As for visual analysis, Verger et al [23] reported a sensitivity, specificity, and accuracy of 76.0%, 57.1%, and 71.9%, respectively, while Popperl et al [26] reported respective values of 94.1%, 71.4%, and 87.5%.

In terms of dynamic ^{18}F-FET PET parameters, the pooled sensitivity and specificity from four studies [24,27,28,30] that utilized time-activity curves (TAC) for ^{18}F-FET uptake in the tumour (curve pattern type II or III) or the slope of the TAC in the late phase of ^{18}F-FET uptake (cut-off value of 0.2 to 0.32 SUV/h) were 72% (95% CI, 56% to 84%) and 78% (95% CI, 60% to 89%), respectively (Figure 6). Significant heterogeneity was observed among the studies for both sensitivity (I^2=73.7%, p=0.01) and specificity (I^2=67.8%, p=0.03). The area under the SROC curve was 0.81 (95% CI, 0.78 to 0.84) (Figure 7). Similar diagnostic performance was achieved when determining the time-to-peak (TTP) of ^{18}F-FET activity from two studies, resulting in corresponding sensitivities, specificities, and accuracies of 64.0%, 76.9%, and 66.7% for TTP <20 min [22], and 69.4%, 80.0%, and 71.7% for TTP <32.5 min [28].

Figure 6: Forest plots of the sensitivity and specificity for TAC or slope (glioma).

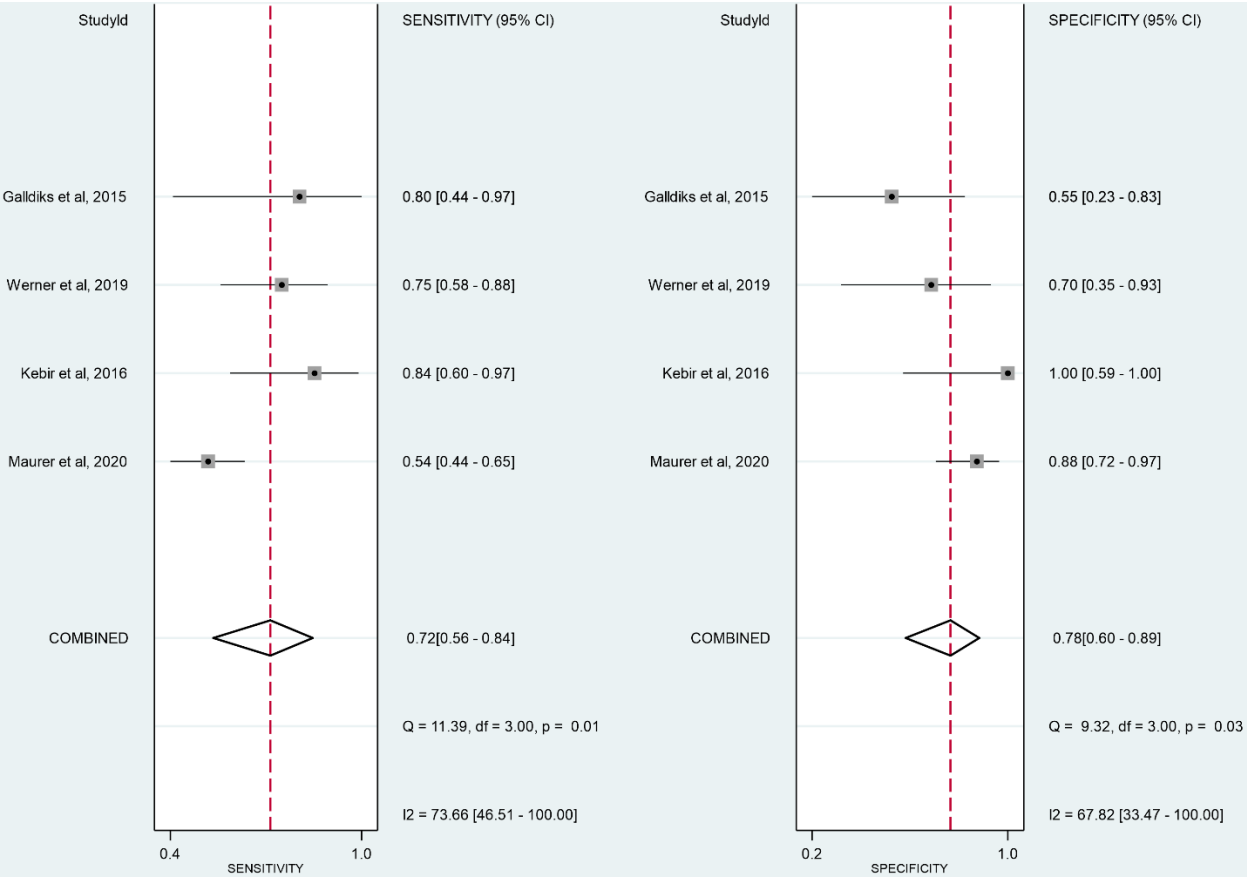
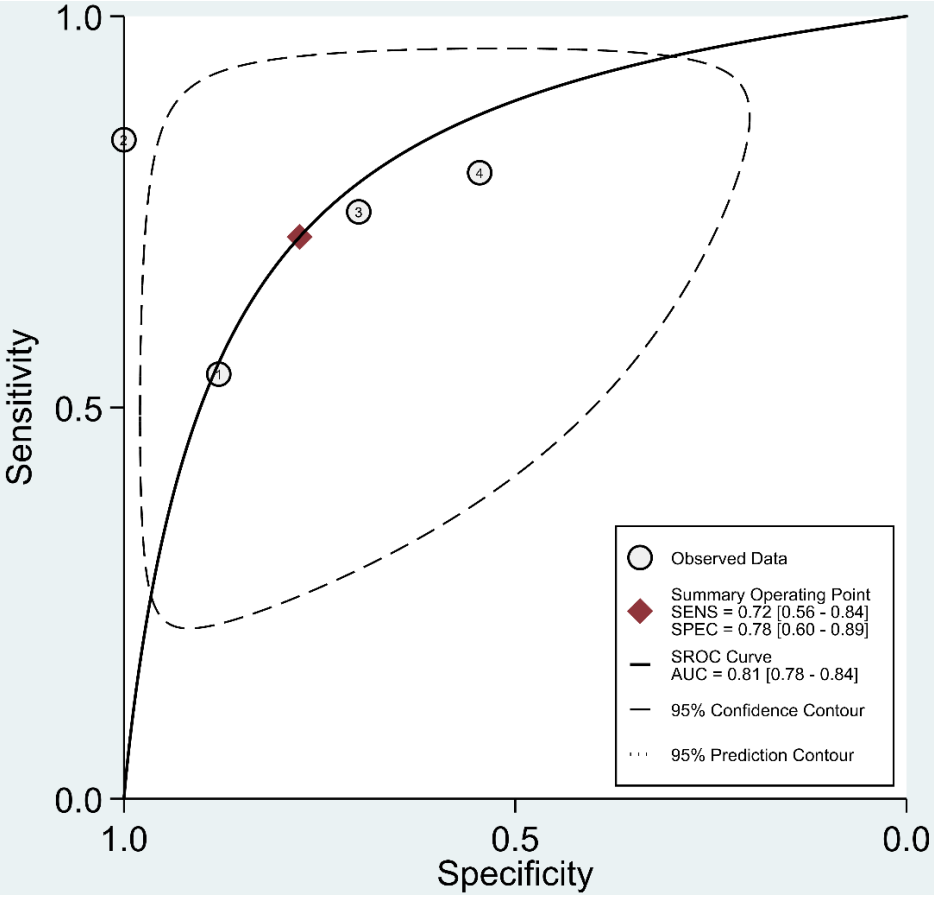


Figure 7: Summary receiver operating characteristic curve for TAC or slope (glioma).



Three of the studies also provided the combined analysis of static and dynamic ^{18}F-FET PET parameters. In particular, combining TBR_{max} >1.95 with slope <0.2 SUV/h revealed a sensitivity of 86.2%, a specificity of 66.7%, and an accuracy of 81.1% [24]. When TBR_{max} >1.95 was combined with slope <0.32 SUV/h, the sensitivity, specificity, and accuracy all improved to 97.2%, 80.0%, and 93.5%, respectively [28]. Furthermore, TBR_{max} or TBR_{mean} >1.95 in combination with TTP <32.5 min revealed a sensitivity of 91.7%, a specificity of 90.0%, and an accuracy of 91.3% [28]. The combined analysis of TBR_{max} >2.3 or TBR_{mean} >2.0 with curve pattern type II or III yielded a sensitivity of 80.0% and 60.0%, respectively, while displaying identical specificity (90.9%). The corresponding accuracies were 85.7% and 76.2% [30].

With respect to diffusion-weighted MRI, the pooled sensitivity and specificity from three studies [21,22,28] that assessed tumour uptake as apparent diffusion coefficient (ADC) values were 61% (95% CI, 52% to 69%) and 79% (95% CI, 62% to 89%), respectively (Figure 8). The I^2 statistic did not reveal the presence of significant heterogeneity for sensitivity (I^2=27.3%, p=0.25) or specificity (I^2=37.0%, p=0.19). The area under the SROC curve was 0.71 (95% CI, 0.67 to 0.75) (Figure 9). For visual assessment of the ADC maps, the sensitivity was 65.8%, the specificity was 70.0%, and the accuracy was 66.7% [28]. The addition of TBR_{max} >1.95 or 2.0 to ADC values increased both the sensitivity (94.7% to 96.9%) and accuracy (88.1% to 89.6%), but at the expense of specificity (60% to 70%) [21,28]. Moreover, fractional anisotropy at an optimal cut-off of 98.9 generated a sensitivity of 64.6%, a specificity of 61.5%, and an accuracy of 63.9% [22]. Perfusion-weighted MRI in the form of corrected (sensitivity, 65.3%; specificity, 76.9%; accuracy, 67.7%) and uncorrected (sensitivity, 61.2%; specificity, 76.9%; accuracy, 64.5%)

relative cerebral blood volume (rCBV) provided similar diagnostic performance. Based on visual analysis of rCBV or relative cerebral blood flow performed comparatively worse, with a sensitivity of 52.0%, a specificity of 57.1%, and an accuracy of 53.1% [23]. Finally, multiparametric analysis that included TBR_{max}, TTP, corrected rCBV, and normalized ADC added value to sensitivity (77.1%), specificity (92.3%), and accuracy (80.3%) [22].

Figure 8: Forest plots of the sensitivity and specificity for ADC maps (glioma).

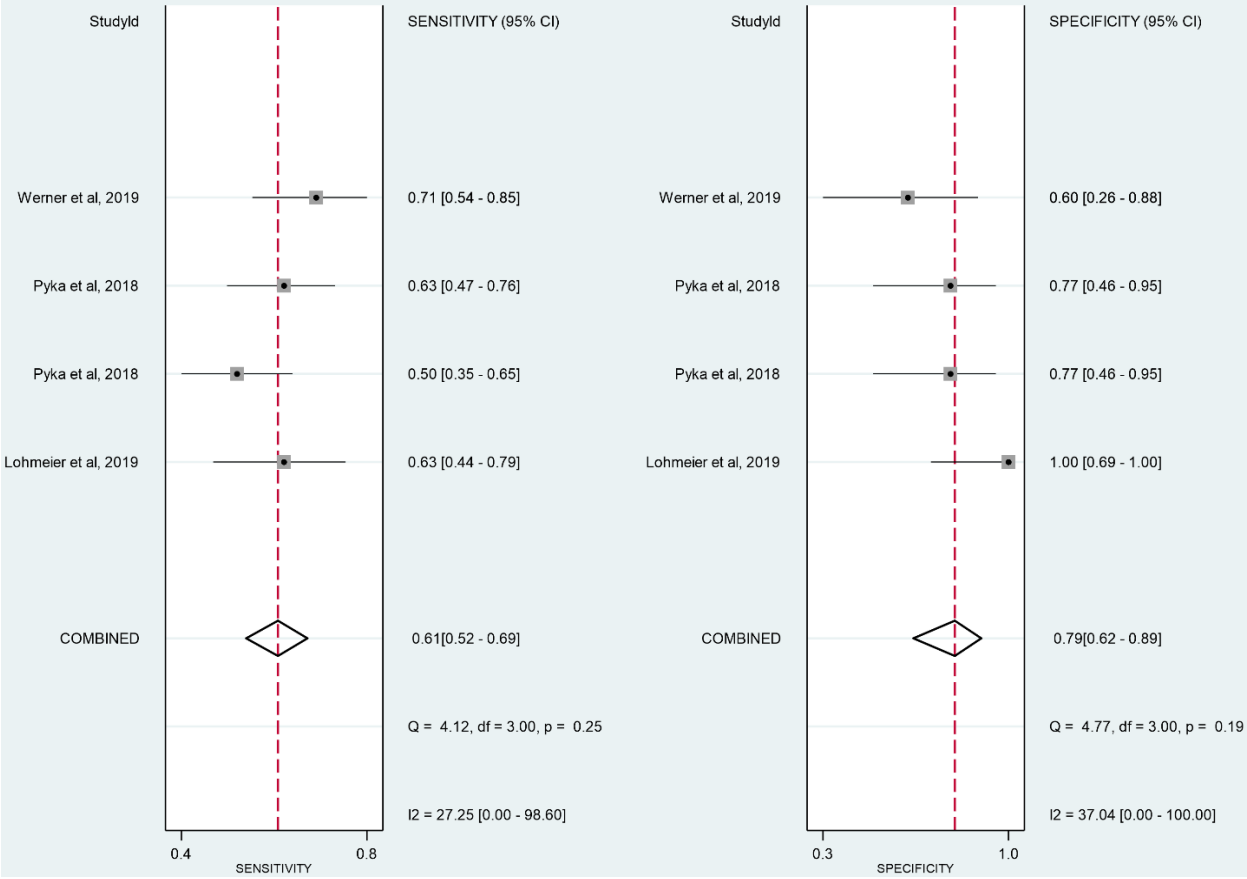
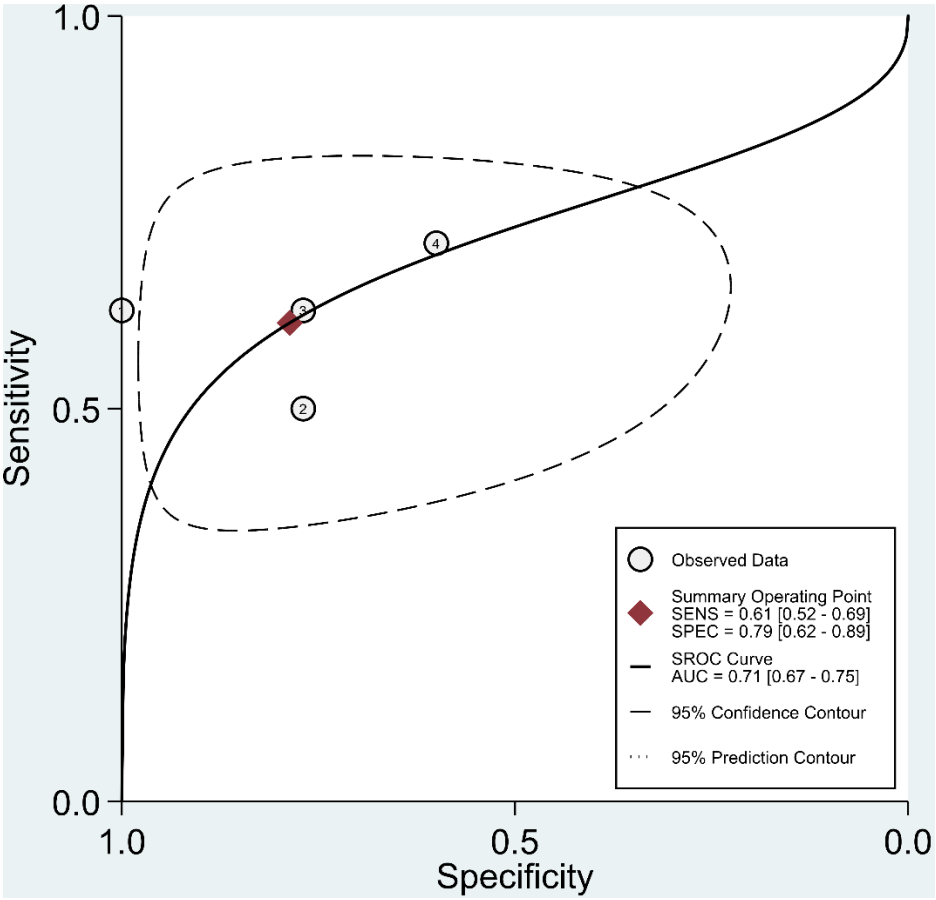


Figure 9: Summary receiver operating characteristic curve for ADC maps (glioma).



Brain metastases

For the differentiation of recurrent brain metastasis from treatment-related changes, five studies investigated the diagnostic performance of ^{18}F-FET PET using various approaches of image analysis. All patients were examined by ^{18}F-FET PET due to having at least one contrast-enhancing lesion on cerebral MRI after radiotherapy [33-36] or radiotherapy in combination with immunotherapy or targeted therapy [32].

For static ^{18}F-FET PET parameters, the pooled sensitivity and specificity from four studies [33-36] that expressed tumour uptake as TBR_{max} with a cut-off value of 2.15 to 3.11 were 82% (95% CI, 74% to 88%) and 82% (95% CI, 74% to 88%), respectively (Figure 10). The I^2 statistic did not reveal the presence of significant heterogeneity for sensitivity (I^2=0%, p=0.93) nor specificity (I^2=0%, p=0.71). The area under the SROC curve was 0.89 (95% CI, 0.86 to 0.92) (Figure 11).

Figure 10: Forest plots of the sensitivity and specificity for TBR_{max} with cut-off of 2.15 to 3.11 (brain metastases).

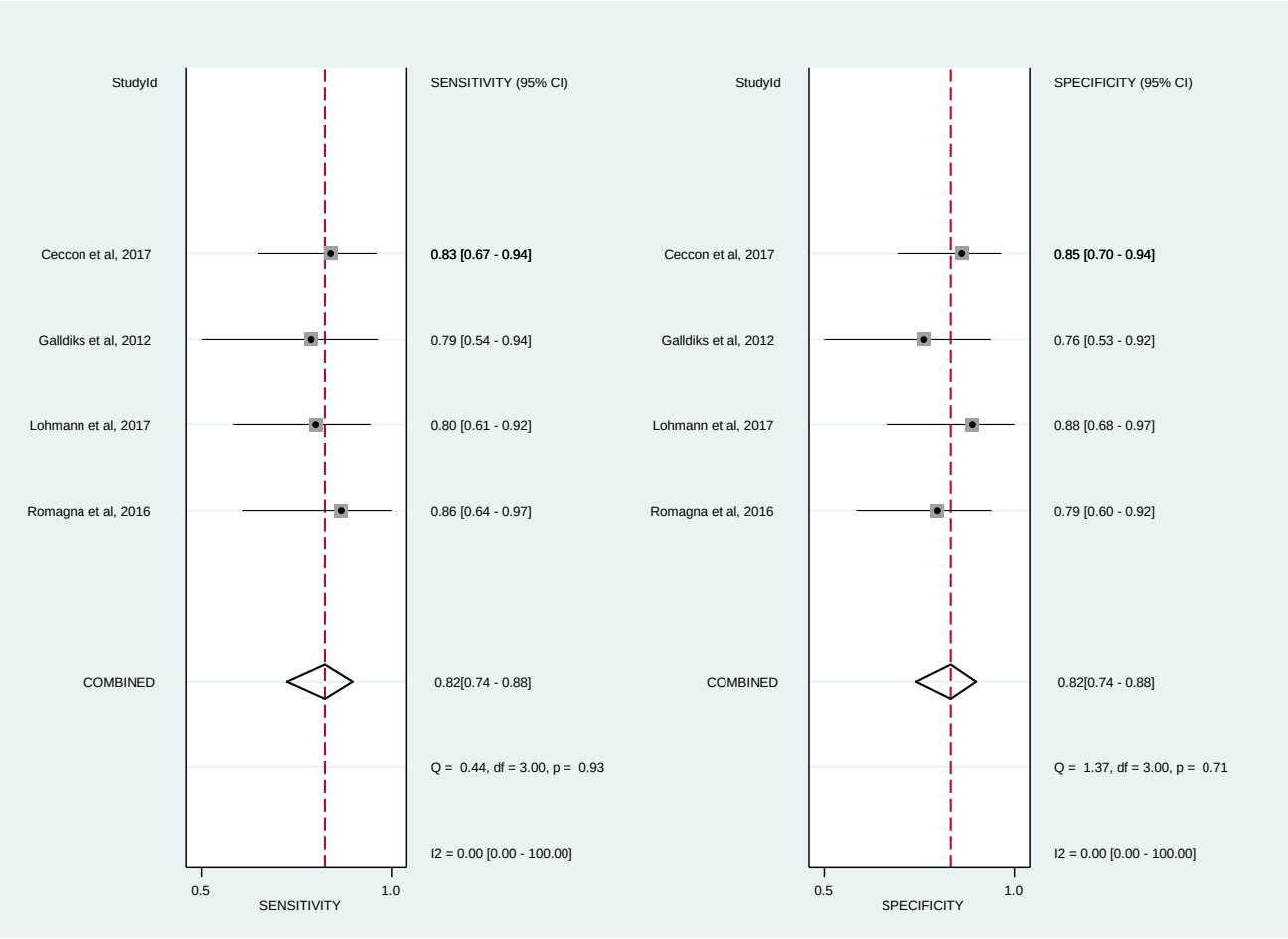
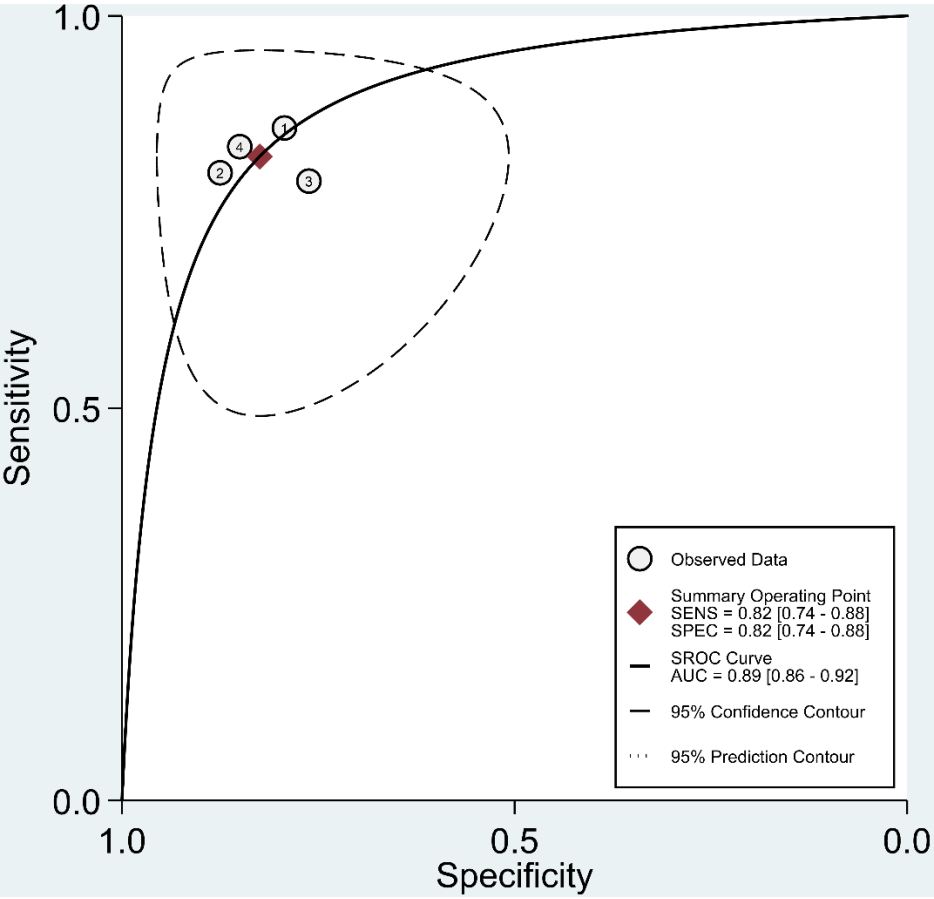


Figure 11: Summary receiver operating characteristic curve for TBR_{max} with cut-off of 2.15 to 3.11 (brain metastases).



Likewise, the pooled sensitivity and specificity from five studies [32-36] that expressed tumour uptake as TBR_{mean} with a cut-off value of 1.95 to 1.99 were 82% (95% CI, 74% to 88%) and 85% (95% CI, 78% to 91%), respectively (Figure 12). The I^2 statistic did not reveal the presence of significant heterogeneity for sensitivity (I^2=0%, p=0.64) nor specificity (I^2=0%, p=0.52). The area under the SROC curve was 0.91 (95% CI, 0.88 to 0.93) (Figure 13). In addition, Lohmann et al [34] demonstrated that the specificity could be increased to 91.7% by combining TBR_{mean} ≥1.99 with TBR_{max} ≥3.11, while maintaining a sensitivity of 80.0% and an accuracy of 85.2%.

Figure 12: Forest plots of the sensitivity and specificity for TBR_{mean} with cut-off of 1.95 to 1.99 (brain metastases).

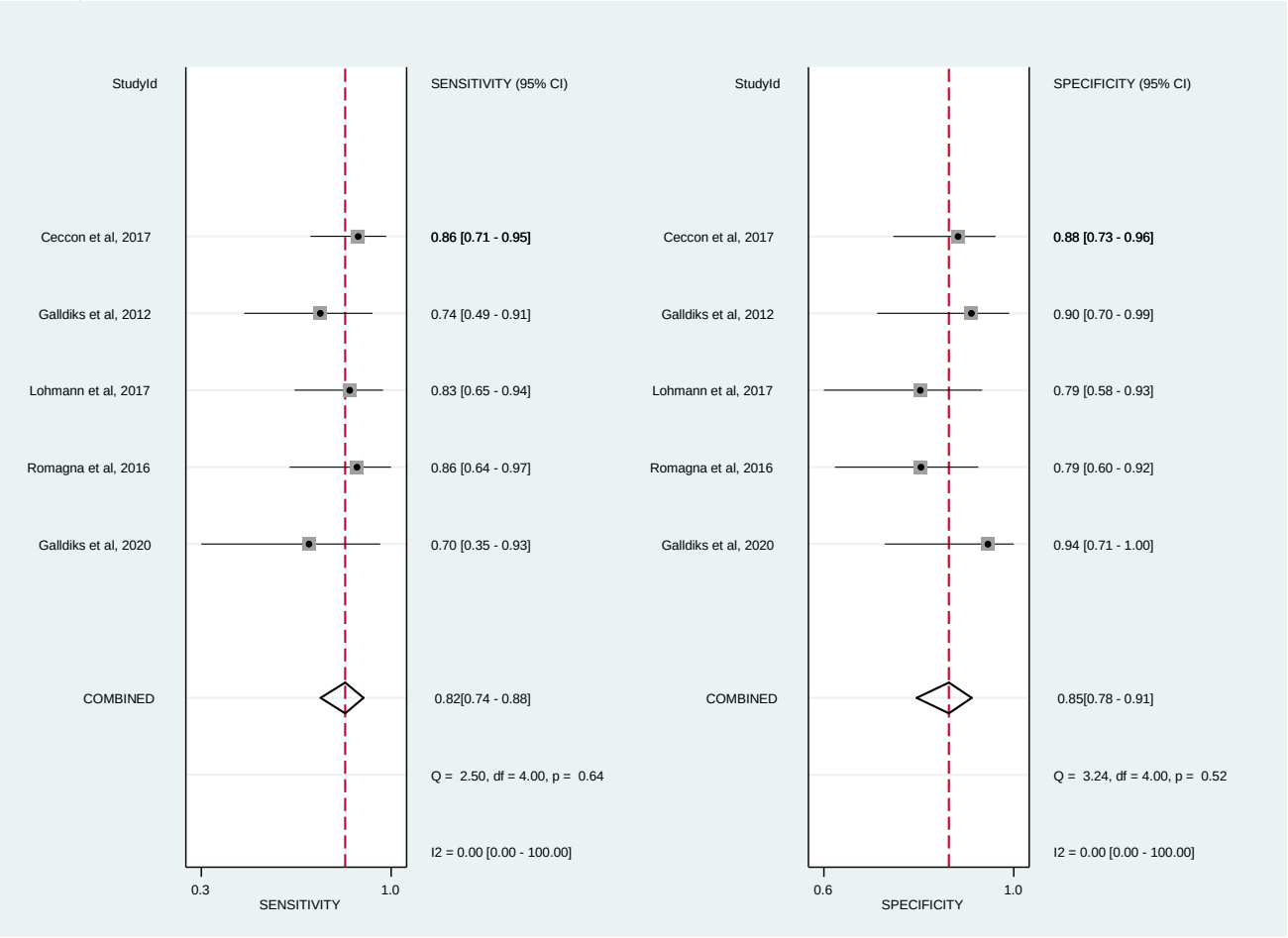
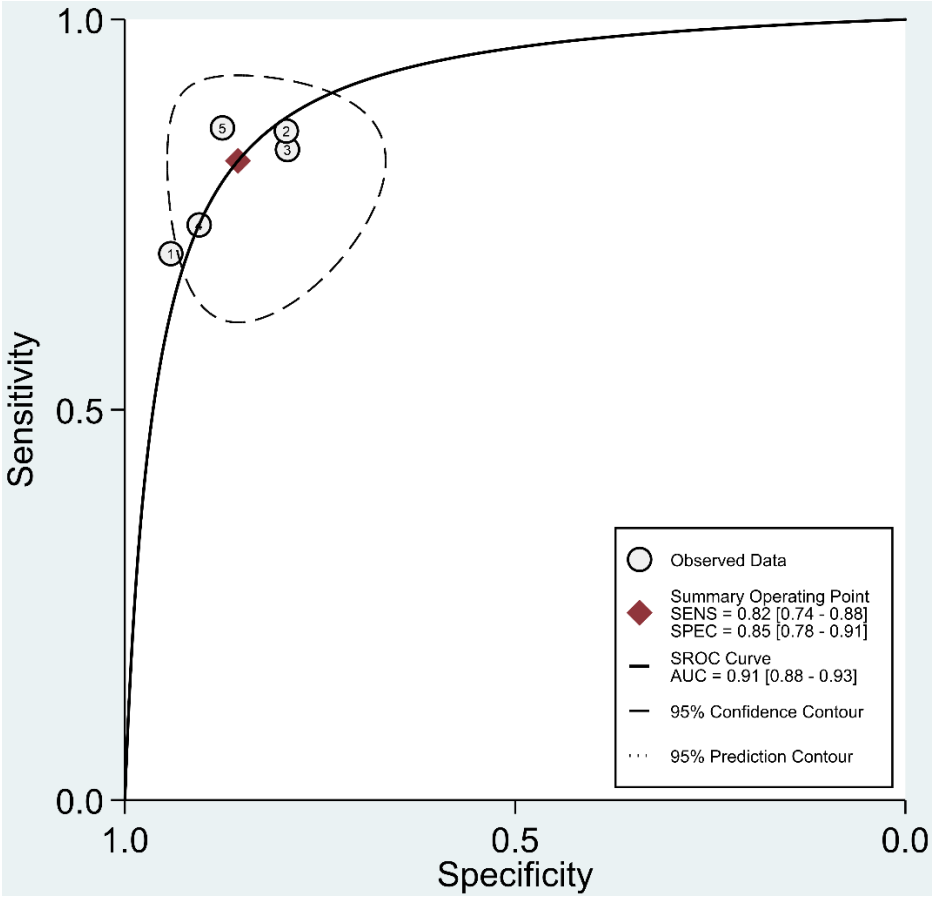


Figure 13: Summary receiver operating characteristic curve for TBR_{mean} with cut-off of 1.95 to 1.99 (brain metastases).



In terms of dynamic ^{18}F-FET PET parameters, the pooled sensitivity and specificity from four studies [33-36] that utilized TAC for ^{18}F-FET uptake in the tumour or the slope of the TAC in the late phase of ^{18}F-FET uptake (cut-off value of 0.125 SUV/h) were 79% (95% CI, 65% to 89%) and 75% (95% CI, 41% to 93%), respectively (Figure 14). Significant heterogeneity was observed among the studies for both sensitivity (I^2=69.7%, p=0.02) and specificity (I^2=82.1%, p<0.001). The area under the SROC curve was 0.84 (95% CI, 0.80 to 0.87) (Figure 15). In contrast, TTP was less sensitive when either a threshold of 27.5 min (sensitivity, 57.1%; specificity, 100%; accuracy, 82.4%) [32] or 32.5 min (sensitivity, 58.3% to 60.0%; specificity, 70.8% to 72.5%; accuracy, 64.8% to 65.8%) [34,36] was applied.

Figure 14: Forest plots of the sensitivity and specificity for TAC or slope (brain metastases).

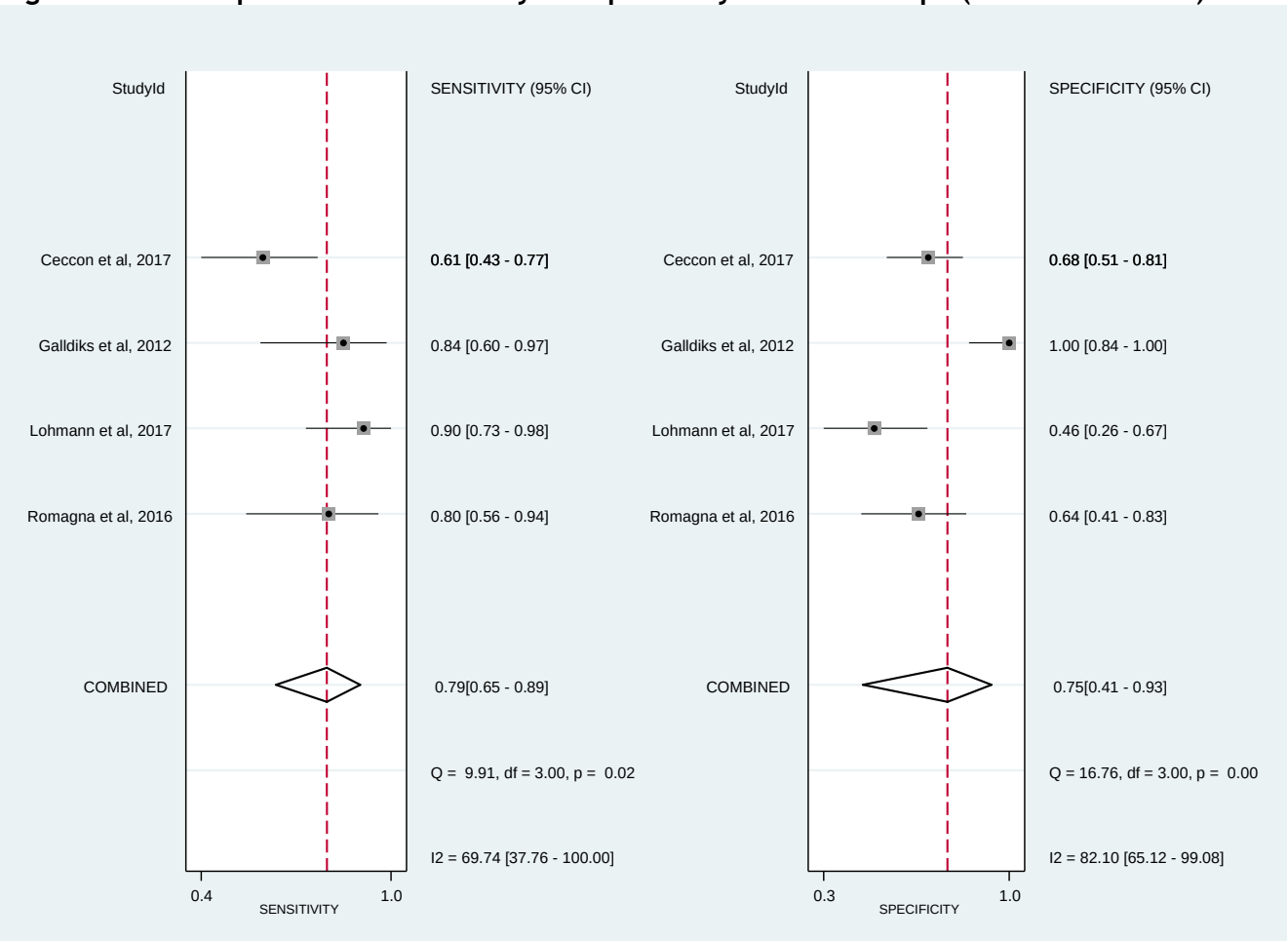
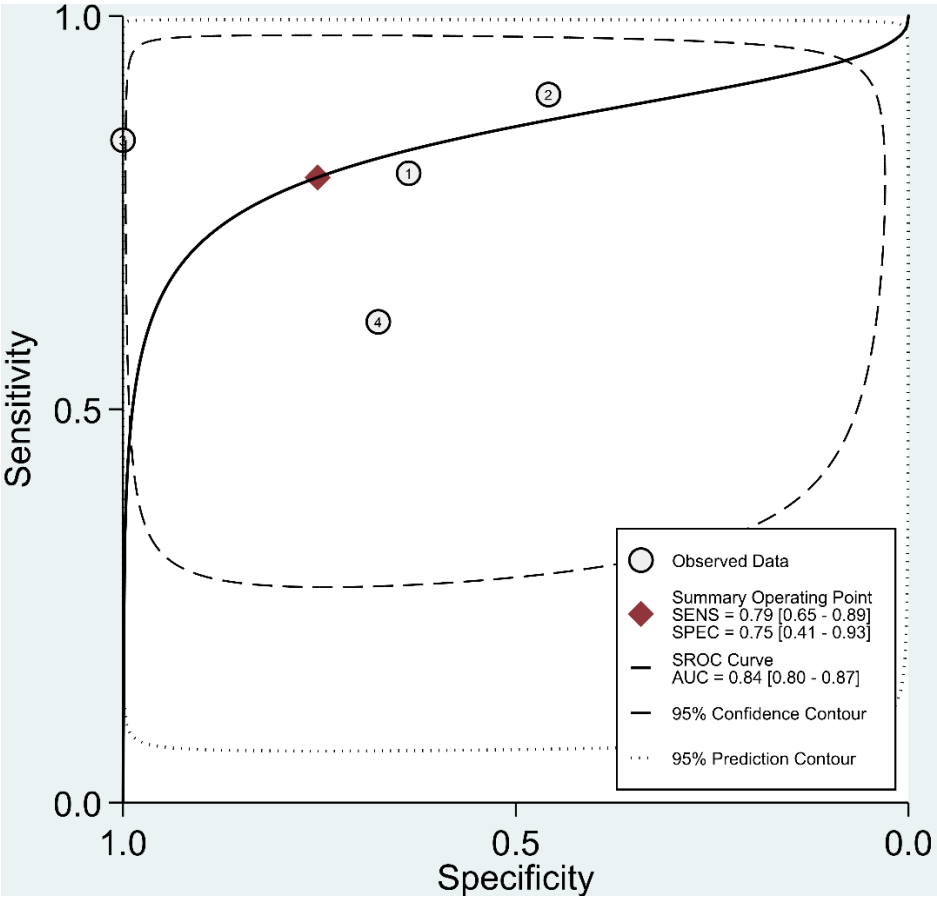


Figure 15: Summary receiver operating characteristic curve for TAC or slope (brain metastases).



All five studies also reported the combined analysis of static and dynamic ^{18}F-FET PET parameters. The presence of TBR_{mean} >1.95 in combination with either TTP <27.5 min (sensitivity, 57.1%; specificity, 100%; accuracy, 82.4%) [32], TAC (sensitivity, 94.7% to 95.0%; specificity, 81.8% to 90.5%; accuracy, 88.1% to 92.5%) [33,35], or slope <0.125 SUV/h (sensitivity, 83.3%; specificity, 92.5%; accuracy, 88.6%) [36] could improve the specificity for differential diagnosis. Likewise, the specificity could be increased with combinations of TBR_{max} >3.11 plus TAC (sensitivity, 73.3%; specificity, 95.8%; accuracy, 83.3%) [34], and TBR_{max} >2.55 plus slope <0.125 SUV/h (sensitivity, 77.8%; specificity, 92.5%; accuracy, 85.5%) [36].

Ongoing, Unpublished, or Incomplete Studies

The National Library of Medicine Database (https://www.clinicaltrials.gov/) was searched on August 3, 2021 for potential trials meeting the selection criteria for this systematic review. There were two ongoing trials identified that would be eligible for inclusion in the update of this evidence summary in the future.

Fluoroethyltyrosine for the Evaluation of Intracranial Neoplasm	
Protocol ID:	NCT04044937
Study type:	Interventional
Estimated enrollment:	199
Last updated:	February 12, 2021

Estimated study completion date:	August 1, 2022
Sponsor:	Thomas Hope, University of California, San Francisco
Status:	Recruiting

Diagnostic Assessment of Amino Acid PET/MRI in the Evaluation of Glioma and Brain Metastases	
Protocol ID:	NCT04111588
Study type:	Observational
Estimated enrollment:	160
Last updated:	December 1, 2020
Estimated study completion date:	October 1, 2024
Sponsor:	Norwegian University of Science and Technology
Status:	Recruiting

DISCUSSION

This review focuses on the use of a novel amino acid transport imaging agent, FET, for the evaluation and management of high-grade brain gliomas and brain metastases. Notably, low-grade gliomas (grades I and II) have been excluded from this analysis. FET has not been used for brain imaging to a great degree in North America but has entered the clinical pathway at some centres in Europe. This imaging agent has also received endorsement through a consensus guidance statement by a consortium of molecular imaging and neuro-oncology societies [37]. Despite growing clinical experience and confidence in the technique, the quality of the evidence is limited, and applicability is challenged by different imaging and analytic techniques applied across different centres with many retrospective studies that are subject to bias.

While MRI represents the standard of care for imaging brain tumours, overtreatment due to false-positive findings suggesting disease recurrence, and undertreatment as seen by out of field recurrence remain major limitations. Based on our review, FET appears to identify areas of disease outside of conventional contrast-enhanced MRI imaging that may impact radiation planning in 39% of cases. While these data lend support for well-designed prospective trials for the use of FET-informed radiation plans, lack of biopsy correlation will continue to be a limitation for future investigations given the impracticality and toxicity of performing brain biopsies. However, prior studies based on neuro-navigated brain biopsies have shown the presence of viable tumour at the site of elevated FET uptake [11].

Compared to MRI, FET provides complementary information regarding treatment response after chemoradiation, as seen through enhanced ability to prognosticate patients. MRI is unable to provide incremental information in this setting but remains standard of care given the lack of alternatives available in current clinical practice although advanced MRI techniques continue to be developed to address this deficiency [38,39]. Much of this benefit likely arises from the ability of FET to cross the blood-brain barrier. Therefore, any perturbation arising from treatment effects does not necessarily affect FET uptake, compared to contrast-enhanced MRI, which is susceptible to these effects.

For the evaluation of the post-treatment mass in the setting of suspected recurrence, variability in imaging analysis, particularly cut-off values, adds uncertainty in our analysis. However, in an effort to overcome this limitation, pooled analyses of both TBR_{mean} (range 1.9-2.3, AUC 0.91) and TBR_{max} (range 1.8-2.3, AUC 0.92) were performed which generated similar results far exceeding the performance of MRI (AUC 0.71) and provide additional support for the effectiveness of FET to discriminate viable tumour from post-treatment effects. Dynamic

analysis has recently been added to static TBR analysis in an effort to improve diagnostic accuracy. Taken alone, analysis of TAC and related parameters provides less favourable performance characteristics compared to TBR (AUC 0.81). However, when combined with TBR analysis, dynamic analysis is able to provide greater diagnostic performance. Both dynamic curve analysis and SUV analysis either in isolation or combined, exceed the performance of MRI ADC maps (AUC 0.71).

Similar to evaluation of primary high-grade gliomas, brain metastases can be subject to both TBR analysis and dynamic analysis. Again, a major limitation is the lack of standard approach to calculating TBR_{mean} and TBR_{max} values, which we elected to pool to facilitate analysis. TBR_{mean} (range 1.95-1.99) provides a high ability to discriminate between treatment related changes and viable tumour (AUC 0.91). TBR_{max} (range 2.15-3.11) provides similar performance (AUC 0.89). Taken together and despite variability in analysis techniques, the overall signal suggests an enhancement over conventional imaging approaches to identify post therapeutic viable tumour. While changes in tumour definition by FET may result in management changes such as surgical resection for true recurrent tumour, or the use of bevacizumab for radiation necrosis, the effect of FET-PET-guided alteration in management on clinical outcomes is unknown. While dynamic analysis provides lower performance alone in comparison to TBR, in combination, these parameters provide high specificity, generally greater than 90%, which may be important to avoid unnecessary re-treatment of brain metastases.

Limitations of this analysis include the retrospective nature of many of the included studies, which may significantly bias our results. The main contributors to study bias include the inability to capture patients who are unable to undergo the examination along with those patients who decline the additional testing due to better health status. The impact of selection bias is unknown but could have significant influence on test results. Many of the included investigations have developed their own cut-off values based on their small cohorts of patients without further validation. This results in variability, which we have attempted to overcome by clustering the values for analysis, which suggest a general trend towards the ability of FET to discriminate post-treatment effects from viable malignancy. Future research should involve prospective trials using standard and agreed-upon threshold values. This is shown both in the setting of primary brain malignancy and brain metastases. In contrast to previous efforts, our approach is unique because we focus on a solitary brain imaging radiotracer, FET, dedicated to treatment planning and management change, prognostication, and evaluation of post-treatment changes in patients with high-grade glioma. To our knowledge, no previous systematic analyses are available for the evaluation of brain metastases with FET.

Future efforts should focus on standardization of techniques, both technical and analytical, with use of simultaneous PET/MRI which is ideally suited for this purpose. This should be followed by validation of these diagnostic parameters in prospective studies with the eventual goal of completing prospective multicentre investigations focused on both quality of life and survival as outcome measures.

CONCLUSIONS

FET imaging may provide incremental diagnostic information compared to standard-of-care imaging in the setting of both primary high-grade gliomas and brain metastases. Based on clustered analysis of existing threshold values for disease, FET appears to provide additional signal for disease activity compared to standard-of-care MRI. However, our overall assessment of this technique remains limited due to study heterogeneity and potential bias and uncertainty related to the design of published investigations. In addition to increased diagnostic performance, FET may inform radiation therapy management plans. In summary, while FET shows promise as a complementary modality to standard-of-care MRI for the management of

primary and metastatic brain malignancies, further study with standardized approaches to image interpretation in well-designed prospective studies are warranted.

INTERNAL REVIEW

The evidence summary was reviewed by Emily Vella and Jonathan Sussman (Scientific Director of PEBC). The Working Group was responsible for ensuring any necessary changes were made.

Acceptance by the Ontario PET Steering Committee

After internal review, the report was presented to the Ontario PET Steering committee. The committee reviewed and formally approved the document on March 24, 2022.

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- Sara Miller for copy editing.

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Appendix 1: Affiliations and Conflict of Interest Declarations

Name	Affiliation	Declarations of interest
Amit Singnurkar, MDCM, MPH, FRCPC Nuclear Medicine Physician	Department of Medical Imaging, University of Toronto, Sunnybrook Health Sciences Centre	No conflict declared
Raymond Poon, MPH Health Research Methodologist	Department of Oncology, McMaster University, Juravinski Hospital Site	No conflict declared
Jay Detsky, PhD, MD, FRCPC Radiation Oncologist	Department of Radiation Oncology, University of Toronto, Sunnybrook Health Sciences Centre	No conflict declared

Appendix 2: Literature Search Strategy

The search was conducted in MEDLINE (1946 to Present), Embase (1974 to 2020 September 17), and Cochrane Database of Systematic Reviews (2005 to September 10, 2020) on September 18, 2020.

MEDLINE and Embase

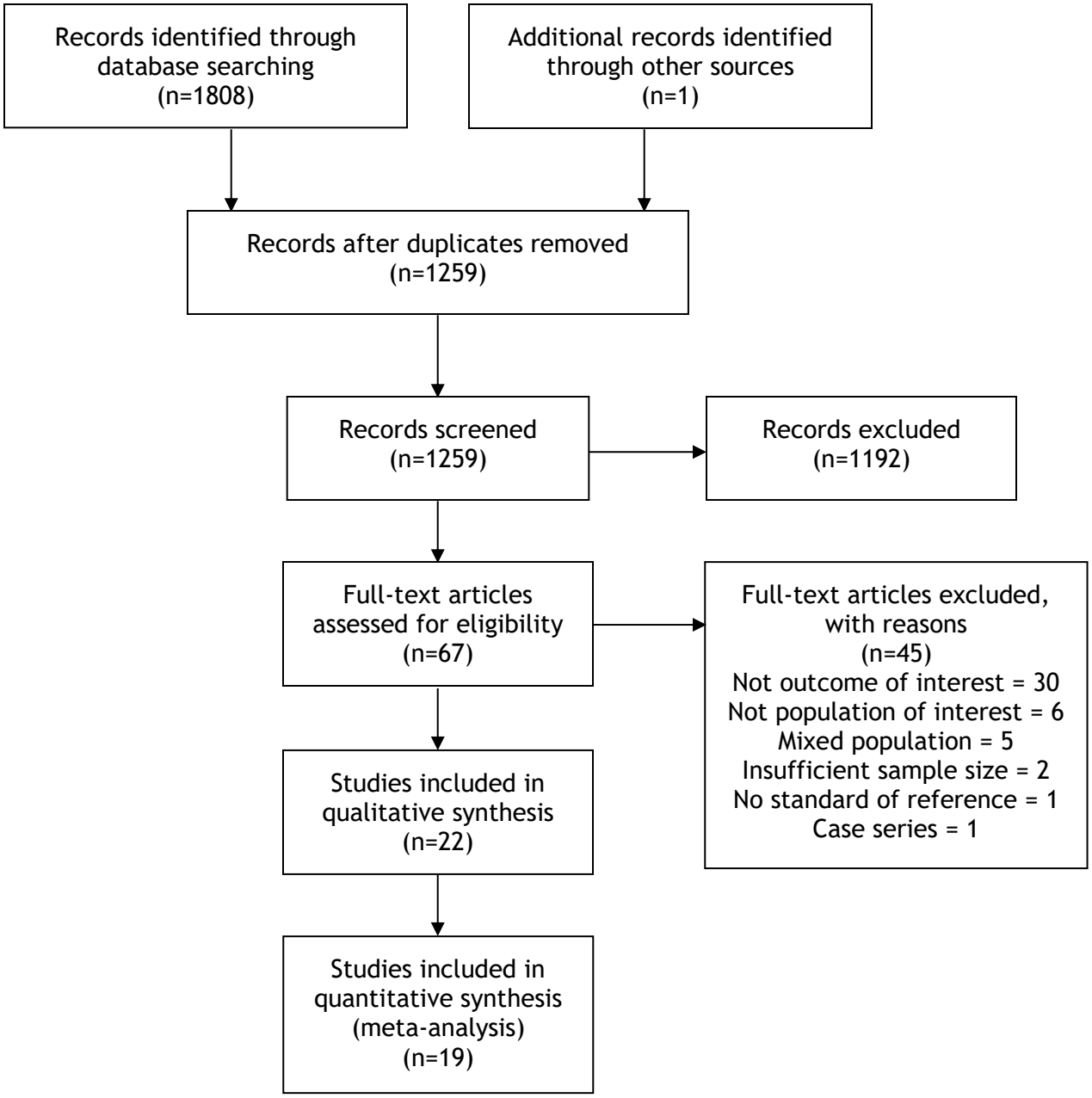
Section A: Disease and/or population	1. exp Brain Neoplasms/ or ((brain or intracranial) adj (cancer$ or tumo?r$ or neoplas$ or metastas$ or malignan$)).mp. or glioma$.mp. or astrocytoma$.mp. or ependymoma$.mp. or oligodendroglioma$.mp. or glioblastoma$.mp. or gbm.mp.
Section B: Intervention or diagnostic test	2. 18f-fluoro-ethyl-tyrosine.mp. or O-2-18f-fluoroethyl-L-tyrosine.mp. or 18f?fet.mp. or fet.mp. or amino acid.mp.
	3. exp Tomography, Emission-computed/
	4. (positron adj emission adj tomograph$).mp.
	5. (pet$ or pet scan$).mp.
	6. or/3-5
	7. 2 and 6
	8. (magnetic resonance imag$ or magnetic resonance spectroscop$).mp.
	9. (dynamic adj4 (MRI or magnet$)).mp.
	10. (diffusion weight$ adj3 (MRI or magnet$)).mp.
	11. (MPMRI or MP-MRI or MR$2 or DWI$ or DW-MRI or DCE$ or NMR$ or fmri).mp.
	12. (T1-weighted or T2-weighted).mp. adj3 imag$.mp.
	13. (MR$1 adj (imag$ or spectroscop$ or scan$ or tomograph$)).mp.
	14. (magnet$ adj (imag$ or spectroscop$ or scan$ or resonance)).mp.
	15. exp Magnetic Resonance Imaging/ or exp Magnetic Resonance Spectroscopy/
	16. or/8-15
	17. 7 and 16
	18. (tomograph$ or ct scan$).mp.
	19. ct.mp.
	20. scan$.mp.
	21. 19 and 20
	22. 18 or 21
	23. 7 and 22
	24. 17 or 23
	25. (positron emission tomography computed tomography or pet ct or pet-ct or pet$ct).mp.
	26. (positron emission tomography magnetic resonance imaging or pet mr$ or pet-mr$ or petmr).mp.
	27. 25 or 26
	28. 2 and 27
	29. 24 or 28
Section C: Exclusion strategy	30. (conference or conference proceeding$ or conference paper$ or in brief or invited comment$).ti,ab.

	31. (editorial or note or letter or erratum or short survey).pt. or abstract report$/ or letter$/ or case stud$/
	32. exp animal/ not (exp human/ or humans/)
	33. or/30-32
Combining Sections A, B, and C	34. 1 and 29
	35. 34 not 33
Limiting the final search by language	36. limit 35 to English language

Cochrane Database of Systematic Reviews

Section A: Disease and/or population	1. ((brain or intracranial) adj (cancer$ or tumo?r$ or neoplas$ or metastas$ or malignan$)).mp. or glioma$.mp. or astrocytoma$.mp. or ependymoma$.mp. or oligodendroglioma$.mp. or glioblastoma$.mp. or gbm.mp.
Section B: Intervention or diagnostic test	2. 18f-fluoro-ethyl-tyrosine.mp. or O-2-18f-fluoroethyl-L-tyrosine.mp. or 18f?fet.mp. or fet.mp. or amino acid.mp.
	3. (positron adj emission adj tomograph$).mp.
	4. (pet$ or pet scan$).mp.
	5. or/3-4
	6. 2 and 5
	7. (magnetic resonance imag$ or magnetic resonance spectroscop$).mp.
	8. (dynamic adj4 (MRI or magnet$)).mp.
	9. (diffusion weight$ adj3 (MRI or magnet$)).mp.
	10. (MPMRI or MP-MRI or MR$2 or DWI$ or DW-MRI or DCE$ or NMR$ or fmri).mp.
	11. (T1-weighted or T2-weighted).mp. adj3 imag$.mp.
	12. (MR$1 adj (imag$ or spectroscop$ or scan$ or tomograph$)).mp.
	13. (magnet$ adj (imag$ or spectroscop$ or scan$ or resonance)).mp.
	14. or/7-13
	15. 6 and 14
	16. (tomograph$ or ct scan$).mp.
	17. ct.mp.
	18. scan$.mp.
	19. 17 and 18
	20. 16 or 19
	21. 6 and 20
	22. 15 or 21
	23. (positron emission tomography computed tomography or pet ct or pet-ct or pet$ct).mp.
	24. (positron emission tomography magnetic resonance imaging or pet mr$ or pet-mr$ or petmr).mp.
	25. 23 or 24
	26. 2 and 25
	27. 22 or 26
Combining Sections A and B	28. 1 and 27

Appendix 3: PRISMA Flow Diagram



Appendix 4: QUADAS-2 Assessment of Study Quality

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
High-grade glioma							
Radiotherapy Planning							
Dissaux et al, 2020 [15]	U	L	L	L	L	L	L
Hayes et al, 2018 [16]	H	L	L	L	L	L	L
Weber et al, 2008 [17]	H	L	L	L	L	L	L
Assessment of Treatment Response							
Galldiks et al, 2012 [18]	L	L	L	L	L	L	L
Galldiks et al, 2018 [19]	U	L	L	L	L	L	L
Buchmann et al, 2019 [20]	L	L	U	L	L	L	L
Recurrence versus Post-Treatment Changes							
Lohmeier et al, 2019 [21]	L	L	U	L	L	L	L
Pyka et al, 2018 [22]	U	L	U	L	L	L	L
Verger et al, 2018 [23]	U	L	H	L	L	L	L
Maurer et al, 2020 [24]	H	L	U	L	L	L	L
Mihovilovic et al, 2019 [25]	L	L	U	L	L	L	L
Popperl et al, 2006 [26]	U	L	U	L	L	L	L
Kebir et al, 2016 [27]	U	L	U	L	L	L	L
Werner et al, 2019 [28]	U	L	U	L	L	L	L
Kertels et al, 2019 [29]	L	L	U	L	L	L	L
Galldiks et al, 2015 [30]	L	L	U	L	L	L	L

Bashir et al, 2019 [31]	L	L	L	L	L	L	L
Brain metastases							
Recurrence versus Post-Treatment Changes							
Galldiks et al, 2021 [32]	U	L	U	L	L	L	L
Romagna et al, 2016 [33]	U	L	U	L	L	L	L
Lohmann et al, 2017 [34]	L	L	U	L	L	L	L
Galldiks et al, 2012 [35]	L	L	U	L	L	L	L
Ceccon et al, 2017 [36]	L	L	U	L	L	L	L

L=Low Risk H=High Risk U=Unclear Risk