Prediction of Meningioma WHO Grade Using PET Findings: A Systematic Review and Meta-Analysis

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ABSTRACT

Background and Purpose: **World Health Organization (WHO) grading of meningiomas reflects recurrence rate and prognosis. Positron emission tomography (PET) investigates metabolic activity, allowing for distinction between low- and high-grade tumors. As preoperative suspicion for malignant meningioma will influence surgical strategy in terms of timing, extent of resection, and risks taken to achieve a total resection, we systematically reviewed the literature on PET-imaging in meningiomas and relate these findings to histopathological analysis.**

Methods: **Searches in PubMed, EMBASE, and The Cochrane Library, from inception to September 2019, included studies of patients who had undergone surgery for a histologically verified intracranial meningioma, with a PET-scan prior to surgery and description of (semi)quantitative PET values for meningiomas from two different WHO groups. Studies comparing more than 1 patient per WHO group were included in the meta-analysis.**

Results: **Twenty-two studies (432 patients) were included. 18fluor-fluorodesoxyglucose (18F-FDG) PET was mostly described to differentiate benign from malignant meningiomas. Pooled data showed differences in mean (95% CI) Standardized Uptake Value (SUV) for WHO II/III compared to WHO I of 2.51 (1.36, 3.66), and in tumor-to-normal (T/N) ratio (T/N ratio) for WHO II/III versus WHO I of .42 (.12, .73).**

Conclusions: **We found that SUV and T/N ratio in 18F-FDG PET may be useful to noninvasively differentiate benign from malignant meningiomas. T/N ratio seems to have a high specificity for the detection of high-grade meningiomas. Other PET tracers were studied too infrequently to draw definitive conclusions. Before treatment strategies can be adapted based on 18F-FDG PET, prospective studies in larger cohorts are warranted to validate the optimal T/N ratio cutoff point.**

Keywords: Meningiomas, WHO grade, positron emission tomography, meta-analysis.

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Introduction

Meningiomas account for approximately one-third of all central nervous system (CNS) tumors, and the incidence increases progressively with age.[1] Ever since the introduction in 1979 of the World Health Organization (WHO) grading system, meningiomas have been a distinct category. In 1993, atypical meningioma (WHO grade II) was introduced into the WHO grading system, and only since 2000, atypical and anaplastic (WHO grade III) meningiomas are clearly defined in terms of histologic criteria.[2] The WHO grade of a meningioma reflects the recurrence rate and prognosis. The 5 years' recurrence rates vary between series and are reported for WHO grades I, II, and III meningiomas to be 5-25%, 30-50%, and 50-94%, respectively.[3–5] Beside on histopathological grade, the recurrence rate of meningiomas also depends on the extent of resection.

Unfortunately, biological aggressiveness, WHO grade, and nowadays also DNA methylation-based classification can only be investigated after surgery.[6,7] Differentiation between low- and high-grade meningiomas using conventional MRI is difficult.[8] Imaging techniques that enable noninvasive, preoperative assessment of tumor biology and WHO grade could potentially be helpful in surgical planning. Suspicion for malignancy in a meningioma will influence timing of surgery, and surgical strategy in terms of extent of resection and the risk a surgeon should take to achieve a total resection, as well as the indication for early postoperative imaging.[9–11]

Positron emission tomography (PET) investigates metabolic activity in tumors and some tracers, for example, in gliomas, even allow for distinction between low- and high-grade tumors.[12] The aim of this study is to systematically review the

available literature on PET imaging in meningiomas and relate these findings to histopathological analysis.

Methods

Literature Search

A literature search was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)-statement.[13] Systematic searches were performed in PubMed, Embase.com, and The Cochrane Library (via Wiley) on September 24, 2019, in collaboration with a medical librarian, to identify all relevant publications. Search terms included indexed terms from MeSH in PubMed, EMtree in EMBASE.com, as well as free text terms. We used free text terms only in The Cochrane Library. Search terms expressing "PET scans" were used in combination with search terms comprising "meningioma." The search was performed without date or language restriction. Duplicate articles were excluded. Reference lists of the included studies were checked to identify additional papers. The full search strategies for all databases are available on request from the corresponding author.

Selection Process

Two reviewers independently screened all titles and abstracts for eligibility. Full text articles were checked for the inclusion and exclusion criteria. Studies were included if they met the following criteria: (i) patients > 18 years old who had undergone surgery for a histologically verified intracranial meningioma; (ii) description of WHO grade; (iii) PET-scan prior to surgery; and (iv) description of (semi)quantitative PET values for meningiomas from at least two different WHO grades. We excluded studies if they were (i) conference abstracts/correspondence; (ii) non-English full text articles; (iii) if the described (semi)quantitative PET values were incomplete (for example, if only elevated PET values of a part of the patient group were described). Differences in judgment regarding inclusion or exclusion were resolved through a consensus procedure. In case of disagreement, a third reviewer was consulted. When there were two publications from the same working group with potentially overlapping patients, we decided to include the study with the largest number of meningioma patients. Studies with potentially overlapping patients for different PET tracers were both included in the analysis.

Data Extraction

One author extracted and processed the relevant data of the selected articles. From each study, information was extracted on: (1) number of patients, (2) tumor characteristics (WHO grade, size), and (3) PET characteristics (Standardized Uptake Value [SUV], tumor-to-normal ratio [T/N ratio], glucose metabolic rate [GMR], scanning technique [static or dynamic]). Some authors were contacted and asked to provide additional data from their published work to include their study in the meta-analysis.

Assessment of Quality

Two reviewers independently evaluated the methodological quality of the full text papers using the Newcastle-Ottawa quality assessment scale for cohort studies (NOS scale),[14] the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2),[15] and critical appraisal of a case study.[16] Differences in judgment were resolved through a consensus procedure. In case of disagreement, a third reviewer was consulted.

The NOS scale was used for cohort studies, the QUADAS-2 for diagnostic studies, and the critical appraisal of a case study was used for studies including 10 patients or less. The NOS scale contains eight items in three categories (selection, comparability, and outcome). To score the ascertainment of exposure, we looked at histopathological diagnosis (category selection). The item "selection of the nonexposed cohort" could only be scored in studies that also assessed a patient group without meningiomas (category selection). The item "demonstration that outcome of interest was not present at start of the study" was not applicable and therefore excluded from the scale for this study (category selection). Studies were awarded with points for the category comparability if a multivariate analysis was performed (one point for tumor volume, two points for multiple variables including tumor volume). To score assessment of outcome, we determined whether PET was performed. Follow-up was considered adequate when PET was performed in 80% or more of the included patients (category outcome). The item "was follow-up long enough for outcomes to occur" was not applicable and therefore excluded from the scale for this study (category outcome). These modifications resulted in a maximum score of six or seven points instead of nine.

For diagnostic studies, we obtained the QUADAS-2 tool, which consists of four key domains: patient selection, index test, reference standard, and flow and timing. Each domain is assessed in terms of risk of bias, and the first three domains are also assessed regarding applicability. Each item that was rated as "low risk of bias" or "low concern regarding applicability" was awarded with one point.

The critical appraisal of a case study tool contains 10 appraisal questions. Studies can be awarded with 10 points in total.

Studies were defined as high-quality studies if they were awarded with $\geq$50% of the maximum amount of points.

Data Analysis

Patients were classified into three groups according to histological diagnosis (meningioma WHO I, II, and III). Differences in SUVs, mean T/N ratio (mean activity of the tumor divided by mean activity of the normal brain), or maximum T/N ratio (maximum activity of the tumor divided by mean activity of the normal brain) among the groups were described. If not provided by the authors, means were calculated for WHO groups.

Studies comparing more than 1 patient per WHO group, with a clear description of the number of patients in each WHO group, were included in the meta-analysis. SUV and T/N ratio values in meningiomas were compared according to WHO grade. Forest plots to present the pooled data were created using Review Manager 5.3. Effect sizes were calculated using random effect models. A subgroup analysis in high-quality studies was also performed. All analyses performed at the patient level were done with SPSS Statistics 25 software. $P < .05$ was considered statistically significant.

Results

Study Characteristics

The literature search generated a total of 1,498 references. After removing all duplicates, 1,106 were screened, leaving

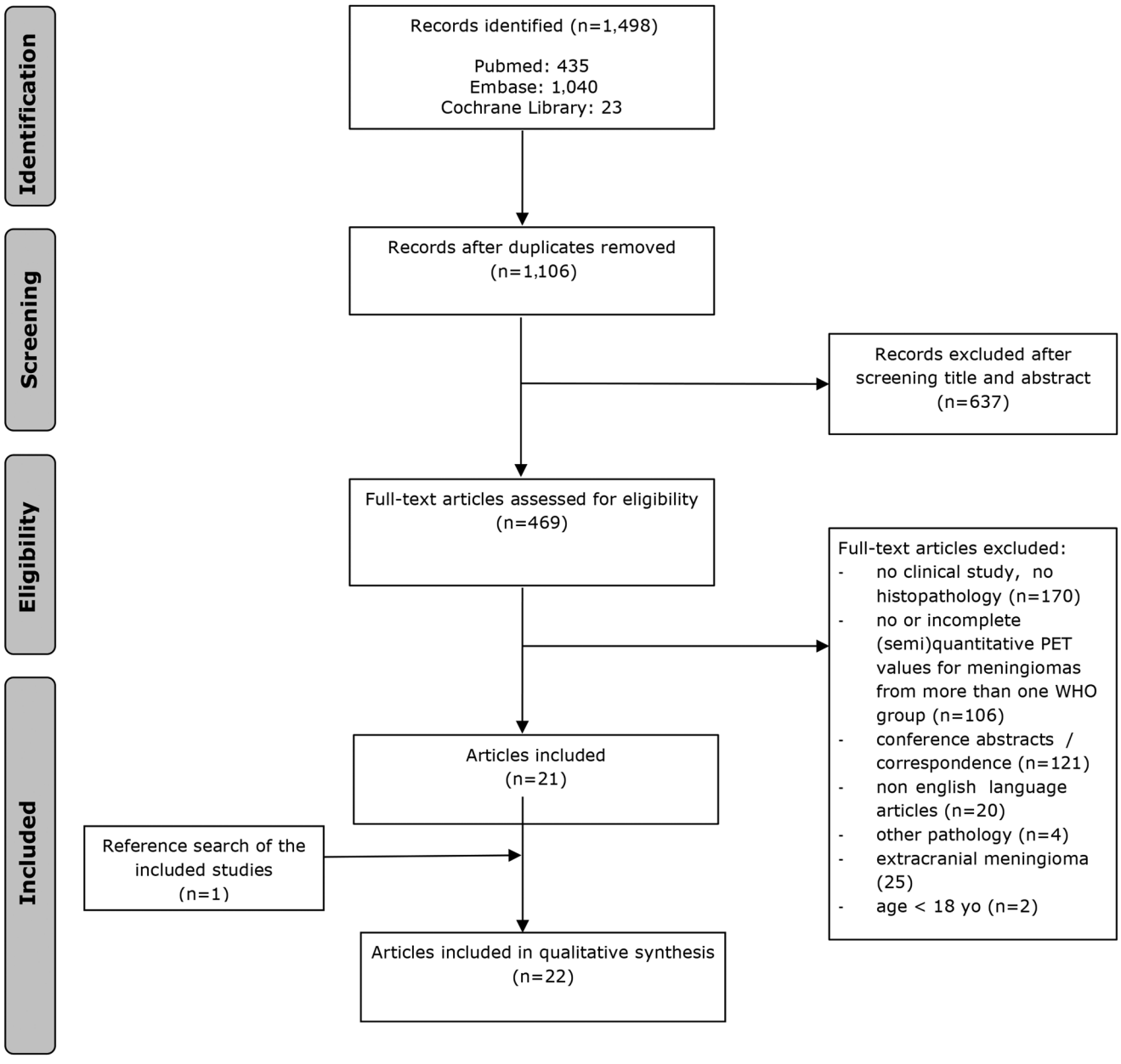


Fig 1. Flowchart of the search and selection procedure of studies.

469 full text papers for review. Finally, 22 studies were included (Fig 1). The most frequent reasons for exclusion were no clear description of histopathology and no description of (semi)quantitative PET values for meningiomas from more than one WHO group. Two publications from Mertens et al describing the same patient group were included since both studies described different PET values (SUV and T/N ratio, respectively).[17,18]

Twenty-two studies described 670 patients with a brain tumor. Four-hundred thirty-two patients harboring a meningioma were included (324 WHO I; 93 WHO II; 15 WHO III). The results of all 22 included studies were reviewed. Out of these 22 studies, 14 could be included in the meta-analysis.

The risk of bias was moderate in most studies. Critical appraisal of a case study was awarded with four points out of 10 and seven points out of 10, respectively, in two studies. The ranges for the NOS scale and for QUADAS-2 were two to six (out of six or seven maximum) and one to six (out of seven maximum), respectively. Only one study received the maximum amount of points (Table 1).

PET Tracers

The PET tracers that were most frequently described to differentiate benign (WHO I) from malignant (WHO II and III) meningiomas were 18fluor-fluorodesoxyglucose (18F-FDG) ($n = 13$) and 11C-methionine (MET) ($n = 3$).

Table 1. Included Studies

Study	Study Design	Number of Patients		WHO Grade			PET	Points for Assessment of Quality (Maximum Points)	Included in Meta-Analysis
		T	*M*	I	II	III			
Arita[10]	Cohort study	51	14	12	2		18F-FDG MET	4 (6)[a]	Yes
Cornelius[9]	Cohort study	24	24	18	3	3	18F-FET	6 (7)[b]	Yes
Di Chiro[21]	Cohort study	17	13	11	1	1	18F-FDG	4 (6)[a]	No
Filss[37]	Cohort study	64	8	6	2		18F-FET	5 (7)[a]	Yes
Giovacchini[24]	Case series	7	7	5	2		18F-FDG 11C-Choline	7 (10)[c]	Yes
Gudjonssona[38]	Case series	8	3	2	1		76Br-Bromide	4 (10) [c]	No
Henn[22]	Cohort study	25	25	21	4		18F-FDG	2 (6)[a]	Yes
Ikeda[39]	Cohort study	37	33	30	3		MET	1 (6)[b]	Yes
Li[40]	Cohort study	21	5	4	1		68Ga-NOTA-PRGD-2	5 (6)[a]	No
Liu[25]	Cohort study	22	12	8	2	2	18F-FDG ACE	5 (7)[a]	Yes
Lee[6]	Cohort study	59	59	43	13	3	18F-FDG	3 (7)[b]	Yes
Mertens[17]	Cohort study	24	2	1	1		18F-FCho	5 (7)[a]	No
Mertens[18]	Cohort study	17	2	1	1		18F-FCho	5 (7)[a]	No
Mitamura[41]	Cohort study	22	22	12	10		18F-FDG MET	4 (6)[a]	Yes
Murakami[42]	Cohort study	23	15	12	3		18F-FDG	5 (7)[a]	Yes
Okuchi[28]	Cohort study	67	67	56	10	1	18F-FDG	2 (6)[b]	Yes
Park[43]	Cohort study	19	19	14	5		18F-FDG	3 (6)[a]	Yes
Rachinger[32]	Cohort study	21	21	16	4	1	68Ga-DOTATATE	5 (7)[b]	No
Sommerauer[44]	Cohort study	23	21	7	11	3	68Ga-DOTATATE	6 (6)[a]	No
Tateishi[27]	Cohort study	34	34	27	7		18F-FDG 18F-Fluoride	2 (6)[b]	No
Xiangsong[26]	Cohort study	11	10	6	4		18F-FDG 13N-NH3	4 (6)[a]	Yes
Yi[45]	Cohort study	74	16	12	3	1	18F-FDG 13N-NH3	5 (7)[a]	Yes
Total		670	432	324	93	15			

Number of patients: *T* = total number of patients in the study; *M* = number of patients with a histologically verified meningioma who underwent a PET scan; WHO = World Health Organization; 13N-NH3 = [13N]Ammonia.
Assessment of quality using: Newcastle-Ottawa Scale,[a] Quality Assessment of Diagnostic Accuracy Studies-2,[b] or critical appraisal of a case study.[c]

O-(2- [18F]fluoroethyl)-L-tyrosine (18F-FET) ($n = 2$), (68Ga)-dodecanetetraacetic acid-tyrosine-3-octreotate (68Ga-DOTATATE) ($n = 2$), 11C-acetate (ACE) ($n = 1$), [13N]Ammonia ([13N]NH3) (13N-NH3) ($n = 2$), 11C-Choline ($n = 1$), 18F-Fluoride ($n = 1$), 76Br-Bromide ($n = 1$), fluorine-18 fluoromethylcholine (18F-FCho) ($n = 2$), and 68Ga-NOTA-PEG4-E[c(RGDfK)] (68Ga-NOTA-PRGD-2) ($n = 1$) were also described. All 22 reviewed studies are presented in Tables 1–4. Dataof 14 studies were pooled and are presented in forest plots (Figs 2–4).

18fluor-Fluorodesoxyglucose

Thirteen studies describing 18F-FDG in meningiomas with different WHO groups included a total of 302 patients (212 WHO I; 58 WHO II; 8 WHO III). In 9 of these 13 studies, PET values (GMR, SUV, and/or T/N ratio) were significantly higher for WHO grades II and III compared to WHO grade I meningiomas. Among those nine studies were the two studies with the largest patient population including 67 and 59 meningiomas patients. Murakami et al performed a dynamic quantitative study to compare T/N ratio between WHO I and II meningioma. K1, K2, and K3 were assessed. K1 (which reflects the transport of 18F-FDG from plasma to tissue) was significantly higher in WHO II than WHO I meningiomas. In all four studies that did not show a significant difference between WHO groups, the comparison was between WHO I and II meningiomas, without WHO III or II/III groups.

One study showed that a T/N ratio (gray matter was used as a normal reference area) of ≥1.0 was the best cutoff value for detecting high-grade meningioma with a specificity of 95% and a sensitivity of 44%.[6]

Eleven studies were included in the meta-analysis (Fig 2). From the study by Murakami et al, the T/N ratios for K1 were used. Forest plots showed significantly higher T/N ratios for WHO II compared to WHO I and WHO II/III compared to WHO I meningiomas (mean difference [95% CI]: .47 [.16, .78] and .42 [.12, .73], respectively). SUV was also found to be significantly higher in WHO II and WHO II/III meningiomas than in WHO I meningiomas (mean difference [95% CI]: 2.10 [.77, 3.42] and 2.51 [1.36, 3.66], respectively).

In the subgroup analysis with high-quality studies, we also found significantly higher T/N ratios for WHO II compared to WHO I and WHO II/III compared to WHO I meningiomas (mean difference [95% CI]: .62 [.23, 1.01] and 1.39 [.62, 2.16], respectively). SUV was found to be significantly higher in WHO II than in WHO I meningiomas (mean difference [95% CI]: 2.14 [.39, 3.88]) as well.

11C-Methionine

MET-uptake related to histopathological meningioma grade has been described in three studies with a total of 74 meningiomas (56 WHO I, 18 WHO II). In two studies, no significant difference was found between WHO I and II meningiomas. Mitamura et al found both SUV_{max} and maximum T/N ratios to be significantly higher when comparing WHO II to WHO I meningiomas ($P = .002$ and $P = .002$, respectively). Pooled data of all 74 patients showed no significant difference in T/N ratio between WHO II and WHO I meningiomas (mean difference [95% CI]: .81 [−1.05, 2.68], Fig 3).

In the subgroup analysis with high-quality studies, we also found no significant difference in WHO II and WHO I meningiomas (mean difference [95% CI]: 1.60 [−.00, 3.21]).

Table 2. PET Tracers: 18F-FDG

Study	Number of Meningioma Patients[a]	WHO Grade I	II	III	II/III	PET	Size of Tumor	SUV or GMR (Mean ± SD)	T/N Ratio (Mean ± SD)	N ORMAL =	*P* (between WHO Grades)
Arita[10] [(b)]	14	12	2			Static			mean T/N .63 ± .09 max T/N 1.06 ± .15 mean T/N .72 ± .22 max T/N 1.19 ± .45	Cerebral cortex	mean T/N I vs. II: P = ns max T/N I vs. II: p = ns
Di Chiro[21]	13	11	1	1	2	Static		GMR 3.86 ± 1.91 [c] GMR 7.5 ± .42 [c]			GMR I vs. II/III: P = .026[c]
Giovacchini[24] [(b)]	7	5	2			Static	29-88 mm[d]	SUV_{max} 5.30 ± .64 [c] SUV_{max} 6.60 ± 2.52 [c]	.93 ± .75 [c] 1.20 ± .43 [c]	Symmetrically in contralateral hemisphere	SUV_{max} I vs. II: P = ns [c] T/N I vs. II: p = ns [c]
Henn[22]	25	21	4			sStatic			.72 ± .22 [c] 1.06 ± .39 [c]	Contralateral cortex	T/N I vs. II: P = ns [c]
Lee[6]	59	43	13	3	16	Static	4.5 ± 1.6 cm		.65 ± .35 .94 ± .40	Gray matter	T/N I vs. II/III: P = .002
Liu[25] [(b)]	12	8	2	2	4	Static		SUV 2.35 ± .91 SUV 3.39 ± 1.41 [c] SUV 6.28 ± .28 [c] SUV 4.83 ± 1.86	.62 ± .18 1.25 ± .78 [c] 3.41 ± 2.57 [c] 2.33 ± 1.99	Contralateral cortex	SUV I vs. II: P = ns [c] SUV I vs. III: P = .044 [c] SUV I vs. II/III: P = .048 [c] T/N I vs. II: P = ns [c] T/N I vs. III: P = .044 [c] T/N I vs. II/III: P = .028 [c]
Mitamura[41] [(b)]	22	12	10			Static	4.03 ± 1.30 cm 4.33 ± 1.14 cm	SUV_{max} 5.76 ± 2.23 SUV_{max} 9.25 ± 2.16	max T/N .62 ± .23 max T/N 1.06 ± .47	Contralateral cortex	SUV_{max} I vs. II: P = .003 max T/N I vs. II: P = .02

(*Continued*)

Table 2. Continued

Study	Number of Meningioma Patients[a]	WHO Grade I	II	III	II/III	PET	Size of Tumor	SUV or GMR (Mean ± SD)	T/N Ratio (Mean ± SD)	N ORMAL =	*P* (between WHO Grades)
Murakami[42]	15	12	3			Dynamic			K1 1.09 ± .38 [c] K2 1.57 ± .85 [c] K3 .98 ±.67 [c] K1 2.07 ± .78 [c] K2 2.57 ± 1.59 [c] K3 1.19 ±.13 [c]		K1 I vs. II: $P = .009$ [c] K2 I vs. II: P = ns [c] K3 I vs. II: P = ns [c]
Okuchi[28]	67	56	10	1	11	Static	27.2-36.8 mm[d] 26.6-48.3 mm[d]	SUV_{max} 5.63 ± 1.64 SUV_{max} 8.16 ± 2.31	max T/N .56 ± .19 max T/N .83 ± .28	Contralateral gray matter	SUV_{max} I vs. II/III: P = .001 max T/N I vs. II/III: $P = .0034$
Park[43]	19	14	5			Static	3.68 ± 1.75 cm 5.24 ± 1.10 cm	3.58 ± 1.74 5.10 ± 3.55	.81 ± .45 .75 ± .53	Contralateral gray matter	SUV I vs. II: P = ns T/N I vs. II: P = ns
Tateishi[27] [b]	24	?	?			Dynamic		SUV_{max} 4.6 ± 1.1 SUV_{max} 7.1 ± 2.6			SUV_{max} I vs. II: $P = .002$
Xiangsong[26] [b]	9	6	3			Static	.9-5.7 cm[d]		1.02 ± .20 [c] 2.37 ± .50 [c]	White matter	T/N I vs. II: $P = .024$ [c]
Yi[45] [b]	16	12	3	1	4	Static			.54 ± .19 1.87 ± .85	Gray matter	T/N I vs. II/III: $P < .001$
Total	302	212	58	8	37						

[a] Number of patients with a histologically verified meningioma who underwent a PET scan.
[b] Study in which multiple PET tracers are assessed.
[c] Calculated using SPSS. *P* values were analyzed using Mann-Whitney test.
[d] Tumor size described as the range of largest dimension of lesions.
WHO= World Health Organization; SD = standard deviation; ns = not significant; GMR = mean glucose metabolic rate; SUV = Standardized Uptake Value; T/N ratio = tumor-to-normal ratio; Tateishi = only total amount of meningioma patients is described.
All the data represent mean ± standard deviation unless otherwise indicated.

Table 3. PET Tracers: MET

Study	Number of Meningioma Patients[a]	WHO Grade I	II	III	II/III	PET	Size of Tumor	SUV or GMR (Mean ± SD)	T/N Ratio (Mean ± SD)	NORMAL =	P (between WHO Grades)
Arita[10, b]	19	14	5			Static	45.1 ± 39.2 ml 46.5 ± 53.4 mL		mean T/N 2.45 ± .67 max T/N 3.74 ± 1.04 mean T/N 2.13 ± .63 max T/N 4.52 ± 1.13	Cerebral cortex	mean T/N I vs. II: P = ns max T/N I vs. II: P = ns
Ikeda[39]	33	30	3			Static			2.99 ± 1.07 [c] 2.35 ± .36 [c]	Gray matter	T/N I vs. II: P = ns [c]
Mitamura[41 b]	22	12	10			Static	4.03 ± 1.30 cm 4.33 ± 1.14 cm	SUV_{max} 5.49 ± 1.02 SUV_{max} 8.7 ± 2.59	max T/N 4.22 ± .93 max T/N 6.64 ± 1.58	Uninvolved frontal cortex	SUV_{max} I vs. II: P = .002 max T/N I vs. II: P = .002
Total	74	56	18								

[a] Number of patients with a histologically verified meningioma who underwent a PET scan.
[b] Study in which multiple PET tracers are assessed.
[c] Calculated using SPSS. P values were analyzed using Mann-Whitney test.
WHO = World Health Organization; SD = standard deviation; ns = not significant; GMR = mean glucose metabolic rate; SUV = Standardized Uptake Value; T/N ratio: tumor-to-normal ratio.
All the data represent mean ± standard deviation unless otherwise indicated.

Other Tracers

For 18F-FET, two studies described T/N ratios for meningiomas from different WHO groups. In the study by Cornelius et al, T/N ratios for late 18F-FET-uptake (20-40 minutes after injection) were significantly higher for WHO III versus WHO I and WHO II/III versus WHO I meningiomas ($P = .017$; $P = .006$, respectively). For the late phase, receiver operating characteristic (ROC) analysis showed that T/N ratio of 18F-FET-uptake had significant power to differentiate low-grade (WHO I) from high-grade (WHO II and III) meningiomas (AUC .87 ± .18, sensitivity 83%, specificity 83%, optimal cutoff 2.3; $P < .01$). Pooled data from the two 18F-FET studies did not reveal a significant difference in T/N ratio between WHO II and WHO I meningiomas (mean difference [95% CI]: .28 [−.01, .57], Fig 4). All studies in this pooled data analysis for 18F-FET were of high quality.

For 68Ga-DOTATATE, a neuronavigation-guided biopsy study has been performed in 21 patients. Preoperative MR-imaging and 68Ga-DOTATATE PET scans were fused and used to obtain 115 biopsies during tumor resection. 68Ga-DOTATATE was not found to be useful in noninvasively grading meningiomas. Another study with 21 patients harboring 25 meningiomas showed a different result. SUV_{max} was significantly lower for WHO II versus WHO I, and for WHO II/III versus WHO I ($P = .0003$; $P = .0003$, respectively). Unfortunately, these two studies could not be pooled because of missing information regarding standard deviations of one study.

For ACE, 13N-NH3, 11C Choline, 76Br-Bromide, and 68Ga-NOTA-PRGD2, no significant differences in PET uptake were found. One study, in which different WHO grades were compared after injection with 18F-Fluoride, was included. A significant difference was found for SUV_{max} between 27 WHO I and 7 WHO II meningiomas with higher uptake values in the WHO II group ($P = .034$).

Mertens et al published two papers describing 18F-FCho in space-occupying lesions in the brain. Only two of the patients had a meningioma. Both SUV and T/N ratio were lower in the patient with a WHO II compared to the patient with a WHO I meningiomas.

Discussion

We systematically reviewed the available literature on PET-imaging in meningiomas and related this to histopathological analysis. After pooling all data, 18F-FDG PET seems useful to noninvasively differentiate benign from malignant meningiomas. Both SUV and T/N ratio are significantly higher in high-grade compared to low-grade meningiomas. These findings were confirmed when performing a subgroup analysis in high-quality studies only. However, larger patient cohorts are warranted to validate the optimal T/N ratio cutoff point before pre- and postsurgical strategies can be adapted.

For patients in whom an atypical or malignant tumor is suspected (because of rapidly progressive growth and/or neurological deficits) and the tumor resection is expected to be difficult, 18F-FDG PET could be useful in the preoperative planning. A high T/N ratio may influence surgical strategy in terms of timing and it may help a surgeon to carefully weigh up the risk of a wide resection (including dural tail and a rim of seemingly nor-

Table 4. PET Tracers: Other Tracers

Study	Number of Meningioma Patients[a]	WHO Grade I	II	III	II/III	PET	Size of Tumor	SUV or GMR (Mean ± SD)	T/N Ratio (Mean ± SD)	NORMAL =	*P* (between WHO Grades)
18F-FET											
Cornelius[9]	24	18	3	3	6	Dynamic			EP: 3.52 ± .86 [c] LP: 2.1 ± .22 [c] EP: 3.43 ± .75 [c] LP: 2.4 ± .26 [c] EP: 3.2 ± .44 [c] LP: 2.5 ± .2 [c] EP: 3.32 ± .56 [c] LP: 2.45 ± .22 [c]	Contralateral brain (including gray and white matter)	mean T/N ratio Early phase: [c] I vs. II, I vs. III, II vs. III, I vs. II/III: P = ns Late phase: I vs. II: P = ns [c] I vs. III: P = .017 [c] II vs. III: P = ns [c] I vs. II/III: P = .006 [c]
Filss[37]	8	6	2			Dynamic	7.81-37.86 ml 4.9-16.28 ml Range of tumor volumes measured on MRI		mean T/N 2.32 ± .33 [c] mean T/N 2.52 ± .47 [c]	Contralateral brain (including gray and white matter)	mean T/N I vs. II: P = ns [c]
Total	32	24	5	3	6						
68Ga-DOTATATE											
Rachinger[32]	21	16	4	1	5	Static		SUV_{max} 9.9 SUV_{max} 10.3			SUV_{max} I vs. II/III: P = ns
Sommerauer[44]	21 patients with 25 tumors	7	11	3	14	Dynamic	63-31,777 mm^3 Range of tumor volumes measured on MRI	SUV_{max} 29.30 ± 23.44 [c] SUV_{max} 6.65 ± 4.30 [c] SUV_{max} 8.37 ± 2.99 [c] SUV_{max} 6.99 ± 4.04 [c]			SUV_{max} I vs. II: P = .0003 [c] SUV_{max} II vs. III: P = ns [c] SUV_{max} I vs. III: P = ns [c] SUV_{max} I vs. II/III: P = .0003 [c]
Total	42	23	15	4	19						

Continued

Table 4. *Continued*

ACE											
Liu[25, b]	12	8	2	2	4	Static		2.75 ± 1.52 1.94 ± 1.04 [c] 4.46 ± .16 [c] 3.20 ± 1.58	3.07 ± 1.43 3.90 ± .69 [c] 5.21 ± .52 [c] 4.55 ± .90	Contralateral cortex	SUV I vs. II: P = ns [c]SUV I vs. III: P = ns[c]SUV I vs. II/III: P = ns T/N I vs. II: P = ns [c]T/N I vs. III: P = ns [c]T/N I vs. II/III: P = ns
13N-NH3											
Xiangsong[26, b]	10	6	4			Static	.9-5.7 cm[d]		7.30 ± 3.07 [c] 7.50 ± .85 [c]	White matter	T/N I vs. II: P = ns [c]
Yi[45, b]	16	12	3	1	4	Static			3.47 ± 1.28 3.76 ± 2.02	Gray matter	T/N I vs. II/III: P = ns
Total	26	18	7	1	4						
11C-Choline											
Giovacchini[24]	7	5	2			Static	29-88 mm[d]	SUV_{max} 3 ± .80 [c] SUV_{max} 5.25 ± .86 [c]	6.31 ± 1.23 [c] 6.47 ± 1.34 [c]	Symmetrically in contralateral hemishere	SUV_{max} I vs. II: P = .021[c] T/N I vs. II: P = ns [c]
18F-Fluoride											
Tateishi[27, b]	34	27	7			Dynamic		SUV_{max} 10.7 SUV_{max} 16.5			SUV_{max} I vs. II: P = .034

Continued

Table 4. *Continued*

76Br-Bromide								
Gudjonssona[38]	3	2	1	Dynamic	9, 29, 45 cc Tumor volumes measured on MRI or CT		1.95 ± 2.33 [c] 3.2	Cortex mirror area
18F-FCho								
Mertens[17]	2	1	1	Dynamic			max T/N 28.86 max T/N 11.64	Contralateral frontal lobe
Mertens[18]	2	1	1	Static		SUV_{max} 5.81 SUV_{max} 2.87	35.25 22.31	Contralateral frontal lobe
Total	2	1	1					
^{68}Ga-NOTA-PRGD2								
Li[40]	5	4	1	Static		SUV_{max} 3.87 ± 2.70 [c] SUV_{max} 5.68	16.16 ± 12.56 [c] 15.35	

[a] Number of patients with a histologically verified meningioma who underwent a PET scan.
[b] Study in which multiple PET tracers are assessed.
[c] Calculated using SPSS. *P* values were analyzed using Mann-Whitney test.
[d] Tumor size described as the range of largest dimension of lesions,
WHO = World Health Organization; SD = standard deviation;
ns = not significant; GMR = mean glucose metabolic rate; SUV = Standardized Uptake Value; T/N ratio = tumor-to-normal ratio; EP = early phase; LP = late phase.
All the data represent mean ± standard deviation unless otherwise indicated.

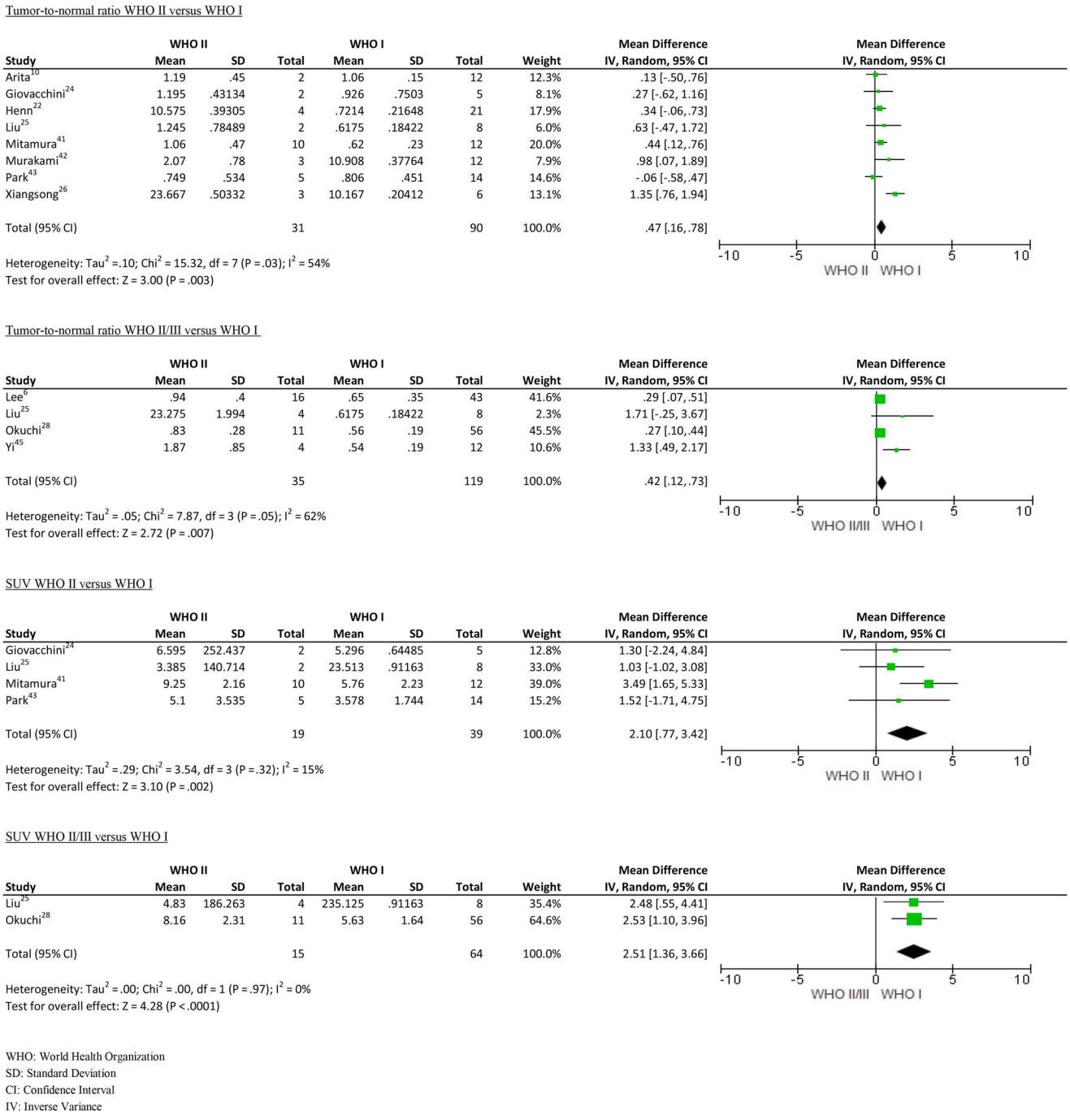
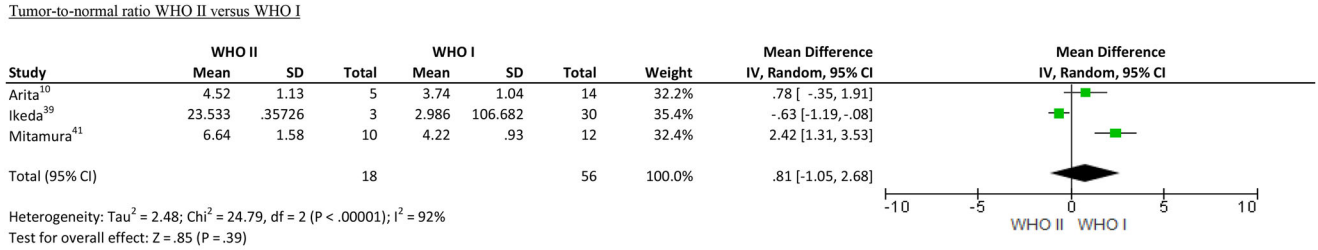


Fig 2. Pooled data 18F-FDG.

mal dura),[19,20] to the risk of recurrences for high-grade meningiomas.

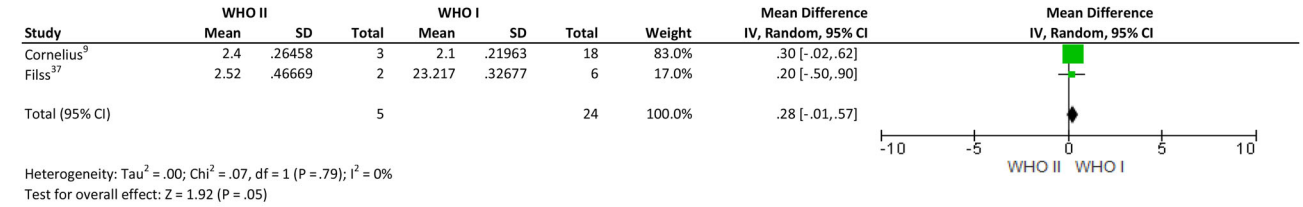
In this review, 18F-FDG as a tracer was represented most frequently since 18F-FDG is a widely used tracer in oncological PET-imaging and has been available for decades. Whether 18F-FDG-uptake is related to biological aggressiveness of meningiomas has been reported inconsistently.[10,21–27] Overall, we found that studies with a larger number of patients are more likely to show a significant difference in 18F-FGD-uptake between different WHO groups. Studies in which patients from WHO group II and III are combined also tend to show a significant difference more often compared to studies that asses the difference in 18F-FDG-uptake between WHO I and II meningiomas.[6,28] This was also found in the study by Lippitz et al, in which the relative tumor 18F-FDG-uptake (tumor/contralateral cortex) was significantly different between WHO I and WHO II/III meningiomas in 48 meningiomas. Uptake values for the different WHO groups were not available in the manuscript; therefore, this study was not included in our review.[29]

For 18F-FDG, a T/N ratio threshold of 1.05 in primary meningiomas and .85 in tumor recurrences has been proposed for the detection of higher tumor grading. This results in a specificity of .88 and a negative-predictive value of .98. Specificity



WHO: World Health Organization
SD: Standard Deviation
CI: Confidence Interval
IV: Inverse Variance

Fig 3. Pooled data MET.



WHO: World Health Organization
SD: Standard Deviation
CI: Confidence Interval
IV: Inverse Variance

Fig 4. Pooled data 18F-FET.

was found to be even higher (.96) in subjects who had fastened overnight before the PET was performed.[23] Lee et al revealed that a T/N ratio of 1.0 was the best cutoff value for detecting high-grade meningioma with a specificity of 95%.[6] Because of the low number of high-grade meningiomas, the reported sensitivity and positive predictive values are low.

An important disadvantage of 18F-FDG is its high uptake in gray matter that may result in low T/N ratios. Furthermore, in slow growing tumors such as meningiomas, which may exhibit a moderately increase in glucose metabolism, 18F-FDG PET may not reliably detect meningiomas.[30] It has been shown that fastening overnight before the PET is performed increases its specificity for the detection of higher tumor grading.[23] Since the 18F-FDG-uptake is affected by blood glucose levels, due to competitive inhibition, a SUV_{max} corrected by the blood glucose level (SUV_{gluc}) may also be a method to increase the accuracy of 18F-FDG PET in detecting the presence of high-grade tumors.[31] The influence of fasting and blood glucose levels on SUV and T/N ratio needs to be studied further. Moreover, we need to assess which normal reference area (gray or white matter) should be used for the T/N ratio to increase its value in detecting high-grade meningiomas.

Besides 18F-FDG, the other tracers in this review were studied sparingly, and included small numbers of patients. Therefore, it is difficult to conclude whether or not those tracers are useful to differentiate benign from malignant meningiomas. For 18F-FET, a T/N ratio of 2.3 has been proposed as a cutoff point to differentiate low-grade (WHO grade I) from high-grade (WHO grade II or III) meningiomas (AUC .87 ± .18, sensitivity 83%, specificity 83 %). In Rachinger's biopsy study as described earlier in this manuscript, no difference for 68Ga-DOTATATE SUVmax was found between WHO I and II/III meningiomas. ROC analysis for SUVmax for tumor versus tumor free tissue also showed an optimal cutoff value of 2.3.[9,32] Unfortunately, these cutoff points have not been validated in other studies.

In addition to the importance of a preoperative estimation of the WHO grade of a meningioma, tumor extension and its relation to surrounding tissue is important to achieve a safe and maximally extensive resection of the tumor. MET is an amino acid analog tracer with a high uptake in meningiomas, but a low uptake in the normal cortex, resulting in a better delineation of meningiomas than when 18F-FDG is used.[30,33] 11C-Choline is also a tracer with hardly any uptake in normal cortex, resulting in a better visibility of tumor extension in choline compared to 18F-FDG.[24] For the detection of intrasellar invasion of meningiomas, 18F-FET can be useful as 18F-FET does not accumulate in the pituitary gland.[33] Furthermore, 68Ga-DOTATOC PET has been shown to be more sensitive than MRI in detecting meningiomas.[34] Thus, PET that provides additional information regarding tumor delineation (evaluation of tumor invasion in surrounding dura mater) can also be of great value, especially when this can be integrated into neuronavigation systems. A tracer that binds to malignant cells but not to normal cortex or meninges is ideally required but currently does not exist. Molecular imaging with PET using zirconium-89 (89Zr)-labeled monoclonal antibodies visualizes and quantifies uptake of radiolabeled monoclonal antibodies. As meningiomas have a leaky blood-brain barrier, it may be possible in the future to

use zirconium-89 (89Zr)-labeled monoclonal antibodies to detect malignant meningioma cells.[35]

Some limitations need to be addressed. First, it proved difficult to obtain additional information from some authors regarding individual patient PET values in order to include more studies in the meta-analysis. Second, (semi-)quantitative PET values depend on multiple variables (eg, fasting time before infection, PET protocol [dynamic or static], tumor size, delineation of the tumor, tumor location, timing of the scan, tracer dose, used reference area [gray or white matter]). As a normal reference area, gray matter was used in the majority of the studies. Some studies, however, did not clarify their normal reference area. It was not possible to integrate all those variables in our analyses, although they may have influenced the pooled results. Lastly, some of the included studies have a high risk of bias.

The Response Assessment in Neuro-Oncology (RANO) Working Group published evidence-based recommendations for the use of PET-imaging in the diagnosis and follow-up of patients with meningiomas to guide clinicians from all disciplines involved in the management of patients with these tumors.[36] They concluded that up to then, only preliminary evidence for a potential benefit of PET for noninvasive meningioma grading was present (evidence level 3). Our systematic review includes more recent studies, with additional information.

In conclusion, analysis of the available literature regarding PET as a diagnostic tool to estimate the WHO grade of a suspected meningioma showed that glucose consumption of meningiomas assessed by 18F-FDG PET might be useful preoperatively, but evidence is low. 18F-FDG PET T/N ratio seems to have a high specificity for the detection of high-grade meningiomas. This, in turn, can influence timing of surgery, the surgical strategy in terms of extent of resection, and risks taken to achieve a total resection.

All other tracers in this review have been studied with too low patient numbers to recommend the use of those tracers for preoperative differentiation of benign from malignant meningiomas.

Future prospective studies in larger patient cohorts are necessary to confirm the role of 18F-FDG in the detection of high-grade meningiomas. Validating the optimal T/N cutoff point and assessing whether preoperative PET-grading leads to improved survival rates for patients with WHO II or III meningioma will be necessary.

References

1. Ostrom QT, Gittleman H, Truitt G, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the united states in 2011–2015. Neuro Oncol 2018;20:iv1-iv86.
2. Scheithauer BW. Development of the WHO classification of tumors of the central nervous system: a historical perspective. Brain Pathol 2009;19:551-64.
3. Claus EB, Bondy ML, Schildkraut JM, et al. Epidemiology of intracranial meningioma. Neurosurgery 2005;57:1088-95.
4. Rogers L, Gilbert M, Vogelbaum MA. Intracranial meningiomas of atypical (WHO grade II) histology. J Neurooncol 2010;99:393-405.
5. Jaaskelainen J, Haltia M, Servo A. Atypical and anaplastic meningiomas: radiology, surgery, radiotherapy, and outcome. Surg Neurol 1986;25:233-42.
6. Lee JW, Kang KW, Park SH, et al. 18F-FDG PET in the assessment of tumor grade and prediction of tumor recurrence in intracranial meningioma. Eur J Nucl Med Mol Imaging 2009;36:1574-82.
7. Sahm F, Schrimpf D, Stichel D, et al. DNA methylation-based classification and grading system for meningioma: a multicentre, retrospective analysis. Lancet Oncol 2017;18:682-94.
8. Hsu CC, Pai CY, Kao HW, et al. Do aggressive imaging features correlate with advanced histopathological grade in meningiomas? J Clin Neurosci 2010;17:584-7.
9. Cornelius JF, Stoffels G, Filss C, et al. Uptake and tracer kinetics of O-(2-(18)F-fluoroethyl)-L-tyrosine in meningiomas: preliminary results. Eur J Nucl Med Mol Imaging 2015;42:459-67.
10. Arita H, Kinoshita M, Okita Y, et al. Clinical characteristics of meningiomas assessed by (1)(1)C-methionine and (1)(8)F-fluorodeoxyglucose positron-emission tomography. J Neurooncol 2012;107:379-86.
11. Slot KM, Verbaan D, Bosscher L, et al. Agreement between extent of meningioma resection based on surgical Simpson grade and based on postoperative magnetic resonance imaging findings. World Neurosurg 2018;111:e856-62.
12. Dunet V, Pomoni A, Hottinger A, et al. Performance of 18F-FET versus 18F-FDG-PET for the diagnosis and grading of brain tumors: systematic review and meta-analysis. Neuro Oncol 2016;18:426-34.
13. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 2009;62:e1-34.
14. Wells G SB, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2015. Available at: www.ohri.ca/programs/clinical_epidemiology/oxford.asp. September 24, 2019.
15. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529-36.
16. Critical appraisal of a case study. In: Center for Evidence-Based Management. Available at: www.cebma.org/wp-content/uploads/Critical-Appraisal-Questions-for-a-Case-Study.pdf. September 24, 2019.
17. Mertens K, Bolcaen J, Ham H, et al. The optimal timing for imaging brain tumours and other brain lesions with 18F-labelled fluoromethylcholine: a dynamic positron emission tomography study. Nucl Med Commun 2012;33:954-9.
18. Mertens K, Ham H, Deblaere K, et al. Distribution patterns of 18F-labelled fluoromethylcholine in normal structures and tumors of the head: a PET/MRI evaluation. Clin Nucl Med 2012;37:e196-203.
19. Slot KM, Verbaan D, Uitdehaag BM, et al. Can excision of meningiomas be limited to resection of tumor and radiologically abnormal dura mater? Neuronavigation-guided biopsies of dural tail and seemingly normal dura mater, with a review of the literature. World Neurosurg 2014;82:e832-6.
20. Kinjo T, al-Mefty O, Kanaan I. Grade zero removal of supratentorial convexity meningiomas. Neurosurgery 1993;33:394-9.
21. Di Chiro G, Hatazawa J, Katz DA, et al. Glucose utilization by intracranial meningiomas as an index of tumor aggressivity and probability of recurrence: a PET study. Radiology 1987;164:521-6.
22. Henn W, Cremerius U, Heide G, et al. Monosomy 1p is correlated with enhanced in vivo glucose metabolism in meningiomas. Cancer Genet Cytogenet 1995;79:144-8.
23. Cremerius U, Bares R, Weis J, et al. Fasting improves discrimination of grade 1 and atypical or malignant meningioma in FDG-PET. J Nucl Med 1997;38:26-30.
24. Giovacchini G, Fallanca F, Landoni C, et al. C-11 choline versus F-18 fluorodeoxyglucose for imaging meningiomas: an initial experience. Clin Nucl Med 2009;34:7-10.
25. Liu RS, Chang CP, Guo WY, et al. 1–11C-acetate versus 18F-FDG PET in detection of meningioma and monitoring the effect of gamma-knife radiosurgery. J Nucl Med 2010;51:883-91.

26. Xiangsong Z, Xingchong S, Chang Y, et al. 13N-NH3 versus F-18 FDG in detection of intracranial meningioma: initial report. Clin Nucl Med 2011;36:1003-6.
27. Tateishi U, Tateishi K, Shizukuishi K, et al. 18F-Fluoride PET/CT allows detection of hyperostosis and osseous involvement in meningioma: initial experience. Clin Nucl Med 2013;38: e125-31.
28. Okuchi S, Okada T, Yamamoto A, et al. Grading meningioma: a comparative study of thallium-SPECT and FDG-PET. Medicine 2015;94:e549.
29. Lippitz B, Cremerius U, Mayfrank L, et al. PET-study of intracranial meningiomas: correlation with histopathology, cellularity and proliferation rate. Acta neurochir Suppl 1996;65:108-11.
30. Valotassiou V, Leondi A, Angelidis G, et al. SPECT and PET imaging of meningiomas. Sci World J 2012;2012:1-11.
31. Nozawa A, Rivandi AH, Kesari S, et al. Glucose corrected standardized uptake value (SUVgluc) in the evaluation of brain lesions with 18F-FDG PET. Eur J Nucl Med Mol Imaging 2013;40:997-1004.
32. Rachinger W, Stoecklein VM, Terpolilli NA, et al. Increased 68Ga-DOTATATE uptake in PET imaging discriminates meningioma and tumor-free tissue. J Nucl Med 2015;56:347-53.
33. Cornelius JF, Langen KJ, Stoffels G, et al. Positron emission tomography imaging of meningioma in clinical practice: review of literature and future directions. Neurosurgery 2012;70:1033-41.
34. Afshar-Oromieh A, Giesel FL, Linhart HG, et al. Detection of cranial meningiomas: comparison of (6)(8)Ga-DOTATOC PET/CT and contrast-enhanced MRI. Eur J Nucl Med Mol Imaging 2012;39:1409-15.
35. Jauw YW, Menke-van der Houven van Oordt CW, Hoekstra OS, et al. Immuno-positron emission tomography with Zirconium-89-labeled monoclonal antibodies in oncology: what can we learn from initial clinical trials? Front Pharmacol 2016;7:131.
36. Galldiks N, Albert NL, Sommerauer M, et al. PET imaging in patients with meningioma-report of the RANO/PET Group. Neuro Oncol 2017;19:1576-87.
37. Filss CP, Galldiks N, Stoffels G, et al. Comparison of 18F-FET PET and perfusion-weighted MR imaging: a PET/MR imaging hybrid study in patients with brain tumors. J Nucl Med 2014;55:540-5.
38. Gudjonssona O, Bergstrom M, Kristjansson S, et al. Analysis of 76Br-BrdU in DNA of brain tumors after a PET study does not support its use as a proliferation marker. Nucl Med Biol 2001;28:59-65.
39. Ikeda H, Tsuyuguchi N, Kunihiro N, et al. Analysis of progression and recurrence of meningioma using (11)C-methionine PET. Ann Nucl Med 2013;27:772-80.
40. Li D, Zhang J, Ji N, et al. Combined 68Ga-NOTA-PRGD2 and 18F-FDG PET/CT can discriminate uncommon meningioma mimicking high-grade glioma. Clin Nucl Med 2018;43:648-54.
41. Mitamura K, Yamamoto Y, Norikane T, et al. Correlation of (18)F-FDG and (11)C-methionine uptake on PET/CT with Ki-67 immunohistochemistry in newly diagnosed intracranial meningiomas. Ann Nucl Med 2018;32:627-33.
42. Murakami M, Imahori Y, Kimura S, et al. Positron emission tomography elucidates transport system and tumor proliferation in meningiomas. Oncol Rep 2005;14:853-9.
43. Park Y, Jeon B, Oh H, et al. FDG PET/CT assessment of the biological behavior of meningiomas. J Korean Neurosurg Soc 2006;40:428-33.
44. Sommerauer M, Burkhardt JK, Frontzek K, et al. 68Gallium-DOTATATE PET in meningioma: a reliable predictor of tumor growth rate? Neuro Oncol 2016;18:1021-7.
45. Yi C, Shi X, Yu D, et al. The combination of 13N-ammonia and 18F-FDG PET/CT in the identification of metabolic phenotype of primary human brain tumors. Nuklearmedizin 2019;58: 272-8.