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SYSTEMATIC REVIEW

Discrimination between primary low-grade and high-grade glioma with ^{11}C -methionine PET: a bivariate diagnostic test accuracy meta-analysis

^{1,2}ANNA FALK DELGADO, MD, PhD, MSc and ³ALBERTO FALK DELGADO, MD, PhD

¹Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden

²Department of Neuroradiology, Karolinska University Hospital, Stockholm, Sweden

³Department of Surgical Sciences, Uppsala University, Uppsala, Sweden

Address correspondence to: Dr Anna Falk Delgado

E-mail: anna.falk-delgado@sll.se

Objective: To perform a meta-analysis evaluating the diagnostic accuracy of ^{11}C -methionine (MET) positron emission tomography (PET) to discriminate between primary low-grade glioma (LGG) and high-grade glioma (HGG).

Methods: A systematic database search was performed by a librarian in relevant databases with the latest search on 07 November 2016. Hits were assessed for inclusion independently by two authors. Individual patient data on relative MET uptake was extracted on patients examined pre-operatively with MET PET and subsequent neuropathological diagnosis of astrocytoma or oligodendroglioma. Individual patient data were analysed for diagnostic accuracy using a bivariate diagnostic random-effects meta-analysis model with restricted maximum likelihood estimation method. Bivariate meta-regression and subgroup analyses assessed study heterogeneity and validity. This

study is registered with PROSPERO, number CRD42016050747.

Results: Out of 1828 hits, 13 studies comprising of 241 individuals were included in the quantitative and qualitative analysis. MET PET had an area under the bivariate summary receiver operating characteristics curve of 0.78 to discriminate between LGG and HGG and a summary sensitivity of 0.80 with 95% confidence interval (CI) (0.66–0.88) and a summary false positive rate of 0.28, 95% CI (0.19–0.38). Heterogeneity was described by; bias in patient inclusion, study quality, and ratio method. Optimal cutoff for relative MET uptake was 2.21.

Conclusion: MET PET had a moderately high diagnostic accuracy for the discrimination between primary LGG and HGG.

Advances in knowledge: MET PET can be used as a clinical tool for the non-invasive discrimination between LGG and HGG with a moderately high accuracy at cut-off 2.21.

INTRODUCTION

Gliomas are classified according to the World Health Organization (WHO) neuropathological guidelines into different grades and subtypes. Grade I and II pertain to low-grade gliomas (LGG) with slower growth and longer survival than high-grade glioma (HGG), WHO Grade III and IV. Further, HGG and LGG have different clinical management. Astrocytomas and oligodendrogliomas are the most common gliomas in adults.¹

There have been conflicting results with regard to the diagnostic test accuracy (DTA) for ^{11}C -methionine (MET) positron emission tomography (PET) to discriminate between LGG and HGG. Several studies have not been able to demonstrate a difference in MET uptake between glioma malignancy grades.^{2–7} Non-invasive diagnosis of glioma malignancy grade is of special interest before an accurate

neuropathological diagnosis can be obtained; in patients deemed inoperable or at longitudinal follow up.

MET uptake have been found to correlate with cell density,⁸ microvascular density,⁹ O6-methylguanine-DNA methyltransferase promotor methylation¹⁰ and are transported into cell cytoplasm across microvascular beds by L-type amino acid transporter 1 (LAT-1) transporters.¹¹ A certain degree of passive flux of MET across broken blood brain barrier (BBB) has been proposed^{8,12} in, for example inflammation and high-grade tumours.

As of today, MET PET has a role in differentiating between tumour recurrence and radiation injury.^{13,14} Further, MET PET guides biopsies and delineates tumour margins¹⁵ pre-operatively. MET uptake has been correlated with survival^{16–18} and malignant tumour progression.¹⁹ However,

its role in discriminating between glioma grades is unclear. Due to differences in the clinical management and prognosis between LGG and HGG and the fact that not all patients are suitable for surgical resection and neuropathological diagnosis, there is a need for a non-invasive clinical tool to differentiate between LGG and HGG pre-operatively.

We are unaware of any previous meta-analysis evaluating the DTA of MET PET to discriminate between primary LGG and HGG. Hence, this meta-analysis was performed, aiming to evaluate the DTA of MET PET in the pre-operative evaluation of adult patients with suspected primary glioma sequentially verified through neuropathological diagnosis.

METHODS AND MATERIALS

Reporting guidelines and protocol registration

This meta-analysis was reported with adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,²⁰ and performed according to current recommendations for meta-analyses on DTA imaging studies.²¹ This meta-analysis also adheres to the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.²² The study protocol is registered in PROSPERO International prospective register of systematic reviews at <https://www.crd.york.ac.uk> with registration number CRD42016050747.

Eligibility criteria

Potentially eligible studies according to PICO (population, intervention/index test, control/gold standard, observation/diagnostic accuracy) reported on the pre-operative evaluation by MET PET in adult patients (>18 years) with suspected glioma (WHO astrocytoma or oligodendroglioma confirmed by neuropathology), and presenting individual patient data (IPD). No restrictions were set for language, publication years or publication status.

Exclusion criteria at abstract and title screening were; non-glial tumours, paediatric patients (<18 years), non-quantitative data, case studies, reviews, editorials, duplicate cohorts, non-central nervous system tumours, recurrent tumours, non-Hebrew text and studies reporting on only LGG or HGG. Further exclusion criteria at full-text evaluation were; incomplete data, not original research, non-WHO classification, technical reports, non-MET tracer, full text not available, non-English language and grey literature (PhD thesis, trial protocols). Exclusion criteria at IPD level were; oligoastrocytomas, Grade I pilocytic astrocytoma, paediatric patients (<18 years).

Information sources and electronic search strategy

Information sources included; Medline (Ovid), Embase (<http://www.embase.com>), Web of Science Core Collection and the Cochrane Library (Wiley). Information sources on grey literature covered; International Clinical Trials Registry Platform (<http://www.who.int/ictrp/en/>), OAIster (<http://oaister.worldcat.org/>) and Bielefeld Academic Search Engine (<https://www.base-search.net/>) with the latest search on 07 November 2016.

The electronic search was performed by a librarian experienced in systematic searches and presented in [Figure 1](#).

The search was performed without limitations and is presented in full in the [Supplementary Material](#) (supplementary material available online).

Study selection and data collection process

Titles and abstracts were screened for possible inclusion in the meta-analysis by one author (MD, PhD) with 6 years experience of MET PET in brain tumour evaluation and 9 years experience in performing clinical meta-analyses. Any issues related to the study inclusion process were discussed with a second author (MD, PhD with 4 years experience in meta-analysis). Relevant articles from screening were assessed in full-text by one author (same as above). Included full-text studies were qualitatively evaluated by their adherence to the Standards for the Reporting of Diagnostic accuracy studies (STARD) 2015²³ guidelines.

IPD collection on relative (to a contralateral region) MET uptake and neuropathological subtype was performed onto preformed extraction sheets independently by two authors (MD, PhD with experience in meta-analysis) with succeeding check for congruency. Extracted study characteristics included; first author, year published, PET scanner, MET dose, ratio method (SUV ratio or uptake ratio), definition of tumour and contralateral region of interest, and IPD data; MET uptake in tumour and contralateral area.

Statistical analysis

On a per study basis, the IPD on relative methionine uptake (tumour MET uptake or SUV divided with a contralateral region) and neuropathological subtype was summarized in mean and standard deviation stratified for LGG and HGG, low-grade astrocytoma (LGA) and high-grade astrocytoma and low-grade oligodendroglioma (LGO) and high-grade oligodendroglioma.

For each study, relative IPD MET and the corresponding neuropathological diagnosis (WHO HGG and LGG) was cross-tabulated to extract data on diagnostic potential to discriminate between LGG and HGG. On a per study basis, data from cross-tabulation with the area under characteristic receiver curve (AUC), optimal cut-off, sensitivity and specificity at optimal cut-off, and the true-positive, false-negative, false-positive (FP) and true-negative counts were extracted. Data from cross tabulation was further evaluated with DTA meta-analysis with a continuity correction of 0.5 used for zero counts.

Univariate descriptive summary statistics with per study sensitivity, specificity and 95% confidence interval (CI) were calculated and presented as forest plots for the main outcome. Between study variance was estimated by χ^2 evaluating equality of sensitivities and specificities. Further, the sensitivity was plotted in function of the FP rate in receiver operating characteristics (ROCs) space as a cross-hair and ellipse plot. To take into account, the often negatively correlated relationship between sensitivity and specificity in DTA studies, data were fitted to a bivariate normal model for the logit-transformed pairs of

Figure 1. PRISMA flow chart of included and excluded studies.

¹ From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit www.prisma-statement.org.

sensitivities and FP rates implemented in mada's reitsma function. This model estimated the sensitive and FP rate with 95% CI and the area under the ROCs curve. The overall diagnostic potential for MET PET to discriminate between LGG and HGG was visually presented as a summary ROCs curve.

Additional analyses were pre-specified and included bivariate meta-regression and subgroup analyses based on study quality adherence, patient selection bias and ratio method. Bivariate meta-regression was applied to test for moderating covariates on the effect estimate. A subgroup comprising studies with high quality adherence represented a sensitivity test for the validity of the meta-analysis findings. To take into account, the possibility of patient selection bias in studies including suspected LGGs and in studies including more patients with LGG than HGG indicating

a non-consecutive series of patients, these studies were analysed separately in a subgroup analysis. This was based on epidemiological data that the HGG glioma Grade IV is the most common glial tumour and hence, would be in majority in a consecutive series of patients with brain tumours.

Finally, all IPD was analysed as derived from a single large cohort to test for biases in the material. In these final analyses, IPD was stratified for glioma grade (Grade II, III and IV) and subtype (astrocytoma and oligodendroglioma) and the AUC with 95% CI and optimal cutoff was calculated according to DeLong.²⁴

Statistical analyses were performed in R²⁵ with packages; pROC²⁶ and mada.²⁷

Table 1. Results from cross tabulation of included studies

First author	Year of publication	AUC	Optimal cut-off	Sensitivity (%)	Specificity (%)	TP (n)	FN (n)	FP (n)	TN (n)
Berntsson	2013	0.71	1.90	100	57	4	0	6	8
Boss	2010	1.00	1.53	100	100	3	0	0	2
Coope	2007	0.97	1.93	89	100	8	1	0	4
Gumprecht	2007	0.92	1.56	92	100	12	1	0	2
Kameyama	1990	0.79	2.25	50	100	2	2	0	7
Miyake	2012	0.90	1.96	100	80	38	0	2	8
Ogawa	1993	0.84	2.19	61	93	14	9	1	13
Okita	2014	0.42	1.72	60	58	3	2	5	7
Sadeghi	2006	0.81	3.31	100	63	6	0	3	5
Tateishi	2014	1.00	2.30	100	100	9	0	0	4
Tietze	2015	0.64	5.04	43	100	3	4	0	2
Torii	2005	0.84	1.54	82	80	14	3	2	8
Yamamoto	2008	0.78	1.29	100	75	10	0	1	3

AUC, area under curve; FN, false-negative; FP, false-positive; TN, true-negative; TP, true-positive.

RESULTS

Study selection with flow chart

Searches identified 1828 hits with 989 records remaining after removal of duplicates. The 989 records were screened for possible inclusion. After exclusion of 782 records, 209 articles were evaluated in full-text. Reasons for exclusion of 196 full-text articles, together with the full search strategy and PRISMA flow diagram is presented in Figure 1. Ultimately, 13 studies^{10,15,28–38} were included in the qualitative and quantitative synthesis. Grey literature search identified six registered protocols of not yet published studies aiming to evaluate the DTA of MET PET and two PhD theses.

Descriptive summary of data on included studies

Included 13 studies comprised 241 patients (89% astrocytomas and 11% oligodendrogliomas). In total, 93 patients with LGG (77 LGA, 16 LGO) and 148 patients with HGG (140 A, 8 O) were included in the meta-analysis. Relative MET uptake, mean (SD), in LGG was 1.88 (0.93), 3.08 (1.39) in HGG, 1.86 (0.96) in LGA, 3.06 (1.38) in high-grade astrocytoma, 1.97 (0.74) in LGO and 3.35 (1.64) in high-grade oligodendroglioma. Relative uptake values, mean (SD) in Grade I glioma was 1.09 (NA, $n = 1$), 1.89 (0.93) in Grade II, 2.65 (1.04) in Grade III and 3.38 (1.53) in Grade IV. Diagnostic accuracy varied between studies with calculated AUC from cross-tabulation ranging between 0.42 and 1.00. Full data from cross-tabulation is presented in Table 1. Adherence to STARD quality assessment ranged between 29 and 62% of relevant quality issues addressed in the individual studies (Table 2). In statistical analysis, quality adherence was dichotomously categorized as high (>50%) or low (<50%) adherence to quality guidelines. Study characteristics and quantitative data are presented in Tables 2 and 3. IPD data is presented in Supplemental Table 1.

Meta-analysis

Sensitivity and specificity of individual studies are presented as forest plots in Figure 2. There was considerable heterogeneity in sensitivities across studies described by χ^2 ($p < 0.001$) but equality of specificities ($p = 0.56$). A cross-hair plot and an ellipse plot describing the diagnostic accuracy across studies are presented in Figure 3.

Fitting the data to a bivariate diagnostic random-effects meta-analysis model with restricted maximum likelihood estimation method yielded a summary sensitivity of 0.80 (0.66–0.88) and a FP rate of 0.28 (0.19–0.38). The summary AUC was 0.78. The summary ROC curve presented in Figure 4 further illustrates the diagnostic potential of MET PET to differentiate between LGG and HGG.

Bivariate meta-regression and subgroup analysis

The following covariates were evaluated for a moderating effect on the diagnostic potential to discriminate between LGG and HGG by MET PET in bivariate meta-regression; bias in patient inclusion (studies including suspected LGG^{28,31} and studies including more LGG than HGG,^{10,32,34}) high study quality,^{10,29,30,35,38} and SUV ratio method.^{10,15,32,33,35,38} The covariates' moderating effect on the sensitivity and on the FP rate was evaluated.

Studies including suspected LGGs and/or more LGG than HGG was a significant moderator on the FP rate ($p = 0.04$). In accordance with this, the AUC in the pertaining subgroup analysis (studies including suspected LGG and studies with more LGG than HGG) decreased to 0.65. Further, the heterogeneity of sensitivities from the main analysis ($n = 13$ studies) were lost in this subgroup analysis indicating more homogenous results across studies.

Table 2. Qualitative and quantitative characteristics of included studies

First author	Year of publication	STARD evaluation % (n/34)	PET CT (Yes/No)	PET scanner	Methionine dose (range or mean MBq/mCi)	Semi-quantitative analysis	Tumour ROI	Contralateral ROI region
Berntsson	2013	47 (16/34)	Yes	ECAT EXACT HR +/- Discovery ST	NA	Uptake ratio (NOS)	Max tumour	GM
Boss	2010	53 (18/34)	Yes	Biograph 16	585–764	Uptake ratio (NOS)	Mean tumour	Frontal GM
Coope	2007	56 (19/34)	Yes	ECAT EXACT HR +	740	Uptake ratio (NOS)	Max tumour	Mirror region
Gumprecht	2007	41 (14/34)	Yes	ECAT HR	300–400	Uptake ratio (NOS)	Mean tumour	GM
Kameyama	1990	29 (10/34)	Yes	ECAT II/PT-931	222–925/6–25	SUV	SUV tumour	SUV GM
Miyake	2012	44 (15/34)	Yes	ECAT EXACT HR +	113–389	SUV	SUV max tumour	SUV mean in normal brain (NOS)
Ogawa	1993	32 (11/34)	No (CT and PET)	Headtome III/Headtome IV	555–1,480/15–40	SUV	SUV tumour	SUV temporal GM
Okita	2014	50 (17/34)	Yes	Eminence Sophia SET-3000 GCT/X	111–222/3–6	SUV	SUV max tumour	SUV mean frontal GM
Sadeghi	2006	44 (15/34)	Yes	ECAT 962 h +	260	Uptake ratio (NOS)	Max tumour	Corona radiata
Tateishi	2014	62 (21/34)	Yes	Biograph 16	370	SUV	SUV max tumour	SUV GM
Tietze	2015	44 (15/34)	Yes	Biograph PET/CT system	500	Uptake ratio (NOS)	Max tumour	GM
Torii	2005	44 (15/34)	No (MRI and PET)	Headtome IV	7.4/0.2 per kg	Uptake ratio (NOS)	Max tumour	Frontal GM
Yamamoto	2008	56 (19/34)	Yes	ECAT EXACT HR +	6 per kg	SUV	SUV tumour	SUV mean GM

GM, grey matter; NA, not available; NOS, not otherwise specified; PET, positron emission tomography; ROI, region of interest; STARD, standards for reporting studies of diagnostic accuracy (% adherence to 34 quality items); SUV, standardized uptake value.

Table 3. Number of included patients and uptake ratios stratified for WHO grade and histological subtype

First author	Year of publication	Total patients included/ LGG/ HGG/LGA/ HGA/ LGO/ HGO (n)	Uptake ratio LGG [mean (SD)]	Uptake ratio HGG [mean (SD)]	Uptake ratio LGA [mean (SD)]	Uptake ratio HGA [mean (SD)]	Uptake ratio LGO [mean (SD)]	Uptake ratio HGO [mean (SD)]
Berntsson	2013	18/14/4/8/3/6/1	2.07 (0.82)	2.43 (0.44)	2.14 (1.00)	2.57 (0.42)	1.98 (0.56)	2 (NA)
Boss	2010	5/2/3/2/3/0/0	1.00 (0.42)	1.96 (0.26)	1.00 (0.42)	1.96 (0.26)	NA	NA
Coope	2007	13/4/9/2/8/2/1	1.80 (0.10)	2.56 (0.65)	1.8 (0.18)	2.45 (0.59)	1.81 (0.03)	3.47 (NA)
Gumprecht	2007	15/2/13/2/13/0/0	1.44 (0.06)	2.87 (1.18)	1.44 (0.06)	2.87 (1.18)	NA	NA
Kameyama	1990	11/7/4/7/4/0/0	1.64 (0.40)	2.20 (0.56)	1.64 (0.40)	2.20 (0.56)	NA	NA
Miyake	2012	48/10/38/9/37/1/1	1.87 (1.05)	3.80 (1.66)	1.91 (1.10)	3.72 (1.62)	1.52 (NA)	6.54 (NA)
Ogawa	1993	37/14/23/14/23/0/0	1.60 (0.57)	2.52 (0.75)	1.60 (0.57)	2.52 (0.75)	NA	NA
Okita	2014	17/12/5/8/4/4/1	1.75 (0.34)	1.88 (0.48)	1.68 (0.37)	2.02 (0.42)	1.88 (0.26)	1.32 (NA)
Sadeghi	2006	14/8/6/7/6/1/0	3.13 (1.40)	4.65 (1.11)	2.97 (1.42)	4.65 (1.11)	4.30 (NA)	NA
Tateishi	2014	13/4/9/2/6/2/3	1.68 (0.38)	3.32 (0.64)	2.00 (0.00)	3.53 (0.70)	1.35 (0.07)	2.90 (0.17)
Tietze	2015	9/2/7/2/6/0/1	4.02 (1.29)	5.17 (1.75)	4.02 (1.29)	5.24 (1.90)	NA	4.76 (NA)
Torii	2005	27/10/17/10/17/0/0	1.35 (0.39)	2.08 (0.49)	1.35 (0.39)	2.08 (0.49)	NA	NA
Yamamoto	2008	14/4/10/4/10/0/0	1.76 (1.60)	3.02 (0.92)	1.76 (1.60)	3.02 (0.92)	NA	NA
Total (all studies)	NA	241/93/148/77/140/16/8	1.88 (0.93)	3.08 (1.39)	1.86 (0.96)	3.06 (1.38)	1.97 (0.74)	3.35 (1.64)

HGA, high-grade astrocytoma; HGG, high-grade glioma; HGO, high-grade oligodendroglioma; LGA, low-grade astrocytoma; LGG, low-grade glioma; LGO, low-grade oligodendroglioma; NA, not available; SD, standard deviation; WHO, World Health Organization.

Figure 2. (a) Forest plot of per study sensitivity with 95% CI. Study 1 = Berntsson 2013, Study 2 = Boss 2010, Study 3 = Coope 2007, Study 4 = Gumprecht 2007, Study 5 = Kameyama 1990, Study 6 = Miyake 2012, Study 7 = Ogawa 1993, Study 8 = Okita 2014, Study 9 = Sadeghi 2006, Study 10 = Tateishi 2014, Study 11 = Tietze 2015, Study 12 = Torii 2005, Study 13 = Yamamoto 2008. (b) Forest plot of per study specificity with 95 % CI. CI, confidence interval.

Loss of heterogeneity was also found in the subgroup of studies with high quality adherence according to STARD^{10,29,30,35,38} and for studies reporting on MET uptake ratio^{28–31,34,36,37} rather than SUV^{10,15,32,33,35,38} ratio. The subgroup of studies reporting on SUV ratio had an AUC of 0.83 compared to uptake ratio with AUC 0.78. Study quality adherence was not a significant covariate in the meta-regression and showed similar AUC (0.85 vs 0.84) between subgroups in the sensitivity analysis, thereby indicating sufficient validity of the main meta-analysis. However, the heterogeneity in sensitivities also present in the main analysis including all studies was lost in the subgroup analysis of studies having a high quality adherence. This indicates that higher STARD adherence improves homogeneity of results between studies but does not affect the effect size of the outcome. Meta-regression and subgroup analysis is presented in Table 4.

Results from analysis treating the whole data set as a single cohort showed similar AUC for discriminating between LGG

Figure 3. (a) ROC cross-hair plot of included studies ($n = 13$). The cross-hairs plot the sensitivity and the false-positive rate in ROC-space. (b) ROC ellipse plot describing study point estimates and confidence regions as ellipses. ROC, receiver operating characteristic.

and HGG in astrocytic tumours [AUC = 0.81 95% CI (0.74–0.87)] compared to oligodendroglial tumours [AUC = 0.80 95% CI (0.57–1.00)]. The potential for MET PET to separate Grade

Figure 4. A summary receiver operating characteristics curve with individual study point estimates ($n = 13$) depicted as triangles and summary meta-analysis confidence region (large circle) around the summary estimate (small circle). S-ROC, summary receiver operating characteristics curve.

Table 4. Meta-regression and subgroup analysis (bivariate)

		Bivariate meta-regression (significance <i>p</i>)		Subgroup analysis (significance <i>p</i>)		
Study characteristics (<i>n</i> studies)		<i>p</i> sensitivity	<i>p</i> false- positive rate	χ^2 sensitivities <i>p</i> heterogeneity	χ^2 specificities <i>p</i> heterogeneity	AUC
Grade						
	Suspected LGG or LGG > HGG (5)	0.75	0.04	0.18	0.38	0.65
	More HGG than LGG (8)	...	...	<0.001	0.96	0.86
Quality						
	High quality adherence (5)	0.57	0.56	0.24	0.53	0.85
	Low quality adherence (8)	...	...	<0.001	0.393	0.84
Ratio						
	SUV ratio (6)	0.75	0.53	<0.001	0.28	0.83
	Uptake ratio (7)	...	...	0.18	0.73	0.78

AUC, area under curve; HGG, high-grade glioma; LGG, low-grade glioma; SUV, standardized uptake value.

II from Grade IV gliomas was higher [AUC = 0.84 95% CI (0.78–0.90), at optimal cutoff 2.26] than between glioma Grade II and III [AUC = 0.75 95% CI (0.67–0.83), at optimal cutoff 2.21]. The best cutoff for differentiating between LGG and HGG was 2.21.

DISCUSSION

MET PET had a moderately high DTA to differentiate between LGG and HGG with an AUC of 0.78. The DTA increased in subgroups of studies with low selection bias and in studies reporting on SUV ratio rather than uptake ratio. Further, DTA was higher when differentiating between glioma Grades II and IV than between grades II and III. The diagnostic accuracy in terms of AUC was >0.80 in several subgroups indicating its potential clinical use for differentiating between LGG and HGG in a clinical setting. Taking into account that perfusion MRI has showed equal or higher AUC for differentiation LGG from HGG, the primary clinical use of MET PET should not be able to differentiate LGG from HGG.³⁹ However, when MET PET is used to direct stereotactic biopsy, in pre-surgical planning or when evaluating for pseudo-progression the moderate ability for MET PET to discriminate between LGG and HGG could be of importance.

The strengths of this meta-analysis pertain mainly to an extensive literature search including several relevant databases and grey literature. The study aggregates a large data set using robust methodology. In order to increase the transparency of the study and to reduce bias in result reporting the study protocol was registered in PROSPERO. This study used the current statistical recommendations for DTA meta-analysis.^{21,22}

Aggregated IPD help answer more questions than selected studies. Subgroup analyses and meta-regression helps understand the driving forces behind the results. Further, meta-analysis increase power and narrows confidence intervals compared to individual studies. We are able to estimate a more accurate optimal cutoff value for the discrimination between LGG and

HGG. To the best of our knowledge, we are unaware of any previous published meta-analysis on this topic.

Data from historical studies might limit future extrapolation and clinical utility because of differences in gold standard. We adhered this meta-analysis to the current glioma classification of WHO 2016¹ by excluding tumours classified as oligoastrocytomas and gliomatosis cerebri.

This study has some limitations. Heterogeneity between included studies were substantial in the main analysis (LGG vs HGG). Although expected in a DTA meta-analysis, we strove to assess the driving forces behind the heterogeneity by performing subgroup analysis and meta-regression. Heterogeneity was lower in studies with selection bias towards LGGs, in studies with high quality adherence, and in studies reporting on MET uptake ratio, rather than MET SUV ratio, which suggest that these studies are more similar, reflecting a lower heterogeneity. Key issues related to MET PET as a clinical adjunct in glioma evaluation is the relatively short half-life of the MET (20 min) requiring a nearby cyclotron.⁴⁰ Further, permeability⁸ and passive flux over a broken BBB might confound findings and hamper diagnostic utility.¹² One change from the protocol was that included studies were not evaluated according to QUADAS-2 (quality assessment of diagnostic accuracy studies) but to their adherence to STARD guidelines. This change between protocol and manuscript pertained to difficulty in applying QUADAS-2 for studies not adhering to STARD guidelines.

Strengths of this meta-analysis with regard to previous studies is that this is to our knowledge, the first meta-analysis to evaluate the DTA of MET PET in this patient cohort of glioma. Our study shows additional usage for MET PET. Another strength is the separation of LGG and HGG into specific grades. Taking into account, the most often characteristic appearance of a glioma Grade IV, the diagnostic potential to discriminate between glioma Grade II and III is of a high clinical concern.

Previous studies evaluating the DTA of MET PET to discriminate between LGG and HGG have shown inferior results when including oligodendroglial tumours.⁴¹ While our study contradicts these results, the explanation can be our adherence to the WHO 2016 guidelines¹ by excluding oligoastrocytomas. Excluding oligoastrocytomas in the analysis yielded a similar AUC for the discrimination between LGG and HGG in astrocytomas and oligodendrogliomas respectively. This finding is supported by Shinozaki et al who found a higher MET uptake in oligodendrogliomas without 1p19q co-deletion compared to co-deleted oligodendrogliomas. Although astrocytomas and oligodendrogliomas differ in biological structure, this study indicates a common accumulation of MET with increasing grade.

With 2016 WHO guidelines for brain tumour classification, glial tumours are more readably divided into astrocytic and oligodendroglial tumours with mixed oligoastrocytic tumours divided into either astrocytic or oligodendroglial tumour group based primarily on its 1p19q codeletion and IDH mutation status. Before this new classification, oligoastrocytic tumour grade was more difficult to evaluate from a neuropathological point of view and this might have led to some misclassification of tumour grades in the past. By excluding these tumours in this meta-analysis, we minimized the influence of this potential bias. New diagnostic studies need to evaluate the efficacy of MET PET in tumours previously classified as oligoastrocytomas.

Our results are in line with a study by Singhal et al who found significant differences between LGG and HGG.¹⁷ Our results show that MET uptake increases with increasing malignant grade and that the differences in MET uptake are more evident between glioma Grade II and Grade IV than between glioma Grade II and Grade III. These results indicate an upregulated transport mechanisms of MET with increasing glioma grade but

can partly also reflect a flux across broken BBB in glioma Grade IV with necrosis compared to lower grades with more intact BBB.

The findings from the bivariate meta-regression and subgroup analysis that suspected LGGs are more difficult to categorize in LGG and HGG may mainly reflect the fact that this group contain more Grade II and III tumours than Grade IV tumours.

We found an optimal cut-off for differentiating between LGG and HGG at 2.21. This cut-off has previously been reported in a cohort of recurrent glioma.¹⁸ Our cut-off at 2.21 is higher than previously suggested by Torii et al who analysed 67 patients with glioma in a mixed cohort of paediatric and adult patients and a range of different glial cell tumours not merely attributing to astrocytomas and oligodendrogliomas.³⁷ Takano et al reported an optimal cutoff for low-grade and high-grade non-enhancing gliomas at 2.0, the slight discrepancy against our results probably explained by patient selection bias with non-enhancing gliomas accumulating less MET than enhancing gliomas.⁴²

Accumulating available evidence, this meta-analysis points on the diagnostic utility of MET PET to differentiate between LGG and HGG. This is an important additional usage of MET PET in the pre-operative evaluation of suspected glioma where MET PET is performed to delineate tumour margins or direct biopsy. The potential for MET PET to discriminate between glioma grades should not be neglected, and highlights the role for MET PET in the work up for glioma assessment.

CONCLUSION

MET PET had a moderately high diagnostic potential to discriminate between LGG and HGG in primary glioma.

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