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ORIGINAL ARTICLE

Re-evaluation of the diagnostic performance of ^{11}C-methionine PET/CT according to the 2016 WHO classification of cerebral gliomas

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Abstract

Purpose We evaluated the usefulness of ^{11}C-methionine (MET) positron emission tomography/computed tomography (PET/CT) for grading cerebral gliomas according to the 2016 WHO classification with special emphasis on the presence of the isocitrate dehydrogenase 1 (*IDH1*) gene mutation and 1p/19q codeletion.

Methods In total, 144 patients underwent MET PET/CT before surgery. The ratios of the maximum standardized uptake value (SUV) of the gliomas to the mean SUV of the contralateral cortex on MET PET/CT (MET TNR) were calculated.

Results The median MET TNRs in *IDH1*-mutant and *IDH1*-wildtype tumours were 1.95 and 3.35, respectively. From among 74 *IDH1*-mutant tumours, the oligodendrogliomas showed a higher median MET TNR than the astrocytic tumours (2.90 vs. 1.40, $P < 0.001$). In grade II, III and IV *IDH1*-mutant astrocytic tumours, the median MET TNRs were 1.20, 2.05 and 2.20, respectively (grade II vs. grade III, $P < 0.0001$; grade II vs. grade IV, $P = 0.023$). In oligodendrogliomas, the MET TNR was lower fin grade II tumours than in grade III tumours (2.30 vs. 3.30 $P = 0.008$). In differentiating low-grade (grade II) from high-grade (grade III and IV) gliomas, receiver operating characteristic analysis showed a higher area under the curve for wildtype tumours (0.976) than for all tumours (0.852; $P < 0.001$) and *IDH1*-mutant tumours (0.817; $P = 0.004$).

Conclusion *IDH1*-mutant tumours showed lower MET uptake than *IDH1*-wildtype tumours. Regardless of *IDH1* mutation status, oligodendrogliomas with 1p/19q codeletion showed MET uptake as high as that in high-grade *IDH1*-wildtype tumours. Therefore, MET uptake for glioma grading was more consistent for *IDH1*-wildtype tumours than for *IDH1*-mutant tumours.

Keywords Glioma · ^{11}C-Methionine PET/CT · *IDH1* mutation · Grading

Introduction

L-[Methyl-^{11}C]-methionine (MET) is the most widely used radiotracer for imaging of cerebral gliomas because of its low cortical background uptake and high tumour uptake. These properties permit clear delineation of tumour boundaries, and the pinpointing of foci of more aggressive biology [1]. Uptake of MET mediated by the sodium-independent L-type amino acid transporter reflects the degree of cell proliferation, and is related to increased synthesis of proteins and nonprotein molecules, such as DNA, RNA and lipids, as well as elevated transamination and transmethylation [2–6]. Compared with fluorodeoxyglucose (FDG), which has high cortical background uptake, MET provides better detection of lower-grade gliomas [7]. In general, MET uptake is lower in low-grade gliomas than in high-grade gliomas, which has prognostic implications. However, accurate grading based on MET uptake on PET/CT may be challenging due to the significant

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overlap of MET uptake between low-grade and high-grade gliomas [1].

The 2016 World Health Organization (WHO) classification of cerebral gliomas incorporates gene expression profiles in addition to histopathological phenotypes, which has led to a significant reclassification of gliomas [8]. This revised classification has led to improved diagnosis of oligoastrocytoma as either astrocytoma or oligodendroglioma (OD), and consequently has led to better overall survival of patients with OD [9]. Among gene expression profiles, a mutation encoding for isocitrate dehydrogenase 1 (IDH1) has substantially improved the classification and prognostication of gliomas. Patients with *IDH1*-mutant gliomas have better outcomes than patients with *IDH1*-wildtype gliomas. *IDH1*-mutant gliomas can be further categorized into 1p/19q codeleted ODs and 1p/19q intact astrocytomas.

Despite the new WHO classification leading to improved diagnosis, only a few studies have evaluated radiolabelled amino acid PET/CT for glioma grading based on this new classification, or for characterization of MET uptake in relation to *IDH1* mutation and 1p/19q codeletion status [10–14]. Moreover, the use of different radiolabelled amino acid tracers such as MET, 3,4-dihydroxy-6-[^{18}F]fluoro-l-phenylalanine (^{18}F-FDOPA) and *O*-(2-^{18}F-fluoroethyl)-L-tyrosine (^{18}F-FET) has yielded conflicting results. Here, we evaluated the usefulness of ^{11}C-MET PET/CT for grading cerebral gliomas according to the 2016 WHO classification, and for relating MET uptake in gliomas with *IDH1* mutation and 1p/19q codeletion status.

Materials and methods

Patients

This study included 144 patients with histologically confirmed cerebral glioma (79 men, 65 women; median age 45 years, range 23–77 years). All patients had undergone contrast-enhanced magnetic resonance imaging (CE MRI) and MET PET/CT prior to surgery between July 2013 and July 2018. The intervals between CE MRI and MET PET/CT were 2 to 65 days, with a median interval of 10 days. Patients underwent surgery a short time after initial imaging (mean 6.5 days, range 1–20 days). All gliomas were classified using the 2016 WHO classification. The presence of the *IDH1* mutation was assessed using immunohistochemistry (IHC) to detect IDH1 R132H protein expression. *IDH1* sequencing was performed when the IHC results were negative. The 1p/19q codeletion status was analysed by fluorescence in situ hybridization. The Institutional Review Board of our university approved this retrospective study, and the requirement to obtain informed consent was waived.

PET/CT protocol

All patients fasted for at least 6 h before MET injection. Approximately 555 MBq (15 mCi) of MET was administered intravenously, and dynamic scans were acquired for 40 min. Summed frames acquired from 20 to 40 min after injection were used for image reconstruction. Imaging was performed using a PET/CT scanner (Discovery 600; General Electric Medical Systems, Milwaukee, WI, USA) with a spiral CT scan for attenuation correction with a 0.8 s rotation time, 200 mA, 120 kVp, 3.75 mm section thickness, 0.625 mm collimation, and 9.375 mm table feed per rotation. PET data were reconstructed iteratively using an ordered-subsets expectation maximization algorithm.

Image analysis

PET/CT images were reviewed and analysed on a dedicated workstation by consensus between two nuclear medicine physicians. PET/CT and CE MRI scans were registered using MIM-6.5 software (MIM Software Inc., Cleveland, OH, USA). Volumes of interest were manually drawn over the tumours and contralateral cortex as the reference tissue, and the maximum standardized uptake value (SUVmax) of the tumour and the mean SUV (SUVmean) of the contralateral cortex were measured. When no increases in MET uptake were observed, SUVmax was measured within the boundary of the tumour on CE MRI. The SUV was calculated as follows: (decay-corrected activity in kilobecquerels per tissue volume in millilitres)/(injected MET activity in kilobecquerels per body mass in grams). The ratio of SUVmax of the glioma to SUVmean of the contralateral cortex was then calculated as the tumour-to-contralateral cortex ratio (TNR) on MET PET/CT.

Statistical analysis

The Mann-Whitney *U* test and the Kruskal-Wallis test were used to compare the TNR of MET on PET/CT with WHO grade on pathology. Receiver operating characteristic (ROC) analysis was used to compare the diagnostic performance of MET TNR for glioma grading and predicting *IDH1* mutation and 1p/19q codeletion status. The Bonferroni and Dunnett methods were used in post hoc analyses. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA) and R 2.13.0 software (http://www.r-project.org; The R Foundation for Statistical Computing, Vienna, Austria). Except for post hoc analyses, a *P* value less than 0.05 was considered statistically significant.

Results

Patient characteristics

The clinicopathological characteristics of the patients are summarized in Table 1. The median SUV of each classification of all gliomas included in this study are summarized in Table 2.

MET uptake in relation to *IDH1* mutation status in all tumours

There were 74 *IDH1*-mutant tumours (43 grade II, 26 grade III and 5 grade IV) and 70 *IDH1*-wildtype tumours (7 grade II, 13 grade III and 50 grade IV). The median MET TNRs in *IDH1*-mutant and *IDH1*-wildtype tumours were 1.95 (interquartile range, IQR, 1.30–2.90) and 3.35 (IQR 2.80–4.40), respectively. The MET TNRs were significantly different between *IDH1*-mutant and *IDH1*-wildtype tumours ($P < 0.0001$). Using a cut-off TNR of 2.6 for differentiating *IDH1*-mutant from *IDH1*-wildtype tumours, the ROC analysis showed an area under the curve (AUC) of 0.785 (SD = 0.038, 95% CI 0.710–0.860, $P < 0.0001$; Supplementary Fig. 1).

Table 1 Patient characteristics

Characteristic	Value
Age (years), median (range)	48 (26–80)
Sex, *n* (%)	
Male	79 (54.9)
Female	65 (45.1)
Karnofsky performance score, median (range)	90 (50–100)
WHO 2016 grade, *n* (%)	
II	50 (34.7)
III	39 (27.1)
IV	55 (38.2)
Histology, *n* (%)	
Astrocytoma	111
Grade II	35 (31.5)
Grade III	21 (18.9)
Grade IV	55 (49.5)
Oligodendroglioma	33
Grade II	15 (45.5)
Grade III	18 (54.5)
IDH1 mutation, *n* (%)	
Mutant	74 (51.4)
Wildtype	70 (48.6)
Surgical procedure, *n* (%)	
Total resection	83 (57.6)
Partial resection	61 (42.4)

Table 2 SUVs of gliomas

Characteristic	SUV, median (interquartile range)
Grade	
II ($n = 50$)	1.40 (1.20–1.90)
III ($n = 39$)	2.90 (2.23–3.40)
IV ($n = 55$)	3.70 (3.00–4.80)
IDH1 mutation	
Wildtype ($n = 70$)	3.35 (2.80–4.40)
Mutant ($n = 74$)	1.95 (1.30–2.90)
Astrocytoma	
IDH1-wildtype	
Grade II ($n = 7$)	1.50 (1.35–1.85)
Grade III ($n = 13$)	2.70 (2.28–3.25)
Grade IV ($n = 50$)	3.70 (3.00–4.80)
IDH1-mutant	
Grade II ($n = 28$)	1.20 (1.20–1.40)
Grade III ($n = 8$)	2.05 (1.80–2.60)
Grade IV ($n = 5$)	2.20 (1.90–3.48)
Oligodendroglioma	
Grade II ($n = 15$)	2.30 (1.83–3.25)
Grade III ($n = 18$)	3.30 (2.50–4.20)

MET uptake in relation to histological grade and 1p/19q codeletion status in all *IDH1*-mutant tumours

Of the 74 *IDH1*-mutant tumours, ODs showed higher MET TNRs ($n = 33$, median 2.90, IQR 2.20–3.60) than astrocytic tumours ($n = 41$, median 1.40, IQR 1.20–1.90, $P < 0.001$; Supplementary Fig. 2). The median MET TNRs of *IDH1*-mutant astrocytic tumours of grades II, III and IV were 1.20 (IQR 1.20–1.40), 2.05 (1.80–2.60) and 2.20 (1.98–3.48), respectively (Fig. 1). The MET TNRs differed significantly between grade II and grade III tumours, and between grade II and grade IV tumours ($P < 0.0001$ and 0.023, adjusted, respectively), but did not differ between grades III and IV tumours ($P = 0.494$, adjusted; Supplementary Fig. 2). The median MET TNRs of the ODs differed between grades II and III, with higher uptake in grade III tumours (2.30, 1.83–3.25 vs. 3.30, 2.50–4.20, $P = 0.008$; Figs. 1 and 2, Supplementary Fig. 2). The median MET TNR of grade II ODs was higher than that of grade II *IDH1*-mutant astrocytomas, but similar to that of grade II and III wildtype astrocytomas (Supplementary Fig. 3). The median MET TNR of grade III ODs was higher than that of grade III *IDH1*-mutant astrocytomas, but similar to that of grade III or IV wildtype astrocytic tumours (Supplementary Fig. 4).

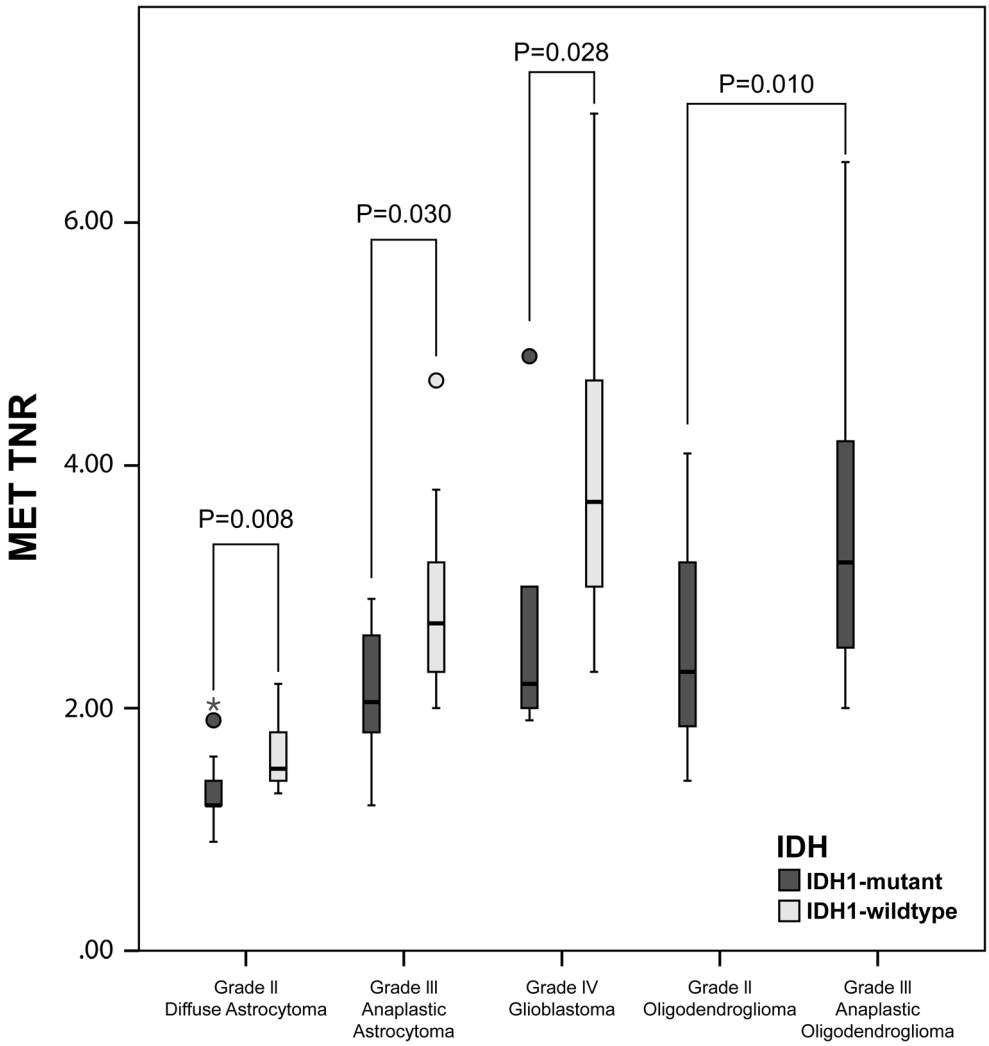

Fig. 1 In all gliomas, the tumour SUVmax to contralateral cortex SUVmean ratio of ^{11}C-MET uptake was correlated with *IDH1* mutation status, WHO grade, and 1p/19q codeletion. (*circles* outliers, >1.5 times interquartile range; *asterisk* extreme outlier, >3 times interquartile range)

MET uptake in relation to histological grade and *IDH1* mutation status in astrocytic tumours

Of 111 astrocytic tumours, 41 were *IDH1*-mutant (28 grade II, 8 grade III and 5 grade IV), and 70 were *IDH1*-wildtype (7 grade II, 13 grade III and 50 grade IV). The median MET TNRs in *IDH1*-mutant and *IDH1*-wildtype tumours were 1.20 (IQR 1.20–1.40) and 1.50 (1.35–1.85), respectively, in grade II tumours, 2.05 (1.80–2.60) and 2.70 (2.28–3.25), respectively, in grade III tumours, and 2.20 (1.98–3.48) and 3.70 (3.00–4.80), respectively, in grade IV tumours. MET TNRs differed significantly between *IDH1*-mutant and *IDH1*-wildtype astrocytic tumours within each grade (Figs. 1 and 3).

MET uptake in relation to grading by the 2016 WHO classification

The median MET TNRs in low-grade (grade II) and high-grade (grades III and IV) tumours were 1.40 (IQR 1.20–1.90) and 3.70 (3.00–4.78), respectively, in all tumours, 1.50 (1.35–1.85) and 3.50 (2.90–4.60), respectively, in *IDH1*-wildtype tumours, and 1.40 (1.20–1.98) and 2.90 (2.20–3.78), respectively, in *IDH1*-mutant tumours. With a cut-off TNR of 2.25 for differentiating low-grade from high-grade gliomas, ROC analysis showed a higher AUC (0.976) in wildtype tumours than in all tumours (AUC 0.852, $P < 0.001$) and *IDH1*-mutant tumours (AUC 0.817, $P = 0.004$; Supplementary Fig. 5).

Discussion

IDH1 mutation status is of the utmost importance in the classification and prognostication of gliomas. Patients with *IDH1*-mutant gliomas have better outcomes than patients with *IDH1*-wildtype gliomas [8]. In our previous study with FDG PET/CT, we also found that *IDH1* mutation status was the most important factor for identification of patients with the best prognosis [15]. Furthermore, ^{18}F-FDG uptake in *IDH1*-mutant gliomas was lower than that in *IDH1*-wildtype

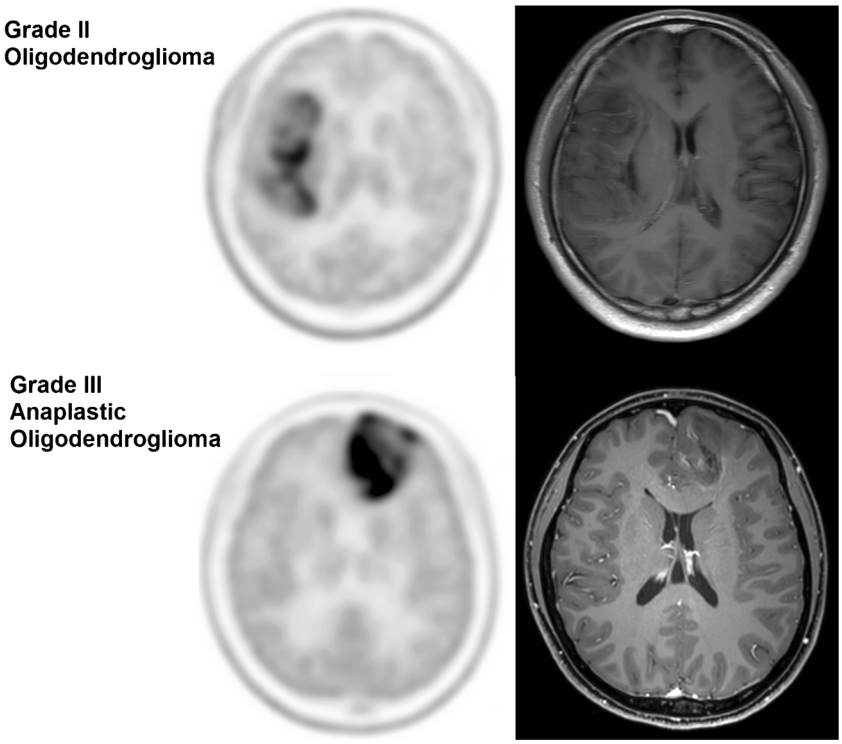

Fig. 2 Transverse ^{11}C-MET PET and contrast-enhanced T1-weighted MR images in (*top*) a patient with grade II oligodendroglioma with a relatively low tumour SUVmax to contralateral cortex SUVmean ^{11}C-MET ratio (MET TNR) of 2.58, and (*bottom*) a patient with a grade III anaplastic oligodendroglioma with a high MET TNR of 3.41

gliomas. Similar to FDG uptake, *IDH1*-mutant tumours showed significantly lower MET uptake than *IDH1*-wildtype tumours in this study (median MET TNR 1.95 vs. 3.35, $P < 0.001$). Only one study has so far related MET uptake to *IDH1* mutation status; however, not all tumours were classified based on the 2016 WHO classification, including 18

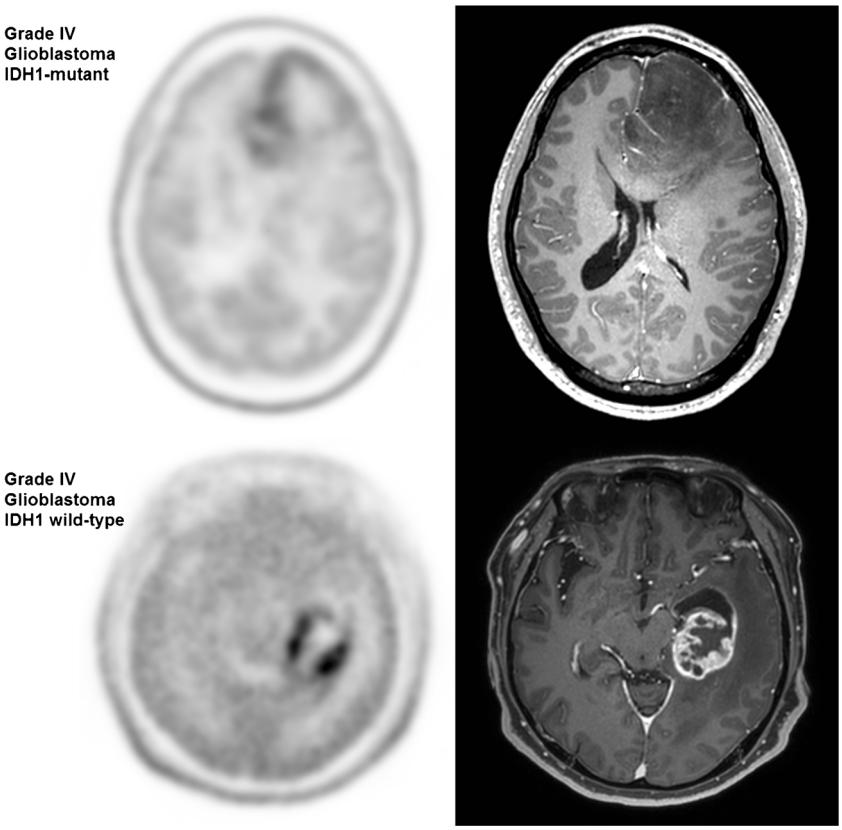

Fig. 3 Transverse ^{11}C-MET PET and contrast-enhanced T1-weighted MR images in (*top*) a patient with grade IV *IDH1*-mutant glioblastoma with a low tumour SUVmax to contralateral cortex SUVmean ^{11}C-MET ratio (MET TNR) of 1.97, and (*bottom*) a patient with grade IV *IDH1*-wildtype glioblastoma with a high MET TNR of 3.04

oligoastrocytomas among 109 gliomas. Nonetheless, the results of the previous study are in accordance with the results of this study, showing significantly lower MET uptake in *IDH1*-mutant tumours [13].

A few studies have used ^{18}F-FDOPA or ^{18}F-FET to relate radiolabelled amino acid uptake to *IDH1* mutation status using the 2016 WHO tumour classification [12, 16]. With static and dynamic FET PET, a lower tumour to brain ratio, a later time to peak value, and a steadily increasing slope of the time–activity curves from 20 to 50 min after injection differentiated *IDH1*-mutant tumours from *IDH1*-wildtype tumours. The *IDH1* mutation was paradoxically associated with increased F-DOPA uptake in diffuse grade II and III gliomas, in contrast to findings with other amino acid tracers including MET and FET. It was concluded that such contradictory results need confirmation.

To provide insight into the contradictions mentioned above, we assessed MET uptake in all *IDH1*-mutant tumours (grades II, III and IV astrocytomas, and grades II and III ODs). Previous studies have shown that MET uptake in gliomas with an oligodendroglial component is higher than in astrocytomas, even among low-grade gliomas [17, 18]. We also found that ODs showed higher MET uptake than astrocytic tumours, regardless of the presence of the *IDH1* mutation. In detail, *IDH1*-mutant astrocytic tumours showed lower MET uptake in lower grade tumours (grade II) than in higher grade tumours (grades III and IV). Among ODs, MET uptake was higher in grade III than in grade II tumours. Indeed, grade III ODs may show MET uptake as high as that in *IDH1*-wildtype glioblastomas. Our results suggest that among grade II and III gliomas, *IDH1*-mutant tumours including large number of ODs are more likely to show high MET uptake, even paradoxically high, compared to *IDH1*-wildtype tumours. Therefore, this point concerning ODs should be taken into consideration for correct correlation between radiolabelled amino acid uptake and *IDH1* mutation status.

In contrast to previous studies, no patients with oligoastrocytoma were included in this study because in the 2016 WHO classification oligoastrocytomas are categorized as either astrocytomas or ODs on the basis of the presence of the *IDH1* mutation and 1p/19q codeletion [9]. The presence of both the *IDH1* mutation and 1p/19q codeletion characterizes ODs, whereas the presence of the *IDH1* mutation without 1p/19q codeletion is indicative of astrocytomas. Accordingly, grades II, III and IV astrocytomas were further categorized as *IDH1*-mutant or *IDH1*-wildtype. When MET TNRs were plotted on the basis of the above-mentioned detailed classification, in each grade of astrocytic tumours, *IDH1*-wildtype tumours showed significantly higher TNRs than their counterpart *IDH1*-mutant tumours.

Most studies have shown lower MET uptake in low-grade gliomas than in high-grade gliomas, but significant overlap between grades limits the value of MET PET and PET/CT for glioma grading [1, 19]. Accordingly, despite its role in biopsy, treatment guiding and prognosis prediction, the value of MET PET for qualitatively and semiquantitatively grading gliomas remains uncertain. In our study, with a cut-off TNR of 2.25 for differentiating low-grade from high-grade gliomas, ROC analysis showed a higher AUC of 0.976 in *IDH1*-wildtype gliomas than in all gliomas combined (AUC 0.852) or in *IDH1*-mutant gliomas (AUC 0.817). The best diagnostic performance of MET uptake for glioma grading was obtained in *IDH1*-wildtype gliomas.

A few studies have shown high MET uptake in *IDH1*-wildtype tumours and ODs. Okubo et al. found that expression of L-system amino acid transporter 1 (LAT1) was significantly correlated with MET uptake in gliomas [20]. Their results indicated that MET transport might be increased by an increased number of microvessels combined with a higher attenuation or activity of *LAT1* in tumour endothelial cells. Kickingereder et al. found that *IDH1*-wildtype tumours cluster at a significantly higher regional cerebral blood volume than *IDH1*-mutant tumours [21]. In addition, Saito et al. suggested that increased expression of LAT1, higher cell density, and higher cerebral blood flow may be reasons for higher MET uptake in ODs than in astrocytomas [22].

The present study had some limitations. First, volumetric parameters (e.g. metabolic tumour volume and total lesional MET uptake) were not measured because the aim of the study was to relate MET uptake to glioma grade, not to patient outcomes. Second, in some tumours, partial resection rather than total tumour removal was performed, with potential downgrading of gliomas. However, in our hospital, MR coregistered with PET/CT is used to guide surgery, such that as much tissue as possible with increased MET uptake is removed. Therefore, surgery is likely to include most regions with aggressive tumour. Third, in tumours without MET uptake, it was difficult to localize the tumour boundary on PET/CT. Coregistering T2, FLAIR and contrast-enhanced T1 images on MRI with MET PET/CT images using fusion software allowed careful exclusion of normal cortex when measuring SUV in these tumours.

In conclusion, *IDH1*-mutant tumours showed significantly lower MET uptake than *IDH1*-wildtype tumours. Regardless of the presence of the *IDH1* mutation, ODs showed high MET uptake, as high as that observed in high-grade *IDH1*-wildtype gliomas. Therefore, MET uptake predicted glioma grade better in *IDH1*-wildtype tumours than in *IDH1*-mutant tumours. These characteristics should be considered to enable the effective use of MET uptake for tumour grading, treatment planning and prediction of prognosis.

Authorship Dongwoo Kim, Joong-Hyun Chun and Mijin Yun had primary responsibility for study design, statistical analysis, coordinating the study, writing the manuscript and revision of the manuscript. Dongwoo

Kim, Se Hoon Kim, Ju Hyung Moon, Seok-Gu Kang, Jong Hee Chang and Mijin Yun contributed to data acquisition, analysis and interpretation.

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Compliance with ethical standards

Conflicts of interest None.

Ethical approval All procedures involving human participants were performed in accordance with the ethical standards of the institutional research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Formal consent is not required for this type of study.

Informed consent The Institutional Review Board of our university approved this retrospective study, and the requirement to obtain informed consent was waived.

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