Multiple positron emission tomography tracers for use in the classification of gliomas according to the 2016 World Health Organization criteria

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Abstract

Background. The molecular diagnosis of gliomas such as isocitrate dehydrogenase (IDH) status (wild-type [wt] or mutation [mut]) is especially important in the 2016 World Health Organization (WHO) classification. Positron emission tomography (PET) has afforded molecular and metabolic diagnostic imaging. The present study aimed to define the interrelationship between the 2016 WHO classification of gliomas and the integrated data from PET images using multiple tracers, including $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG), $^{11}$C-methionine ($^{11}$C-MET), $^{18}$F-fluorothymidine ($^{18}$F-FLT), and $^{18}$F-fluoromisonidazole ($^{18}$F-FMISO).

Methods. This retrospective, single-center study comprised 113 patients with newly diagnosed glioma based on the 2016 WHO criteria. Patients were divided into 4 glioma subtypes (Mut, Codel, Wt, and glioblastoma multiforme [GBM]). Tumor standardized uptake value (SUV) divided by mean normal cortical SUV (tumor–normal tissue ratio [TNR]) was calculated for $^{18}$F-FDG, $^{11}$C-MET, and $^{18}$F-FLT. Tumor–blood SUV ratio (TBR) was calculated for $^{18}$F-FMISO. To assess the diagnostic accuracy of PET tracers in distinguishing glioma subtypes, a comparative analysis of TNRs and TBR as well as the metabolic tumor volume (MTV) were calculated by Scheffe’s multiple comparison procedure for each PET tracer following the Kruskal–Wallis test.

Results. The differences in mean $^{18}$F-FLT TNR and $^{18}$F-FMISO TBR were significant between GBM and other glioma subtypes ($P < .001$). Regarding the comparison between Gd-T1WI volumes and $^{18}$F-FLT MTVs or $^{18}$F-FMISO MTVs, we identified significant differences between Wt and Mut or Codel ($P < .01$).

Conclusion. Combined administration of 4 PET tracers might aid in the preoperative differential diagnosis of gliomas according to the 2016 WHO criteria.

Key Points
• Usefulness of 4 PET tracers for glioma classification based on 2016 WHO criteria.
• Comparison between Gd-T1WI volume and MTV of $^{18}$F-FLT or $^{18}$F-FMISO was effective to classify between Wt and Mut or Codel.

According to the 2007 World Health Organization (WHO) grading criteria, gliomas, the most common primary brain tumors, comprise a heterogeneous group of histological subtypes based on cellular alterations related to tumor aggressiveness.1 Additionally, the 2016 WHO classification of Central Nervous System (CNS) tumors includes molecular genetic profiles for the subclassification of gliomas.2 Mutations in coding sequences of isocitrate dehydrogenase (IDH) 1 and IDH2 and chromosome 1p...
Importance of the Study

This is the first study examining the relationship between the 2016 WHO glioma classification and glioma classification based on multiple PET tracers to evaluate different metabolic pathways, including glucose, amino acid, and nucleic acid metabolism, and the presence of hypoxic regions. The differences in mean \( ^{18} \text{F-FLT} \) TNR and \( ^{18} \text{F-FMISO} \) TBR were significant between GBM and other glioma subtypes. The differences in mean \( ^{11} \text{C-MET} \) TNR were significant between GBM and Mut or Wt. There were significant differences in the MTV of \( ^{18} \text{F-FLT} \) between GBM and Mut or Codel. A comparison between Gd-T1WI volume and the MTV of \( ^{11} \text{C-MET} \) was significant between GBM and Codel or Wt. A comparison between Gd-T1WI volume and the MTV of \( ^{18} \text{F-FLT} \) or \( ^{18} \text{F-FMISO} \) revealed significant differences between Wt and Mut or Codel. We suggest that multiple PET tracers using \( ^{18} \text{F-FDG} \), \( ^{11} \text{C-MET} \), \( ^{18} \text{F-FLT} \), and \( ^{18} \text{F-FMISO} \) are useful for preoperative differential diagnosis of gliomas.

Materials and Methods

Patients

This retrospective, single-center study complied with the precepts established by the Declaration of Helsinki and was approved by the Kagawa University Faculty of Medicine Human Subjects Ethics Committee (no. 2019-027). \( ^{18} \text{F-FDG} \), \( ^{11} \text{C-MET} \), \( ^{18} \text{F-FLT} \), and \( ^{18} \text{F-FMISO} \) were approved for use as PET tracers by the Kagawa University Faculty of Medicine Human Subjects Ethics Committee, and an informed written consent was obtained from all participants.

From April 2009 to March 2019, 130 patients underwent \( ^{18} \text{F-FDG} \), \( ^{11} \text{C-MET} \), \( ^{18} \text{F-FLT} \), and \( ^{18} \text{F-FMISO} \) PET evaluation at Kagawa University Faculty of Medicine in Japan. We included 113 patients in the final diagnosis after excluding those who were not assessed by all 4 PET tracers, did not undergo histopathological and molecular analyses, and were diagnosed with not otherwise specified lesions (Table 1).

According to the 2016 WHO criteria,\(^2\) tumors were classified as diffuse astrocytoma (DA) with isocitrate dehydrogenase (IDH)1/2 mutation (mut) without 1p19q codeletion (DA IDH-mut), anaplastic astrocytoma (AA) with IDH1/2-mut without 1p19q codeletion (AA IDH-mut), oligodendroglioma (OD) with IDH1/2-mut and 1p19q codeletion, anaplastic oligodendroglioma (AO) with IDH1/2-mut and 1p19q codeletion, and GBM with IDH1/2 wild type (wt) (DA IDH-wt), AA with IDH1/2 wt (AA IDH-wt), glioblastoma multiforme (GBM) with IDH1/2-mut (GBM IDH-mut), and GBM with IDH1/2 wt (GBM IDH-wt). In this study, tumors were divided into Mut, Codel, Wt, and GBM glioma subtypes and were evaluated as follows: Mut, DA IDH-mut and AA IDH-mut; Codel, OD and AO; Wt, DA IDH-wt and AA IDH-wt; and GBM, GBM IDH-mut and GBM IDH-wt. All included patients were orally informed with the details regarding the study and provided their informed consent.
PET radiotracers were produced using an HM-18 cyclotron (Sumitomo Heavy Industries, Tokyo, Japan). The radiochemical purity of \(^{11}C\)-MET, \(^{18}F\)-FLT, and \(^{18}F\)-FMISO were >95%. Transmission and regional emission images of the brain were obtained as described in our previous study.\(^{10}\) Fasting was initiated 6 h before all PET studies, and the examination schedule was as follows: MRI, including contrast examination, was performed on day 1, \(^{18}F\)-FMISO was performed on day 2, \(^{18}F\)-FLT was performed on day 3, and \(^{12}C\)-MET was performed on the morning of day 4, followed by \(^{18}F\)-FDG during the afternoon of day 4.

### Image Analyses

The uptake of \(^{18}F\)-FDG, \(^{11}C\)-MET, and \(^{18}F\)-FLT in brain tumors were semiquantitatively assessed by obtaining the standardized uptake values (SUVs). A region of interest around the hottest portion of each lesion was manually set by an observer. The maximum SUV (SUV\(_{\text{max}}\)) was considered as the representative value for each tumor. The maximum tumor-to-normal ratio (TNR) was determined by dividing the tumor SUV\(_{\text{max}}\) by the mean SUV of the normal brain parenchyma (usually contralateral normal cerebral tissue excluding the ventricles). The uptake of \(^{18}F\)-FMISO in the brain tumor was semiquantitatively assessed by evaluating the SUV\(_{\text{max}}\). The \(^{18}F\)-FMISO PET images were converted into average venous blood concentration of \(^{18}F\)-FMISO to obtain the tumor-to-blood ratios (TBRs), allowing for a three-dimensional pixel-by-pixel calculation of the maximum TBR for SUV\(_{\text{max}}\). The tumor volumes were measured by performing a three-dimensional, threshold-based, volume-of-interest analysis of the hyperintensity on fluid-attenuated inversion recovery (FLAIR) images, hyperintensity on diffusion-weighted images (DWI), and contrast-enhanced lesions on gadolinium-enhanced T1-weighted images (Gd-T1WI). For PET studies, the cutoff values of 1.1 on the \(^{18}F\)-FDG TNR, 1.3 on the \(^{11}C\)-MET TNR, 1.3 on the \(^{18}F\)-FLT TNR, and 1.2 on the \(^{18}F\)-FMISO TBR were used to determine the metabolic tumor volume (MTV).\(^{6,8}\) The PET and MRI datasets were transferred to a Linux workstation, and coregistration of \(^{18}F\)-FDG/\(^{11}C\)-MET/\(^{18}F\)-FLT/\(^{18}F\)-FMISO/MRI was performed using Dr. View/Linux, version R2.5 (AJS, Tokyo, Japan). Before the histopathological and molecular diagnoses, 2 radiologists (Y.Y. and Y.N.) analyzed the data to lower the risk of observer bias to the maximum extent possible.

### Statistical Analysis

The relationship of glioma subtypes with the volume on FLAIR, Gd-T1WI, and DWI, mean TNRs on \(^{18}F\)-FDG, \(^{11}C\)-MET, and \(^{18}F\)-FLT in brain tumors were examined. To assess the diagnostic accuracy of PET tracers in distinguishing glioma subtypes, a comparative analysis of TNRs and TBR as well as the MTV were calculated by Scheffe’s multiple comparison procedure of each PET tracer following the Kruskal–Wallis test. All parametric data were expressed as averages with standard deviation. Differences were considered statistically significant at a P value of <.05. The cutoff values for volume on FLAIR,
Results

Patient Characteristics

Table 1 summarizes the characteristics of 113 patients (median age, 56.7 [21–86] years; 60 females and 53 males) classified into Mut (22 cases), Codel (14 cases), Wt (14 cases), and GBM (63 cases) for glioma subtypes.

Correlation of Glioma Subtypes with TNR and TBR Values

Figure 1 shows the correlation of glioma subtypes with the $^{18}$F-FDG, $^{11}$C-MET, and $^{18}$F-FLT TNRs and $^{18}$F-FMISO TBR. The mean $^{18}$F-FDG TNRs were 2.02 ± 0.84, 2.58 ± 0.92, 1.92 ± 0.67, and 3.22 ± 1.47 for Mut, Codel, Wt, and GBM, respectively. The differences in $^{18}$F-FDG TNRs between GBM and Mut were statistically significant ($P = .027$) (Figure 1A). The mean $^{11}$C-MET TNRs for Mut, Codel, Wt, and GBM were 3.32 ± 1.64, 4.74 ± 1.98, 3.79 ± 1.54, and 6.27 ± 2.66, respectively. The differences in mean $^{11}$C-MET TNRs were significant between GBM and Mut ($P < .001$) and GBM and Wt ($P = .006$) (Figure 1B). The cutoff value of $^{11}$C-MET TNRs was 4.424 between GBM and Mut or 4.327 between GBM and Wt. The mean $^{18}$F-FLT TNRs for Mut, Codel, Wt, and GBM were 3.2 ± 2.47, 4.69 ± 2.39, 5.61 ± 3.31, and 15.41 ± 7.03, respectively. The differences in mean $^{18}$F-FLT TNRs between GBM and other glioma subtypes were significant ($P < .001$) (Figure 1C). The cutoff value of $^{18}$F-FLT TNRs was 6.455 between GBM and Mut, 6.389 between GBM and Codel, and 7.563 between GBM and Wt. The mean $^{18}$F-FMISO TBRs for Mut,
Codel, Wt, and GBM were 1.51 ± 0.24, 1.66 ± 0.45, 1.52 ± 0.28, and 2.71 ± 0.85, respectively. The differences in $^{18F}$-FMISO TBRs were statistically significant between GBM and other glioma subtypes ($P < .001$; Figure 1D). The cutoff value of $^{18}$F-FLT TNRs was 1.760 between GBM and Mut, 1.875 between GBM and Codel, and 1.612 between GBM and Wt. (see Supplementary Table 2)

### Correlation of Glioma Subtypes with Volume of MRI and MTVs of 4 PET Tracers

**Figure 2** shows the correlation of glioma subtypes with the volumes of FLAIR, Gd-T1WI, and DWI and MTVs of $^{18F}$-FDG, $^{11C}$-MET, and $^{18F}$-FLT, and $^{18F}$-FMISO.

#### Correlations between glioma subtypes and MRI volumes

There was a significant difference in FLAIR volumes between Mut (7.42 ± 6.25 cm$^3$) and GBM (24.55 ± 14.38 cm$^3$, $P = .035$; Figure 2A). Gd-T1WI volumes were significantly different between GBM (8.28 ± 5.95 cm$^3$) and Mut (0.51 ± 0.87 cm$^3$, $P < .001$), Codel (0.82 ± 1.25 cm$^3$, $P = .036$), and Wt (0.28 ± 0.38 cm$^3$, $P = .006$; Figure 2B). DWI volumes were not significantly different among the glioma subtypes (Figure 2C; Supplementary Table 1).

#### Correlations between glioma subtypes and MTVs of 4 PET tracers

$^{18F}$-FDG MTVs were significantly different between Mut (2.55 ± 4.27 cm$^3$) and GBM (9.47 ± 7.91 cm$^3$) ($P = .010$) (Figure 2D). $^{11C}$-MET MTVs were not significantly different among the glioma subtypes (Figure 2E). $^{18F}$-FLT MTVs were significantly different between GBM (11.59 ± 8.35 cm$^3$) and Mut (2.42 ± 3.78 cm$^3$, $P = .001$) and between GBM and Codel (3.78 ± 4.75 cm$^3$, $P = .031$; Figure 2F). $^{18F}$-FMISO MTVs were significantly different between Mut (1.54 ± 2.27 cm$^3$) and GBM (9.58 ± 7.04 cm$^3$, $P < .001$; Figure 2G; Supplementary Table 2).

#### Correlations among glioma subtypes with the comparison between MTVs of 4 PET tracers and volume of each MRI

**Correlations Among Glioma Subtypes with the Comparison Between MTVs of 4 PET Tracers and FLAIR Volumes.** The MTVs of 4 PET tracers were smaller than that of the FLAIR volumes. No significant differences were observed among the glioma subtypes for comparisons between $^{18F}$-FDG MTVs and FLAIR volumes (Figure 3A) or between $^{11C}$-MET MTVs and FLAIR volumes (Figure 3B). Comparisons between $^{18F}$-FLT MTVs and FLAIR volumes revealed significant differences between GBM (0.49 ± 0.30)
and both Mut (0.16 ± 0.16, P = .021) and Codel (0.15 ± 0.13, P = .004; Figure 3C). Comparisons between 18F-FMISO MTVs and FLAIR volumes revealed significant differences between Mut (0.15 ± 0.13) and GBM (0.36 ± 0.22, P = .003; Figure 3D).

**Correlations Among Glioma Subtypes with the Comparison Between MTVs of 4 PET Tracers and Gd-T1WI Volumes.** The MTVs of 4 PET tracers were much larger than the Gd-T1WI volumes for Mut, Codel, and Wt. For GBM, the MTVs were similar or slightly larger than the Gd-T1WI volumes. Comparisons between 18F-FDG MTVs and Gd-T1WI volumes revealed significant differences between Mut (5.08 ± 4.85) and Wt (21.15 ± 21.80, P < .001) and Codel (2.29 ± 2.84, P = .005), or GBM (1.14 ± 0.66, P < .001; Figure 3E). Comparisons between 11C-MET MTVs and Gd-T1WI volumes demonstrated significant differences between Mut (1.93 ± 1.60) and both Codel (21.41 ± 21.80, P = .005) and Wt (13.67 ± 18.35, P < .001; Figure 3F). Furthermore, comparisons between 18F-FLT MTVs and Gd-T1WI volumes revealed significant differences between Wt (21.21 ± 24.19) and Mut (4.51 ± 3.10), Codel (2.81 ± 4.47), or GBM (1.36 ± 0.56) (P < .001 for all; Figure 3G). Additionally, comparisons between 18F-FMISO MTVs and Gd-T1WI volumes demonstrated significant differences between Wt (12.70 ± 11.85) and Mut (0.34 ± 0.39) and Codel (2.29 ± 2.84, P = .005), or GBM (1.30 ± 0.69, P < .001; Figure 3H).

**Correlation Among Glioma Subtypes with the Comparison Between MTVs of 4 PET Tracers and DWI Volumes.** The 11C-MET, 18F-FLT, and 18F-FMISO MTVs were larger than the DWI volumes. 18F-FDG MTVs were similar or slightly lesser than the DWI volumes. For comparison between the volumes of DWI and MTVs of 18F-FDG, 11C-MET, or 18F-FLT tracers, there were no significant differences among the glioma subtypes (Figure 3I, J, and K). Comparison between MTV of 18F-FMISO and the volume of DWI indicated significant differences between Mut (0.34 ± 0.39) and Wt (1.45 ± 1.10, P = .046) or GBM (1.30 ± 0.69, P = .001; Figure 3L; Supplementary Table 3).

**Illustrative Cases**

Figure 4 shows MRI and 4 PET images with the characteristics of each glioma subtype. The comparative analyses revealed that Mut and Codel could be distinguished by 11C-MET. Since Codel exhibited
a high $^{11}$C-MET accumulation, it was possible to distinguish Mut from Codel using the $^{11}$C-MET TNR cutoff (3.614). A 29-year-old female patient with Mut subtype (AA $IDH$-mut, 1p/19q noncodeletion) detected the accumulation of $^{11}$C-MET (SUV; 4.25, TNR; 2.891) and $^{18}$F-FLT (SUV; 0.59, TNR; 3.105) (Figure 4A). A 38-year-old female patient with Codel subtype (AA $IDH$-mut, 1p/19q codeletion) detected the higher accumulation of $^{11}$C-MET (SUV; 8.54, TNR; 6.672) than the cutoff value of $^{11}$C-MET (3.614) and the accumulation of $^{18}$F-FLT (SUV; 0.63, TNR; 3.316) (Figure 4B). Mut could be distinguished from Wt using the $^{18}$F-FLT TNR cutoff value (3.434). A 58-year-old male with the Wt subtype (AA $IDH$-wt) presented with a higher accumulation of $^{18}$F-FLT (SUV; 1.52, TNR; 5.846) than the cutoff value of $^{18}$F-FLT (SUV; 3.434) and accumulation of $^{11}$C-MET (SUV; 10.6, TNR; 10.291). Therefore, $^{18}$F-FLT TNR could be used to diagnose this case as Wt (Figure 4C). A 69-year-old male patient with GBM presented with high accumulation of $^{18}$F-FDG (TNR; 4.376, MTV; 14,543 cm$^3$), $^{11}$C-MET (TNR; 6.467, MTV; 16,833 cm$^3$), $^{18}$F-FLT (TNR; 44,556, MTV; 15,078 cm$^3$), and $^{18}$F-FMISO (TBR; 4.245, MTV; 13,514 cm$^3$). These results demonstrated that the cutoff of TNR for $^{18}$F-FDG (2.127), $^{11}$C-MET (4.424), and $^{18}$F-FLT (6.455) and TBR for $^{18}$F-FMISO (1.760) and the cutoff of MTV for $^{18}$F-FDG (2.213), $^{18}$F-FLT (3.480), and $^{18}$F-FMISO (1.760) could distinguish between Mut and GBM. The cutoff of TNR for $^{18}$F-FLT (6.389) and TBR for $^{18}$F-FMISO (1.875) and the cutoff of MTV for $^{18}$F-FLT (5.627) could distinguish between Codel and GBM. The cutoff of TNR for $^{18}$F-FLT (4.327) and $^{18}$F-FLT (7.563) and TBR for $^{18}$F-FMISO (1.612) could distinguish between Wt and GBM. Considering these results, case D was diagnosed as GBM (Figure 4D).
18F-FMISO is a nitroimidazole derivative that is exclusively trapped in hypoxic cells. GBM presents with necrosis and hypoxic environment, whereas lower-grade gliomas do not develop necrosis; therefore, 18F-FMISO is more likely to accumulate in the hypoxic GBM environment. The present study results also suggest that 18F-FMISO can differentiate GBM from lower-grade gliomas. In the GBM microenvironment where hypoxia has progressed, hypoxia-inducible factor 1α (HIF1α) associated with hypoxia is activated. Most of GBM leads to upregulating HIF1α. We previously reported that the accumulation of 18F-FMISO was significantly correlated with the expression of vascular endothelial growth factor related to HIF1α. Therefore, it is reasonable to assume that the accumulation of 18F-FMISO would be high in patients with GBM. MTV of 18F-FMISO could be distinguished GBM IDH-wt from GBM IDH-mut, but 18F-FMISO accumulation alone cannot distinguish these subtypes. A recent report showed that not only hypoxia-related signaling pathways but also transforming growth factor β might be related to gliomas with IDH-wt. The comparison between 18F-FMISO MTV and Gd-T1WI volume or DWI volume could be used to distinguish between Mut and Wt. Gd-T1WI is related to the permeability of gadolinium, while DWI reflects on cell density. Because the 18F-FMISO MTV evaluates a wider area the Gd-T1WI and DWI volumes, 18F-FMISO in Wt might evaluate active tumor cell lesions, under hypoxia, and various other conditions. More evidence based on further investigation of larger cohorts is needed to confirm that 18F-FMISO can be used to differentiate between IDH-wt and IDH-mut gliomas.

The present study has several limitations. First limitation is that the metabolism of gliomas exhibiting various molecular changes could not be evaluated using only one PET tracer. In the present study, using 4 PET tracers that could assess different metabolic pathways allowed us to classify the study patients according to the 2016 WHO glioma classification, even though not all metabolic pathways could be evaluated. Codel and Wt could not be distinguished; however, these cases can generally be discriminated by comparing 18F-FMISO and MRI, and further examination using other tracers remains necessary. A second limitation was that few patients with Mut, Codel, and Wt were included in this study. The glioma subtypes were distributed non-normally and not homoscedastically. Therefore, it was Scheffe’s multiple comparison procedure following the Kruskal–Wallis test was used for statistical analyses. The distribution can converge to a normal distribution by securing a greater number of cases; however, this will take time with a single center. The utility of multiple PET tracers in a greater number of patients across multiple institutions should be investigated.

**Conclusion**

This is the first study examining the relationship between glioma classification based on the 2016 WHO classification and multiple PET tracers evaluating different metabolic pathways. We suggest that all PET tracers using 18F-FDG, 11C-MET, 18F-FLT, and 18F-FMISO are useful for the
preoperative differential diagnosis of gliomas according to the 2016 WHO classification.

Supplementary Data
Supplementary data are available at *Neuro-Oncology* Advances online.

Keywords
2016 World Health Organization classification | glioma | positron emission tomography

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