3'-Deoxy-3'-[¹⁸F]fluorothymidine and O-(2-[¹⁸F]fluoroethyl)-L-tyrosine PET in Patients with Suspicious Recurrence of Glioma after Multimodal Treatment: Initial Results of a Retrospective Comparative Study

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Abstract

Purpose The purpose of this study was to compare the uptakes and diagnostic accuracies between 3'-deoxy-3'-[¹⁸F]fluorothymidine (FLT) and O-(2-[¹⁸F]fluoroethyl)-L-tyrosine (FET) PET in patients with a clinical suspicion of having a recurrence of glioma after multimodality treatment.

Methods Thirty-two patients who underwent FLT and FET PET due to abnormal enhancement on magnetic resonance (MR) images were included. According to surgical confirmation or follow-up results, patients were divided into those with therapy-related benign changes (TRBCs) and those with recurrence. Recurrences were divided again into initial low-grade glioma (LGG) and high-grade glioma

(HGG). The uptakes of FLT and FET were compared with the maximum standardized uptake value (SUVmax) and lesion-to-normal ratio (LNR). The diagnostic accuracies were compared via a receiver-operating-characteristic (ROC) curve analysis.

Results The LNRs of FLT in recurrences with initial HGG (8.26 ± 5.02) were significantly higher than those in recurrences with initial LGG (3.43 ± 2.14) and TRBC (1.81 ± 0.60). The LNRs of FET in recurrence with initial HGG (2.70 ± 0.48) and LGG (3.03 ± 1.32) were significantly higher than those in the TRBC (1.60 ± 0.47). The areas under the ROC curve (AUCs) of FLT and FET for initial LGG were 0.768 and 0.893, respectively. The AUCs of FLT and FET for initial HGG were 1.000 and 0.964. However, there were no statistical significances. The results for comparing with SUVmax were the same as those with LNR.

Conclusions Uptakes of FLT were different according to initial grade in patients with recurrent glioma, but those of FET were not. However, there were no statistical significances in the diagnostic accuracies according to initial grade between the two tracers in this study.

Keywords Glioma · Recurrence · Initial grade · FLT · FET · PET

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Introduction

Magnetic resonance imaging (MRI) is the imaging modality of choice for diagnosing brain tumors, but positron emission tomography (PET) may provide significant

additional clinical information in many circumstances [1]. The most widely used PET tracer is ^{18}F -fluorodeoxyglucose (FDG) and this has been successfully applied for the tumor grading of cerebral glioma, as a prognostic parameter, to guide biopsy and to differentiate tumor recurrence from radionecrosis [2–4]. Yet the specificity of FDG for tumor tissue is limited owing to its high uptake in inflammatory tissue, and the clinical usefulness of FDG for making the diagnosis of tumor recurrence is controversial [1, 4]. Another problem for brain tumor imaging is the high uptake of FDG in the normal brain tissue, which prohibits using FDG for defining the extent of tumor.

In contrast to FDG, the uptake of *O*-(2- ^{18}F fluoroethyl)-L-tyrosine (FET) in the normal brain tissue is low and brain tumors are delineated from normal brain tissue with a high level of tumor to brain contrast. Numerous studies have demonstrated that brain tumor imaging using amino acids such as ^{11}C -methionine (^{11}C -MET) are especially useful to determine the extent of cerebral glioma for planning treatment and for guiding a biopsy [5]. The role of amino acid imaging for the grading and prognosis of cerebral glioma is controversial [5]. In spite of the convincing clinical results, the use of ^{11}C -MET remains restricted to a few medical centers with an on-site cyclotron due to the short-lived ^{11}C (20-min half-life versus 109 min for ^{18}F). In recent years, some ^{18}F -labelled amino acids have been developed that allow the more widespread use of amino acid imaging. One of the most promising tracers is FET that can be produced in large amounts (like FDG) for clinical purposes [6, 7]. A number of studies have proven the clinical value of FET PET for determining the extent of cerebral glioma for planning treatment and guiding a biopsy, for the detection of tumor recurrences and for arriving at the prognosis, and especially for low-grade gliomas (LGGs) [8–12].

The fluorinated thymidine analogue 3'-deoxy-3'- ^{18}F fluorothymidine (FLT) has emerged as a promising PET tracer to evaluate tumor proliferation activity. FLT has been applied for imaging various malignant tumors [13]. FLT PET, which can image tumor proliferation, seems to be suitable for evaluating the malignant grade of brain tumors and also for evaluating the treatment response. Although there have been few FLT studies for recurrent glioma, FLT may be feasible to use for detecting recurrent glioma because FLT has a high level of tumor-to-brain contrast in high-grade glioma that is associated with high thymidine kinase 1 (TK1) activity and significant breakdown of the blood-brain barrier (BBB) [14–17].

However, there has been no study to compare FLT and FET in recurrence detection. Therefore, the purpose of this study is to compare the uptakes and diagnostic accuracies between FLT and FET PET in those patients who are suspected of having recurrent glioma after multimodality treatment.

Material and Methods

Patients

Among the patients who were previously diagnosed with glioma and who were treated with multiple modalities (such as operation, chemotherapy and radiotherapy) within a 7-year period from 2003 to 2009, 32 patients (12 men and 20 women, age range: 32–68 years old, mean age: 47.3 ± 10 years old) who underwent FLT and FET PET for determining the presence of recurrence due to an abnormal enhanced lesion on follow-up MRI were included in this retrospective study. The mean interval between the initial treatment and the suspicion of recurrence was 13 months (range: 1–114 months). In four of 32 patients, determination of recurrence and any therapy-related benign change (TRBC) was confirmed by surgical resection, and in the other 28 patients, determination of recurrence and the TRBC was confirmed by clinical follow-up and subsequent MRI with the established criteria [18]. The criteria for recurrence were defined if any of the following occurred: (1) a $\geq 25\%$ increase in the sum of the abnormal enhanced lesions over baseline with using the same techniques as at baseline, (2) a clear worsening of any evaluable disease, (3) the appearance of any new lesion or site, or (4) a failure to return for evaluation due to death or a deteriorating condition (unless it was clearly unrelated to the glioma). We then classified the patients with recurrence according to the initial grading. The patients with initial grade II glioma were classified as recurrence with initial low-grade glioma (LGG) and the patients with initial grade III and IV glioma were classified as recurrence with initial high-grade glioma (HGG). We classified patients with no recurrence as TRBC regardless of their initial grade. The patient characteristics and the FLT and FET PET results are summarized in Table 1.

PET Study

Thirty-two patients underwent both FLT and FET PET within 1 week. Among the 32 patients, 27 patients were examined with an ECAT HR+ PET scanner (Siemens Medical System, Knoxville, Tenn.). The system permitted the simultaneous acquisition of 63 axial images. The axial resolution was 4.0 mm full width at half maximum intensity, and this allowed multidirectional reconstruction of the images without the loss of resolution. The images of the brain were obtained 30 min after the intravenous injection of approximately 370 MBq of FLT and FET. A 20-min emission scan (128×128 matrix) and a 10-min post-emission transmission scan using a ^{68}Ge source were performed. The attenuation-corrected images were reconstructed with an ordered subset expectation maximization (OSEM) algorithm (two iterations and 16 subsets) with

Table 1 Characteristics, the measured values and the histopathologic data of 32 patients who were suspected of having recurrent glioma (*M* male, *F* female, *SUVmax* maximal standardized uptake in tumor, *LNR* lesion-to-normal contralateral cerebral cortex ratio, *Op/CTx/RT* operation/chemotherapy/radiotherapy, *TRBC* therapy-related benign change, *Not* LNR was not calculated because of data loss, *Recur* recurrence)

No.	Sex	Age	Initial histology	Applied treatment modalities	Duration after treatment (months)	FLT		FET		Final diagnosis
						SUVmax	LNR	SUVmax	LNR	
1	M	52	Astrocytoma II	Op/CTx/RT	7	1.20	7.50	2.70	2.45	Recur
2	F	49	Oligodendroglioma II	Op/CTx/RT	60	1.00	4.55	5.40	5.51	Recur
3	F	41	Oligodendroglioma II	Op/CTx	6	0.54	1.93	1.96	3.11	Recur
4	F	49	Oligodendroglioma II	Op/CTx/RT	6	0.60	2.50	2.40	4.00	Recur
5	M	52	Astrocytoma II	Op	18	0.40	1.14	0.70	1.30	TRBC ^d
6	M	57	Oligodendroglioma II	Op/CTx	114	0.40	1.11	2.00	2.30	Recur
7	F	44	Oligodendroglioma II	Op/CTx/RT	17	0.50	2.50	1.90	1.73	Recur
8	F	39	Astrocytoma II	Op/CTx/RT	1	0.87	3.95	1.50	2.14	Recur
9	F	67	Astrocytoma II	Op/CTx	16	0.38	1.65	1.48	1.64	TRBC
10	F	44	Oligodendroglioma II	Op/CTx/RT	12	0.15	Not ^e	1.40	Not	Recur
11	M	48	Oligodendroglioma III	Op/CTx	1	0.30	2.00	1.09	1.28	TRBC
12	F	33	Astrocytoma III	Op/CTx/RT	6	1.30	4.19	2.00	2.50	Recur
13	M	39	Astrocytoma III	Op/CTx/RT	1	0.30	1.25	1.40	2.46	TRBC
14	M	51	Astrocytoma III	Op/CTx/RT	1	2.70	7.71	1.50	2.31	Recur
15	M	35	Astrocytoma III	Op/CTx/RT	1	1.10	5.79	2.19	2.55	Recur
16	F	41	Astrocytoma III	Op/CTx	34	0.44	2.20	1.26	1.47	TRBC
17	M	51	Astrocytoma III	Op/RT	14	2.20	10.48	2.29	2.54	Recur
18	F	41	Astrocytoma III	Op/CTx	34	0.36	1.71	1.13	1.33	TRBC
19	F	33	Glioblastoma IV	Op/CTx	4	3.00	10.00	3.10	2.67	Recur
20	F	50	Glioblastoma IV	Op/CTx/RT	12	1.40	10.00	3.00	2.94	Recur
21	F	47	Glioblastoma IV	Op/CTx/RT	1	0.80	Not	1.10	Not	TRBC
22	F	49	Glioblastoma IV	Op/CTx/RT	3	1.20	8.57	2.80	1.56	Recur
23	M	53	Glioblastoma IV	Op/CTx	1	0.21	1.50	0.77	1.17	TRBC
24	F	49	Glioblastoma IV	Op/CTx/RT	5	1.40	5.83	1.90	3.39	Recur
25	F	41	Glioblastoma IV	Op/RT	19	1.10	7.33	1.90	Not	Recur
26	F	32	Glioblastoma IV	Op/CTx/RT	6	1.50	6.00	2.50	3.01	Recur
27	M	52	Glioblastoma IV	Op/CTx/RT	1	1.00	4.35	1.90	2.47	Recur
28	F	25	Glioblastoma IV	Op	1	1.18	5.62	2.29	2.57	Recur
29	F	63	Glioblastoma IV	Op	1	1.30	7.22	2.40	2.73	Recur
30	M	68	Glioblastoma IV	Op/RT	3	0.42	3.00	1.66	2.18	TRBC
31	F	63	Glioblastoma IV	Op	6	5.24	24.95	2.00	3.45	Recur
32	M	57	Glioblastoma IV	Op/CTx/RT	6	0.94	5.88	2.89	3.07	Recur

segmented attenuation correction. Among the 32 patients, five patients were examined with a Biograph 6 PET/CT scanner (Siemens Medical System, Knoxville, Tenn.). The system permitted the simultaneous acquisition of 109 axial images. The axial resolution was 2.0 mm full width at half maximum intensity. The images of the brain were obtained 30 min after the intravenous injection of approximately 370 MBq of FLT and FET. The CT scan was performed immediately before the PET scan by using a multidetector helical CT scanner. The CT images were created in a matrix

size of 512×512 but they were reduced to a 128×128 matrix to correspond to the PET emission images. The emission data were acquired for 10 min. The PET images were reconstructed using CT for the attenuation correction with the OSEM algorithm (two iterations, eight subsets).

Data Analysis

The FET and FLT uptakes in the brain lesions were semi-quantitatively assessed by evaluating the standardized

uptake value (SUV) and the lesion-to-normal tissue count density ratio (LNR). A region of interest (ROI) was set around the hottest area of each lesion or around the Gd-DTPA enhancement of MRI if increased FET and FLT uptake was absent. The maximum value of the SUV (SUVmax) was regarded as the representative value of each tumor. To calculate the LNR in a suspected recurrence of glioma, a circular ROI (1 cm in diameter) was set on the normal brain parenchyma (usually the contralateral normal frontal cerebral cortex) and the mean value of the SUV (SUVmean) was calculated. The LNR was determined by dividing the SUVmax of the tumor with the SUVmean of the normal brain tissue. To compare the uptakes of FLT and FET between the TRBC and recurrence, the averages of the SUVmax and LNR of each tracer were compared. To compare the diagnostic accuracies of each tracer for differentiating recurrence from TRBC, the areas under the curves (AUCs) of the receiver-operating-characteristic (ROC) curve analysis, according to the initial histologic grade, were compared. The sensitivities and specificities of the FLT and FET PET examinations with the optimal cut-off values were also compared.

Statistical Analysis

The Student *t*-test was used to compare the uptakes of FLT and FET between the TRBC and the recurrence. The Kruskal-Wallis test and Student *t*-test were used to compare the uptakes of FLT and FET among the TRBC and the recurrence with initial LGG and the recurrence with initial HGG. MedCalc Version 7 was used to compare the AUCs of FLT and FET and to determine the optimal cut-off values for differentiating recurrence from TRBC on the ROC analysis. The McNemar test was used to compare sensitivities and specificities. *P* values less than 0.05 were considered significant.

Results

According to surgical confirmations or follow-up results, 23 patients were determined as recurrence and nine patients as TRBC. In 23 patients with recurrence, eight patients were recurrences with initial LGG and 15 patients were recurrences with initial HGG.

The mean FLT SUVmaxs of the recurrence and the TRBC were 1.38 ± 1.08 and 0.40 ± 0.17 (Table 2). That of the recurrence was significantly higher than of TRBC ($p=0.011$). When the recurrences were divided according to initial grade, those of the recurrence with initial LGG and HGG were 0.66 ± 0.34 and 1.77 ± 1.14 . That of the recurrence with initial HGG was significantly higher than of TRBC ($p<0.002$), but there were no statistically significant differences between those of recurrence with initial LGG and TRBC ($p=0.083$, Fig. 1). The mean FLT LNRs of the recurrence and the TRBC were 6.73 ± 4.84 and 1.81 ± 0.60 (Table 2). That of the recurrence was significantly higher than of TRBC ($p=0.008$). Those of the recurrence with initial LGG and HGG were 3.43 ± 2.14 and 8.26 ± 5.02 . That of the recurrence with initial HGG was significantly higher than of TRBC ($p<0.002$), but there were no statistically significant differences between those of recurrence with initial LGG and TRBC ($p=0.058$, Fig. 1).

The mean FET SUVmaxs of the recurrence and the TRBC were 2.34 ± 0.82 and 1.18 ± 0.31 (Table 2). That of the recurrence was significantly higher than of TRBC ($p<0.001$). Those of the recurrence with initial LGG and HGG were 2.41 ± 1.28 and 2.31 ± 0.47 . Those of the recurrence with initial LGG ($p=0.013$) and HGG ($p<0.001$) were significantly higher than of TRBC, but there were no statistically significant differences those of recurrence with initial LGG and HGG ($p=0.790$, Fig. 1). The mean FET LNRs of the recurrence and the TRBC were 2.81 ± 0.83 and 1.6 ± 0.47 (Table 2). That of the recurrence was significantly higher than of TRBC ($p<0.001$). Those of

Table 2 Differences in FLT and FET uptake between the therapy-related benign changes (TBRCs) and the recurrent gliomas. Data are reported as mean $\pm$ SD

Final diagnosis	FLT		FET	
	SUVmax	LNR	SUVmax	LNR
TBRC ($n=9$)	0.40 ± 0.17	1.81 ± 0.60	1.18 ± 0.31	1.60 ± 0.47
Recurrence ($n=23$)	1.38 ± 1.08^a	6.73 ± 4.84^a	2.34 ± 0.82^a	2.81 ± 0.83^a
Initial low grade ($n=8$)	0.66 ± 0.34	3.43 ± 2.14	2.41 ± 1.28^a	3.03 ± 1.32^a
Initial high grade ($n=15$)	$1.77 \pm 1.14^{a,b}$	$8.26 \pm 5.02^{a,b}$	2.31 ± 0.47^a	2.70 ± 0.48^a

^a $p<0.05$ in comparison with TBRCs

^b $p<0.05$ in comparison with recurrence with initially low grade

Fig. 1 **a, b** The differences of the FLT SUVmax ($p < 0.002$) and the LNR ($p < 0.002$) between recurrence with an initial high grade and the TRBC were statistically significant, but the differences of the FLT SUVmax ($p = 0.083$) and the LNR ($p = 0.058$) between recurrence with an initial low grade and the TRBC were not statistically significant, and this represents that the SUVmax ($p = 0.014$) and the LNR ($p = 0.025$) of FLT were significantly different according to the initial

grade. **c, d** The differences of the FET SUVmax ($p < 0.001$) and the LNR ($p < 0.001$) between recurrence with an initial high grade and the TRBC were statistically significant, and the differences of the FET SUVmax ($p = 0.013$) and the LNR ($p = 0.012$) between recurrence with an initial low grade and the TRBC were statistically significant, but this represents that the SUVmax ($p = 0.790$) and the LNR ($p = 0.400$) of FET were not significantly different according to the initial grade

the recurrence with initial LGG and HGG were 3.03 ± 1.32 and 2.70 ± 0.48 . Those of the recurrence with initial LGG ($p = 0.012$) and HGG ($p < 0.001$) were significantly higher than of TRBC, but there were no statistically significant differences between those of recurrence with initial LGG and HGG ($p = 0.400$, Fig. 1).

The optimal cut-off value of the SUVmax for differentiating recurrences from TRBC was 0.44 (sensitivity=91.3%, specificity=88.9%, AUC=0.925) for FLT and 1.66 (sensitivity=87.0%, specificity=100%, AUC=0.978) for FET and there were no statistically significant differences ($p = 0.586, 0.343, 0.223$). The optimal cut-off value of the LNR for differentiating recurrences from TRBC was 3.0 (sensitivity=81.8%, specificity=100%, AUC=0.926) for FLT and 2.18 (sensitivity=85.7%, specificity=87.5%, AUC=0.940) for FET and there were no statistically significant differences ($p = 0.681, 0.343, 0.784$).

The optimal cut-off value of the SUVmax for differentiating recurrences with initial LGG from TRBC was 0.44 (sensitivity=75.0%, specificity=77.8%, AUC=0.785) for FLT and 1.48 (sensitivity=87.5%, specificity=88.9%, AUC=0.951) for FET and there were no statistically significant differences ($p = 0.343, 0.586, 0.124$). The optimal cut-off value of the LNR for differentiating recurrences with initial LGG from TRBC was 2.20 (sensitivity=71.4%, specificity=87.5%, AUC=0.768) for FLT and 1.64 (sensitivity=100%, specificity=75%, AUC=0.893) for FET and there were no statistically significant differences ($p = 0.177, 0.343, 0.391$, Fig. 2).

The optimal cut-off value of the SUVmax for differentiating recurrences with initial HGG from TRBC was 0.80 (sensitivity=100%, specificity=100%, AUC=1.000) for FLT and 1.66 (sensitivity=93.3%, specificity=100%, AUC=0.993) for FET and there were no statistically

Fig. 2 The AUCs of SUVmax for FLT and FET in recurrence with initial LGG (**a**) were 0.785 and 0.951 and the AUCs of LNR for FLT and FET (**b**) were 0.768 and 0.893. The AUCs of SUVmax for FLT and FET in recurrence with initial HGG (**c**) were 1.000 and 0.993 and the AUCs of LNR for FLT and FET (**d**) were 1.000 and 0.964. Although there was no statistically significant difference in AUC between each PET SUVmax and LNR on ROC analysis, the difference in AUC between the FLT and FET PET parameters (SUVmax and LNR) in recurrence with initial LGG was higher than in recurrence with initial HGG

significant differences ($p=0.343, 1.000, 0.656$). The optimal cut-off value of the LNR for differentiating recurrences with initial HGG from TRBC was 3.00 (sensitivity=100%, specificity=100%, AUC=1.000) for FLT and 2.46 (sensitivity=85.7%, specificity=100%, AUC=0.964) for FET and there were no statistically significant differences ($p=0.177, 1.000, 0.357$, Fig. 2).

Discussion

There have been many reported PET studies to differentiate recurrence in patients with glioma after treatment with multimodalities. The early studies conducted prior to 1990 reported that FDG PET had high sensitivity and specificity [19–22]. However, the recent studies have demonstrated some diagnostic limitations of FDG PET due to the FDG uptake by the inflammation in radiation necrosis and the high FDG uptake of normal brain tissue [23, 24].

Studies on ^{11}C -MET have been performed to overcome the limitations of FDG PET. Those studies reported that ^{11}C -MET had potentially better diagnostic performance than FDG for evaluating radiation necrosis [25, 26]. However, because of the short half-life of ^{11}C , the applicability of this

tracer is limited to facilities with on-site cyclotrons and the demand for ^{18}F -labelled analogues has been increasing. Both FLT and FET have been used recently for many studies of brain tumors. These studies are not been limited by cyclotrons, and both FLT and FET have a lower uptake in normal brain than that of FDG. Therefore, we thought that FLT and FET could be used to differentiate recurrence from TRBC in patients with glioma. Many studies have showed that FLT and FET also are useful for identifying recurrent glioma [9, 10, 15, 27]. However, there had been no comparative study for FLT and FET. This study is the first study to compare FLT and FET for identifying recurrent glioma.

In this study, the FET uptakes of glioma were significantly higher than those of TRBC regardless of the initial grade, but there were no significant differences between the HGG and LGG. The FLT uptakes in the initial HGG were significantly higher than those of TRBC, but there were no significant differences between recurrence and TRBC for the initial LGG. These differences of FLT and FET, according to the initial grade, can be explained by the uptake mechanisms of FLT and FET.

FLT is taken up by the cell by passive diffusion and/or facilitated transport and then it is phosphorylated by the activity of TK1 on FLT-monophosphate, which is trapped

Fig. 3a–c A 57-year-old patient (patient number 32) was initially diagnosed with glioblastoma multiforme and the patient was treated with multimodalities (operation, chemotherapy and radiotherapy). The MRI with contrast (**a**) shows a heterogeneous enhancing mass in the

left parietal lobe. The FLT PET (**b**) shows increased uptake of FLT (SUVmax=0.94, LNR=5.88) and the FET PET (**c**) shows increased uptake of FET (SUVmax=2.89, LNR=3.07) in the left parietal lobe

inside the cells. TK1 is involved in the salvage pathway of DNA synthesis, and the activity of TK1 is present in proliferating cells, which peaks in the late G1 and S phases [28]. Although FLT is not incorporated into DNA, in vitro and in vivo studies have shown that FLT uptake reflects the TK1 activity and DNA synthesis [29, 30]. Tumor grading is associated with DNA synthesis, so the FLT uptakes are different according to the tumor grading. Besides TK1 activity, another important factor that could affect FLT uptake in vivo is breakdown of the BBB. In the normal brain, FLT is only slightly able to cross the intact BBB [31, 32]. For this

reason and because of the low proliferation of normal brain tissues, FLT has a very low background uptake in the brain and FLT is significantly taken up by HGG, which is associated with significant BBB breakdown [14–17]. But FLT is not significantly taken up in LGG because of the low TK1 activity and the relatively intact BBB (Figs. 3, 4).

FET penetrates the cells via subtypes of the L-transporter (LAT2), which is restricted to transporting across the epithelium and epithelial blood barriers, while LAT1 is ubiquitous [33, 34]. Because the LAT2 subtype has been identified only in tumor cells and not in inflammatory cells,

Fig. 4a–c A 57-year-old patient (patient number 6) was initially diagnosed with oligodendroglioma II and the patient was treated with multimodalities (operation and chemotherapy). The MRI with contrast (**a**) shows a small enhancing lesion in the left parietal lobe. The FET

PET (**c**) shows increased uptake of FET (SUVmax=2.00, LNR=2.30) but the FLT PET (**b**) does not show an increased uptake of FLT (SUVmax=0.40, LNR=1.11) in the left parietal lobe

LAT2 may be responsible for an even more tumor-specific uptake of FET. So we thought that FET could be useful in differentiating between recurrence and TRBC. According to a previous MET study, it has been shown that MET uptake correlates well with the microvessel count of tumors, and therefore this is also an indirect measure of the microvessel density [35]. Additionally, the MET uptake has been shown to be higher in tumor tissue with BBB breakdown than in tumor tissue without BBB breakdown, probably owing to an additional passive influx of MET [36]. Assuming that MET and FET have somewhat analogous behavior, a higher microvessel density and more severe BBB breakdown should be shown rather a higher FET uptake in recurrence with initial HGG compared with recurrence with initial LGG. However, the uptakes of FET did not reflect the grade of glioma in this study. This might be reasonably explained by a varying extent of BBB breakdown after the different treatment modalities, followed by an unpredictable degree of additional passive influx of FET into the cells. Therefore, FET PET may be of limited value for distinguishing recurrence of initial LGG versus recurrence of initial HGG after multimodality treatment.

Although there were no statistical differences of the diagnostic accuracies between FET and FLT for differentiating recurrence of initial LGG from TRBC on the ROC analysis, the sensitivity of the FET LNR was higher than that of the FLT LNR (100% vs 71.4%, respectively), but the specificity of FET was lower than that of FLT (75.0% vs 87.5%, respectively). We think that the reason for these results is because of the relatively high non-specific background uptake of FET rather than that of FLT.

There are some limitations of this study. First, on the ROC analysis, there were no statistical differences in the diagnostic accuracies between FET and FLT for differentiating recurrence of initial LGG from TRBC, and this is possibly due to the limited number of cases in spite of the significant uptake differences. So, to clarify the difference in diagnostic accuracies between FLT and FET, further study with a large number of patients should be considered. The next limitation is the difference of the imaging acquisition modalities and the imaging reconstruction methods. In 19 of 32 patients, PET scans were performed and those PET imaging were reconstructed by a transmission scan using a ^{68}Ge source, but PET/CT scans were performed in 13 patients and those PET images were reconstructed by CT. Nakamoto et al. [37] and Choi et al. [38] suggested that the CT-based radioactivity concentration values were generally higher than the germanium-based values. Also, Bong et al. [39] reported that the SUV of brain FDG PET or PET/CT images could be different according to the attenuation correction method applied. Therefore, it is possible that the estimated SUV may be different between the estimated value of PET and that of a

PET/CT scan. But in this study, the results with the SUVmax agreed with the results with the LNR. So, we think that our conclusion has no significant error. However, to attain more exact results, performing a prospective study with the same scanner should be considered. The next limitation is the relatively short-term follow-up period. The mean follow-up period was only 13 months and in case of low-grade tumor, 13 months is short to differentiate between recurrence and TRBC due to the slow growing nature of low grade tumor. So, a long-term follow-up study should be considered to achieve more exact diagnostic accuracies. Another limitation is the definition of TRBC. Although TRBC may be divided into TRBC with initial LGG and TRBC with HGG for ideally comparing the uptakes according to the initial grade, TRBC was used as a common control for recurrence regardless of the initial grade in this study due to the limited number of TRBC with initial LGG cases. Finally, one of the limitations is the method of confirming recurrence. Among 32 patients, only four patients were surgically confirmed. So, the effects of malignant transformation on the patients of this study could not be assessed. The duration of malignant transformation is variable, ranging from 4 months to more than 3 years [40–42]. Some clinical studies reported that patients with LGG will undergo malignant transformation within 5 years in approximately 50% of cases [43, 44]. Considering that the follow-up period was relatively short in this study, malignant transformation might not have been common in this study.

Conclusions

Uptakes of FLT were different according to initial grade in patients with recurrent glioma after multimodality treatment, but those of FET were not. However, there were no statistical significances in the diagnostic accuracies according to initial grade between two tracers in this study.

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