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Determination of brain tumor recurrence using ^{11}C-methionine positron emission tomography after radiotherapy

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Abstract

We conducted a prospective multicenter trial to compare the usefulness of ^{11}C-methionine (MET) and ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) for identifying tumor recurrence. Patients with clinically suspected tumor recurrence after radiotherapy underwent both ^{11}C-MET and ^{18}F-FDG PET. When a lesion showed a visually detected uptake of either tracer, it was surgically resected for histopathological analysis. Patients with a lesion negative to both tracers were revaluated by magnetic resonance imaging (MRI) at 3 months after the PET studies. The primary outcome measure was the sensitivity of each tracer in cases with histopathologically confirmed recurrence, as determined by the McNemar test. Sixty-one cases were enrolled, and 56 cases could be evaluated. The 38 cases where the lesions showed uptake of either ^{11}C-MET or ^{18}F-FDG underwent surgery; 32 of these

Shigeru Yamaguchi and Kenji Hirata contributed equally to this work. The study was registered in the University Hospital Medical Information Network Clinical Trials Registry (ID: 000016128)

cases were confirmed to be subject to recurrence. Eighteen cases where the lesions showed uptake of neither tracer received follow-up MRI; the lesion size increased in one of these cases. Among the cases with histologically confirmed recurrence, the sensitivities of ^{11}C-MET PET and ^{18}F-FDG PET were 0.97 (32/33, 95% confidence interval [CI]: 0.85-0.99) and 0.48 (16/33, 95% CI: 0.33-0.65), respectively, and the difference was statistically significant ($P < .0001$). The diagnostic accuracy of ^{11}C-MET PET was significantly better than that of ^{18}F-FDG PET (87.5% vs. 69.6%, $P = .033$). No examination-related adverse events were observed. The results of the study demonstrated that ^{11}C-MET PET was superior to ^{18}F-FDG PET for discriminating between tumor recurrence and radiation-induced necrosis.

KEYWORDS

brain tumors, methionine, positron emission tomography, radiation injuries, recurrences

1 | INTRODUCTION

Radiotherapy for brain tumors is occasionally an indispensable treatment, but radiation-induced necrosis may occur as a late-onset complication. The majority of radiation-induced necroses occur within the range of 6 months to 3 years after treatment,[1] but it has also developed more than 10 years after radiotherapy.[2,3] The incidence of radiation-induced necrosis has been reported as 3%-24%.[4] In addition to being a problematic complication in its own right, radiation-induced necrosis is important because tumor recurrence cannot be easily distinguished by conventional radiological examinations such as computed tomography (CT) or magnetic resonance imaging (MRI).[4] Because the treatment management is quite different, it is highly important to distinguish between tumor recurrence and radiation-induced necrosis. Recurrent tumors should be treated with antitumor treatments such as surgical resection, chemotherapy, and/or radiotherapy, whereas radiation-induced necrosis should not be managed with antitumor treatment. Although histological confirmation by a surgical biopsy can provide a definitive diagnosis for treatment planning, surgery poses the risk of complications or deteriorating clinical conditions.[5] Moreover, the follow-up imaging required to evaluate the accuracy of the diagnosis may delay the treatment decision and thwart a potentially effective therapy.[6] In cases where radiation-induced necrosis becomes symptomatic, bevacizumab, a humanized monoclonal antibody that inhibits vascular endothelial growth factor, is effective to treat the necrotic lesion, reduce the perifocal edema, and improve the clinical condition.[7-10] Therefore, tumor recurrence should be identified by a noninvasive examination.

To distinguish tumor recurrence from radiation-induced necrosis, metabolic imaging would seem to be a reasonable approach.[1,11] With ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET), which is the most widely used metabolic imaging modality, it has been reported to be possible to distinguish these lesions with sensitivity and specificity ranges of 65%-81% and 40%-94%, respectively.[4] However, as the glucose utilization in the normal brain cortex is relatively high, it is sometimes difficult to precisely evaluate the uptake of ^{18}F-FDG in a lesion of interest.[12] In addition, some reports have advocated that ^{18}F-FDG PET is not sensitive enough to detect viable tumor recurrences after stereotactic radiotherapy[13] or with small lesion sizes.[14]

Compared with ^{18}F-FDG, amino acid radiotracers are expected to be able to better differentiate between recurrence and radiation-induced necrosis because amino acids exhibit lower uptake in the normal cerebral cortex than glucose.[15] Methionine is an essential amino acid related to protein synthesis, and ^{11}C-methionine (^{11}C-MET) is a well-known amino acid radiotracer that is widely considered to have good potential as a diagnostic tracer due to its sensitivity of 75%-93% and specificity of 73%-100% for differentiating between tumor recurrence and radiation-induced necrosis.[16-23] However, there are several problems with its clinical use. First, the ^{11}C-MET tracer has not been clinically approved anywhere in the world. Second, almost all previous studies have had a retrospective and single-institutional design, and therefore there are no reliable data of efficacy nor any safety evaluation so far.

To overcome these clinical flaws, we conducted a prospective, multi-institute trial to intraindividually compare the diagnostic efficacy and safety of ^{11}C-MET PET performed under the International Conference for Harmonization - good clinical practice regulations.

2 | MATERIALS AND METHODS

2.1 | Patients

This multicenter, open-labeled, single-arm trial was conducted at three Japanese institutions: Hokkaido University Hospital (Institute A), Osaka University Hospital (Institute B), and Fukushima Medical University Hospital (Institute C). Each institution obtained approval from the local ethical committee board, and each patient provided written informed consent. The study was registered in the University

Hospital Medical Information Network Clinical Trials Registry (ID: 000016128), and post hoc analysis was approved by each of the institutional review boards.

To investigate whether ^{11}C-MET PET is diagnostically more advantageous than ^{18}F-FDG PET in the determination of brain tumor recurrence after radiotherapy, we carried out an intraindividual comparison diagnostic study. Patients were eligible for inclusion in this trial if they had received irradiation for brain tumors or tumors located in sites contiguous to the brain. Patients could be enrolled from more than 6 months after radiotherapy. The patients with suspected recurrent tumors by standard MRI determinations that were difficult to distinguish from radiation-induced necrosis were included. Patients with all types of brain tumor were eligible, including primary or metastatic brain tumors. Patients for whom surgical operation after the PET examination would be impracticable were excluded. Patients were also excluded when the target lesions were strongly suspected of recurrence, as in the case of lesions with satellite lesions beyond the irradiation field.

2.2 | Study design

Figure 1 is a flow chart of this study. The patients underwent ^{18}F-FDG PET and ^{11}C-MET PET scanning; then, the attending physicians at each institution visually evaluated whether the target lesion was a tumor recurrence or if it was a radiation-induced necrosis depending on the appearance of the PET image (on-site open reading). When the target lesion showed an uptake of ^{18}F-FDG and/or ^{11}C-MET tracers, the patient underwent surgery so that the presence of viable tumor cells in the target lesion could be histopathologically evaluated. When the target lesion showed no uptake of ^{18}F-FDG or ^{11}C-MET, the patient received conservative therapy and was revaluated by MRI at 3 months after the PET study. If the size of the target lesion had increased, the patient then underwent surgery to establish the histopathology. If the size of the target lesion was stable or decreased, the target lesion was determined to be an actual radiation-induced necrosis. The size change of the target lesion was assessed, taking into account enhanced T1-weighted MRI, based on RECIST 1.1 criteria.

2.3 | ^{11}C-MET production

^{11}C-MET was synthesized by an on-column synthesis method in accordance with the guidelines and standards for in-hospital PET drugs established by the Japanese Society of Nuclear Medicine.[24] Briefly, a labeling intermediate, ^{11}C-MeOTf, was reacted with a precursor, L-homocysteine thiolactone hydrochloride, loaded on a solid-phase extraction minicolumn (Sep-Pak tC18; Waters Corporation) using an automated synthesis apparatus dedicated to ^{11}C-MET synthesis (C-MET100; Sumitomo Heavy Industries). After purification, the ^{11}C-MET solution of 7% sodium hydrogen carbonate saline (1:5) was sterilized by passage through a 0.22-μm membrane filter. The final volumes, radiochemical purities, and residual ethanol contents of

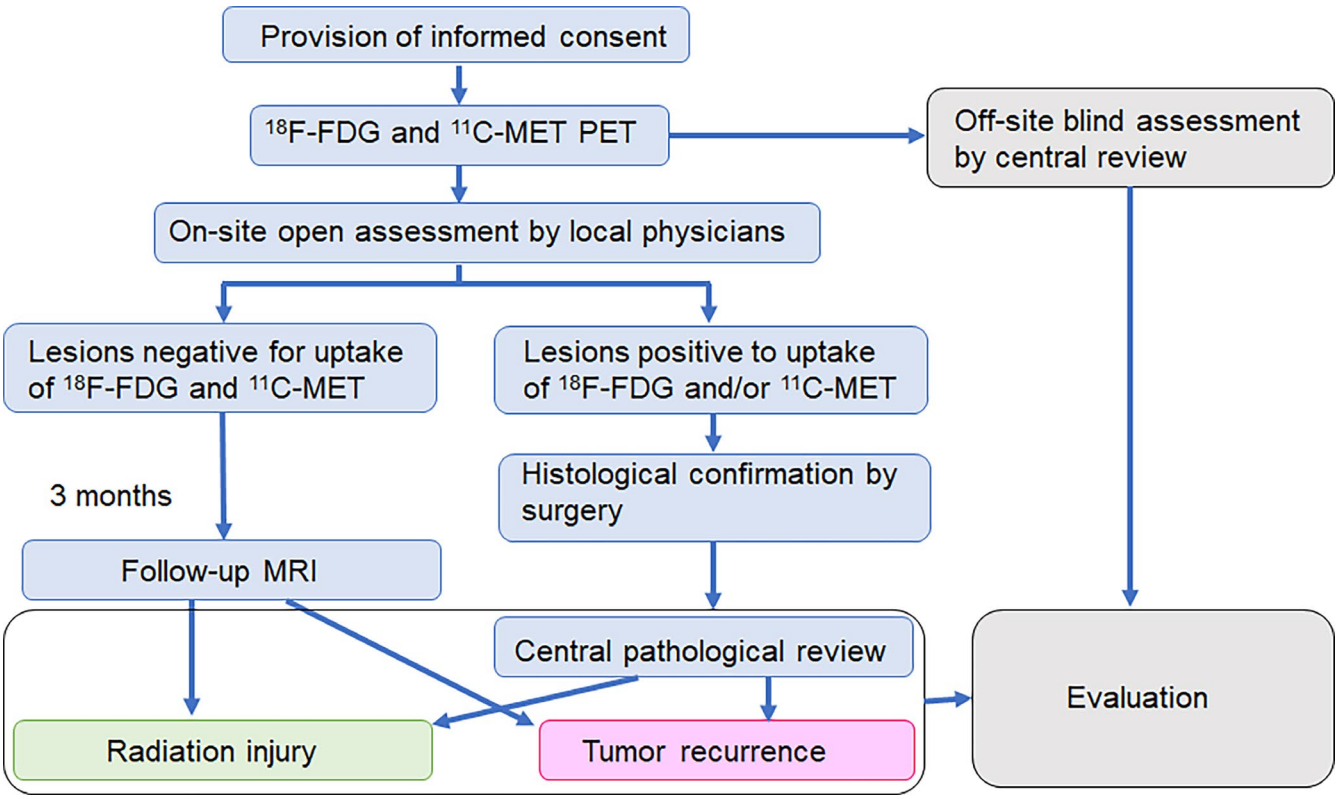

FIGURE 1 Flowchart of the study design

the ^{11}C-MET injections were 7.5-10.0 mL, >95%, <60 μg/mL, respectively. Sterility and bacterial endotoxin tests were negative.

2.4 | ^{11}C-MET and ^{18}F-FDG PET procedures

This study employed four different PET-CT scanners: a Biograph 64 (Siemens) and Gemini TF 64 (Philips) at Institute A, an Eminence-B (Shimadzu Co.) at Institute B, and a Biograph 128 (Siemens) at Institute C. In cases where the ^{11}C-MET PET and ^{18}F-FDG PET were performed on the same day, the ^{11}C-MET PET scan was performed first, and the ^{18}F-FDG PET scan was performed after the ^{11}C-MET counts became negligible. In other cases, the ^{11}C-MET PET and ^{18}F-FDG PET were performed within 1 week.

For the ^{11}C-MET, patients were instructed to fast for at least 3 hours before the ^{11}C-MET injection (250 ± 150 MBq). Twenty minutes after the injection, a 10-minute emission scanning was initiated in 3D mode. The ^{18}F-FDG was produced and delivered to the three institutes by a pharmaceutical company (Nihon Medi-Physics). Patients were instructed to fast for at least 6 hours before the ^{18}F-FDG injection (185 ± 100 MBq). Sixty minutes after the injection, a 10-minute emission scanning was initiated in 3D mode.

For both the ^{11}C-MET and ^{18}F-FDG scanning, the images were reconstructed following the standard protocol used in the daily clinical setting at each institute. More specifically, the reconstruction algorithm and voxel sizes were filtered by backprojection (1.6 × 1.6 × 3.1 mm), the ordered subset expectation maximization (OSEM) algorithm is the most popular algorithm of image reconstruction in PET with time-of-flight (TOF) (1.6 × 1.6 × 3.0 mm), OSEM with TOF (2.0 × 2.0 × 2.0 mm), and the dynamic row-action maximum likelihood algorithm (DRAMA) is an improvement of OSEM and is a high-speed image reconstruction algorithm (1.0 × 1.0 × 3.3 mm) for Biograph 64, Biograph 128, Gemini TF, and Eminence-B, respectively.

2.5 | Surgical procedures

Tissue samplings during surgery were performed using neuronavigation systems at each institution. Tissue was obtained from the lesions that exhibited a positive uptake of ^{18}F-FDG and/or ^{11}C-MET. Before the surgery, PET images were superimposed on the MRI images, and then the biopsy target was set in the lesion with uptake of either tracer. Tissue samplings were performed according to the stereotactic biopsy fashion.

2.6 | Central radiological assessment

The ^{11}C-MET and ^{18}F-FDG PET images were read independently by a third-party reading committee with three members. Information on how the study was conducted, including selection and exclusion criteria, patient background information, the type and dose of radiological agents administered, the order of administration, and the final results were not presented to the third-party readers. The patient MRI images were presented to the third-party readers because a diagnosis of the suspected recurrence location was necessary. The PET images were displayed under the condition that the reader was able to adjust window level and window width manually. Also, both rainbow and gray-scale images were used. In the visual assessment of the ^{11}C-MET PET, the ^{11}C-MET uptake of the target lesion was compared with the surrounding tissues and the entire contralateral brain parenchyma. The ^{11}C-MET uptake was judged as positive when the uptake of the target lesion was higher than that of the reference regions. In the assessment of ^{18}F-FDG PET, the target lesion was evaluated to have a positive uptake when the ^{18}F-FDG accumulation of the target lesion was higher than that of the surrounding white matter excluding physiological accumulation of gray matter.

Each reader assessed the presence or absence of recurrence independently on the ^{11}C-MET PET and ^{18}F-FDG PET images. When the same diagnosis was made by at least two of the three readers, this was considered the final diagnosis.

2.7 | Histopathological assessments

The histopathological diagnosis of each tissue sample was confirmed by the central review. To avoid interobserver differences in the histopathological criteria, one (HN) neuro-pathological specialist, who was blinded to all of the clinical and radiological information except the primary diagnosis, diagnosed all cases. The pathological diagnosis was defined as a recurrent tumor if there were viable tumor cells, and as radiation-induced necrosis if necrosis and radiation-induced changes were present but viable tumor cells were absent.

2.8 | Outcome, post hoc semiquantitative evaluation, and statistical analysis

The primary outcome measure was the diagnostic sensitivity of the ^{11}C-MET PET and ^{18}F-FDG PET in the cases with histopathologically confirmed tumor recurrence. As secondary outcome measure, the diagnostic accuracy of ^{18}F-FDG PET and ^{11}C-MET PET in differentiating tumor recurrence from radiation-induced necrosis by visual assessment was investigated. The sensitivities and diagnostic accuracy of ^{11}C-MET PET and ^{18}F-FDG PET determinations were compared by the McNemar test. The positive predictive value (PPV) of ^{11}C-MET PET was calculated from the results of the off-site reading and the final determination of the diagnosis. The confidence intervals of the sensitivity and PPV were calculated by Wilson's method. Statistical analyses were performed using SAS, version 9.4 (SAS Institute). The level of significance was set at 5%.

For the post hoc semiquantitative evaluation of ^{11}C-MET PET, the standardized uptake value (SUV) was calculated as (tissue

radioactivity concentration [Bq/mL]) × (body weight [g]/injected radioactivity [Bq]). Based on a previously reported method,[25] an experienced nuclear medicine physician placed 10 mm diameter circular regions of interest (ROI) on the highest uptake area within the tumor and the contralateral tissue of each patient. In cases where the tumor uptake was located in the gray matter, the reference ROI was placed in the contralateral gray matter. In cases where the tumor uptake was located in the white matter, the reference ROI was placed in the contralateral white matter. The SUVmax of the tumor and SUVmean of the contralateral tissue were measured, and the target-to-normal (T/N) ratios were calculated by dividing the SUVmax of the tumor by the SUVmean of the contralateral tissue. The predictive abilities of the T/N ratios were assessed using receiver operating characteristic (ROC) curves, which were estimated using logistic regression models. The diagnostic cutoff value was estimated using the ROC curves. The Mann-Whitney *U* test was utilized to compare the median T/N ratio in each group of patients. Post hoc analysis was performed using GraphPad Prism 8.42 (GraphPad Software).

2.9 | Safety of ^{11}C-MET PET

The safety of the ^{11}C-MET was evaluated in all patients. Vital sign measurements (blood pressure, pulse rate, and body temperature), biochemical tests, and urine tests were conducted before and 30 minutes after the ^{11}C-MET PET examinations in all patients. The patients were further monitored for the occurrence of adverse events during the week after the examination. Adverse events were evaluated according to MedDRA (ver. 22.1J).

3 | RESULTS

3.1 | Patient characteristics

A total of 61 patients were enrolled from February 2015 to March 2018 (32 males and 29 females; median age: 55.5 years; range: 10-76 years). One patient withdrew consent before further examination. One patient could not undergo the ^{11}C-MET PET due to poor synthesis ^{11}C-MET quality, making the final number of eligible patients 59. We confirmed that all the images for the 59 patients were of a good enough quality for the qualitative and quantitative assessments.

Table 1 shows the primary diagnoses of the eligible patients, which included 41 primary brain tumors (33 gliomas, three lymphomas, and five other brain tumors), 15 metastatic brain tumors, and three cases with treated tumors located in sites contiguous to the brain (nasopharyngeal carcinoma, maxillary carcinoma, and adenoid cystic carcinoma at the nasal cavity). The median period between the radiotherapy and registration in this study was 21.0 months (range: 6-406 months), and 39 (66%) out of the 59 eligible patients were enrolled from 6 months to 3 years after radiotherapy. The types of radiotherapy were localized irradiation (n = 38), stereotactic irradiation (n = 14), and whole-brain irradiation with/without a localized boost (n = 7). All radiotherapy was performed using X-rays except three cases (proton therapy, one case; and heavy-ion radiotherapy, two cases).

After the ^{11}C-MET and ^{18}F-FDG PET examinations, the patients were categorized into surgical and observation groups, according to the on-site reading of the appearance of tracer uptake by local attending physicians. Forty-one cases where the targeted lesions

TABLE 1 Patient characteristics in the 59 eligible cases

	All eligible (N = 59)	Surgical group (N = 41)	Observation group (N = 18)
Patient age (median, range)	55.5 (10-76)	58	54
Gender (male/female)	32/27	23/18	9/9
Initial diagnosis			
Primary brain tumors	41	32	9
Metastatic brain tumors	15	7	8
Tumors located at brain-contiguous sites	3	2	1
Radiation type			
X-ray	56	40	16
Others	3	1	2
Radiation methods			
Local fractionated (median dose)	38 (60 Gy)	31 (60 Gy)	7 (60 Gy)
Stereotactic (median dose)	14 (35 Gy)	7 (35 Gy)	7 (35 Gy)
Whole brain fractionated (median dose)	7 (50 Gy)	3 (40 Gy)	4 (55.6 Gy)
Period between RT and PET examinations (median months)	21.0	21.6	16.3

Abbreviations: PET, positron emission tomography; RT, radiation therapy.

showed uptake of either ^{11}C-MET or ^{18}F-FDG were assigned to the surgical group; and the remaining 18 cases, where lesions were not detected by either ^{11}C-MET or ^{18}F-FDG, were assigned to the observation group (Table 1).

3.2 | Overall results according to the categorization by the on-site reading

The flowchart and breakdown of eligible patients are shown in Figure 2. Two patients could not undergo surgery because of rapidly decreasing clinical status. Among the 39 patients who underwent surgery, one patient was excluded from the final evaluation due to a violation of protocol—namely, that the biopsy site was not recorded during the surgical procedure. Thus, 56 cases, 38 surgical and 18 observation cases, were assigned as acceptable for inclusion. Among the 38 surgical cases, viable tumor cells were detected in the specimens from targeted lesions in 32 cases (84%), whereas viable tumor cells were not detected in six cases (16%). Representative cases are shown in Figure 3. In the 18 observation cases, only one case (6%) had an increase in the size of the target lesion. This patient underwent resection of the lesion, and tumor recurrence was confirmed histopathologically. In the remaining 17 cases (94%), the size of the target lesion was confirmed to be stable or to have decreased. These lesions were definitively diagnosed as radiation-induced necrosis.

3.3 | Comparative effectiveness of ^{11}C-MET PET and ^{18}F-FDG PET for diagnosing tumor recurrence

As the primary outcome of this study, we evaluated the sensitivities of the ^{11}C-MET PET and ^{18}F-FDG PET for diagnosing tumor recurrence in the 33 cases of histologically confirmed tumor recurrences. A ^{11}C-MET uptake was visually detected in the target region in 32 cases, and an ^{18}F-FDG uptake was detected by the blind central offsite radiological reading in 16 cases (Table 2). The sensitivities of the ^{11}C-MET PET and of the ^{18}F-FDG PET for detecting recurrent lesions were 0.97 (32/33, 95% confidence interval [CI]: 0.85-0.99) and 0.48 (16/33, 95% CI: 0.33-0.65), respectively, and this difference was highly significant by the McNemar test ($P < .0001$).

As the secondary outcome measure, we evaluated the PPV of the ^{11}C-MET PET, and the overall sensitivity, specificity, and accuracy of the ^{11}C-MET PET and ^{18}F-FDG PET for diagnosing tumor recurrence. Table 3 details the overall results according to the offsite visual assessment by the central radiological review and the final definitive diagnosis of the target lesions in all the 56 evaluated cases. For the detection of tumor recurrence, the PPV of ^{11}C-MET PET was 0.84 (32/38, 95% CI: 0.70-0.93). The sensitivity and specificity of ^{11}C-MET PET for tumor recurrence were 97.0% and 73.9%, respectively, and those of ^{18}F-FDG PET were 48.5% and 100%, respectively. Overall, the accuracies of ^{11}C-MET PET and ^{18}F-FDG PET

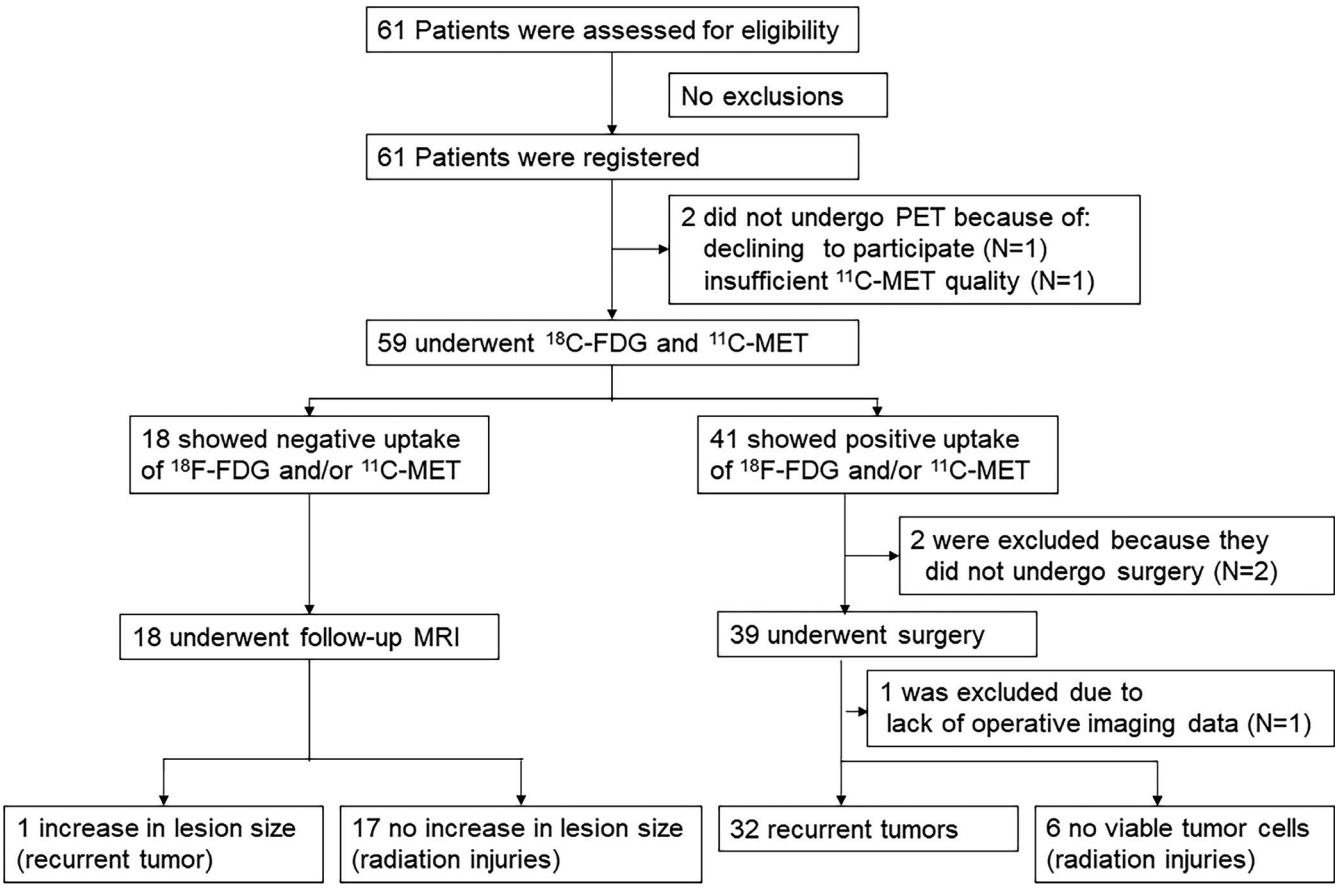

FIGURE 2 Diagram of enrollment and outcomes

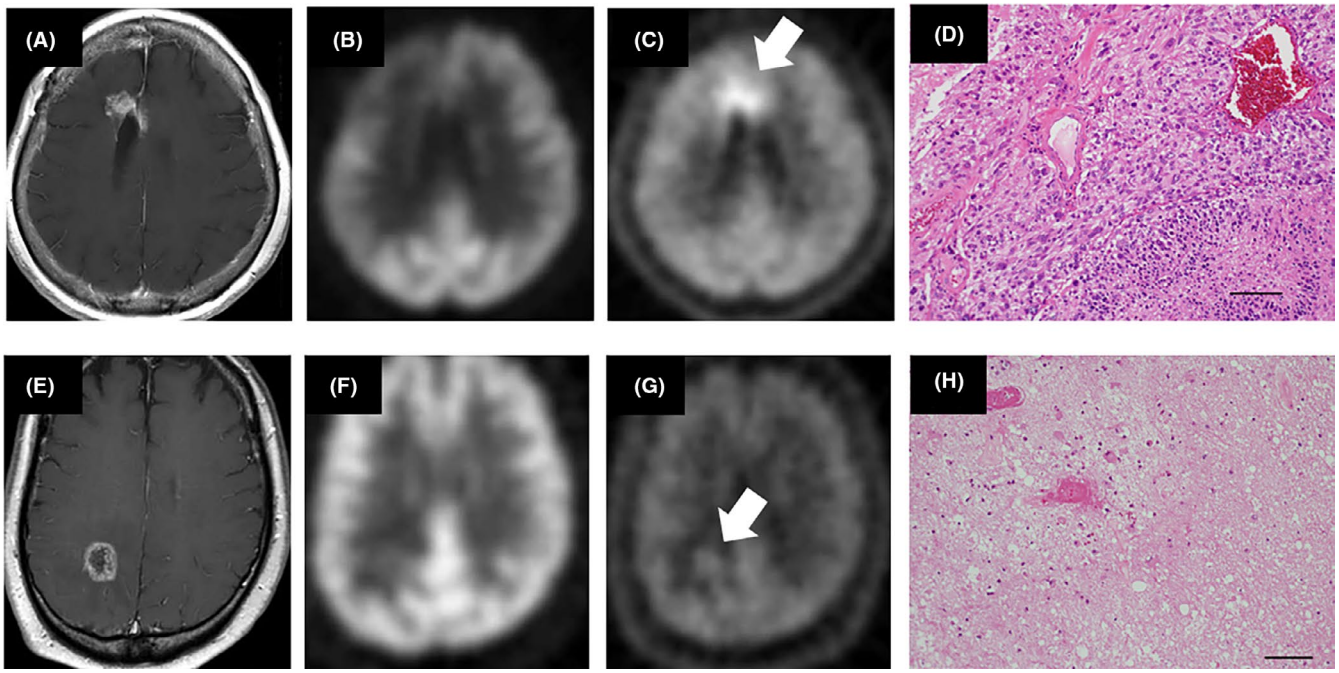

FIGURE 3 Typical cases of tumor recurrence (A-D) and radiation-induced necrosis (E-H) in the surgical group. Contrast-enhanced T1-weighted magnetic resonance images (A, E), ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) images (B, F), ^{11}C-methionine (MET) PET images (C, G). In both cases, the affected lesions did not show an uptake of ^{18}F-FDG but an uptake of ^{11}C-MET was detected (arrows). Histopathological findings of each of the lesions demonstrated tumor recurrence with viable tumor cells (D) and radiation-induced necrosis without viable tumor cells (H), respectively

TABLE 2 Results of the central off-site reading of uptake of ^{11}C-methionine and ^{18}F-fluorodeoxyglucose in the 33 histologically confirmed tumor recurrence cases

	^{18}F-fluorodeoxyglucose		
	Positive	Negative	Total
^{11}C-methionine			
Positive	16	16	32
Negative	0	1	1
Total	16	17	33

were 87.5% and 69.6%, respectively, and the accuracy of ^{11}C-MET PET was statistically better than that of ^{18}F-FDG PET ($P = .033$, McNemar test).

3.4 | Accuracy of ^{11}C-MET PET in distinguishing between tumor recurrence and radiation-induced necrosis in a semiquantitative evaluation

As a post hoc investigation, we compared the semiquantitative ^{11}C-MET uptake value between tumor recurrence and radiation-induced necrosis in the 56 cases that could be evaluated. The ^{11}C-MET T/N ratio in tumor recurrence was significantly higher than that in radiation-induced necrosis (median 2.6 vs 1.6, $P < .0001$) (Figure 4A). The highest T/N ratio in the radiation-induced necrosis was 2.18. The ROC curve generated according to the T/N ratios showed an area under the curve of 0.89. The sensitivity and specificity were 87.9% and 63.6%, respectively, with an optimal cutoff value of 1.7 (Figure 4B). Among the 38 visually "positive" uptake of ^{11}C-MET cases, six cases had no viable tumor cells, and the median T/N ratio of these six cases was 1.88 (range: 1.65-2.18). With regard to the tumor subtype, the optimal cutoff value of primary brain tumors and metastatic brain tumors were 1.74 and 1.97, respectively (Figure S1).

3.5 | Safety of the ^{11}C-MET tracer

The safety of the ^{11}C-MET tracer was evaluated in all 59 cases who actually received the ^{11}C-MET PET examination. Adverse events were observed in 10 patients (16.9%) (Table 4). Only one of these events, elevation of lactate dehydrogenase, was deemed a study-related complication, and therefore the rate of complications due to the ^{11}C-MET tracer was 1.7%. Severe adverse events were observed in two cases. In both cases, the clinical conditions of patients rapidly worsened after the ^{11}C-MET PET examination, because of the primary disease progression. Therefore, no relationships between exacerbation of symptoms and the study drug were determined.

4 | DISCUSSION

The MRI findings of radiation-induced necrosis mimic tumor recurrence, and the evaluation of metabolic activities in the lesions using

TABLE 3 Correlation between groups according to the off-site visual assessment of ^{11}C-methionine uptake, ^{18}F-fluorodeoxyglucose uptake, and final determination of target lesions

	^{11}C-methionine		^{18}F-fluorodeoxyglucose		
	positive	negative	positive	negative	Total
Recurrence	32	1	16	17	33
Radiation injury	6	17	0	23	23
Total	38	18	16	40	56

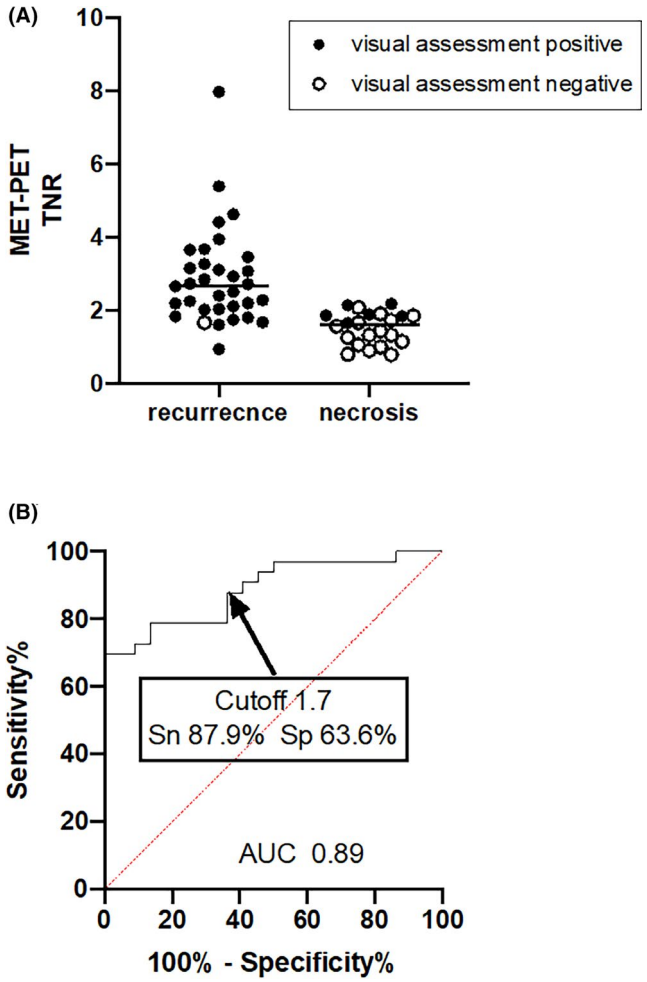

FIGURE 4 A, Dot chart of the target-to-normal (T/N) ratio in ^{11}C-methionine (MET) positron emission tomography (PET). Black dots indicate cases visually diagnosed as positive, and white dots indicate cases visually diagnosed as negative. Black lines represent the median of each group. B, Based on the receiver operating characteristic (ROC) curve analysis for differentiating tumor recurrence from radiation-induced necrosis, the area under the curve (AUC) was 0.89. The sensitivity and specificity were 87.9% and 63.6%, respectively, with a cutoff value of 1.7

TABLE 4 Adverse events after the ^{11}C-methionine PET examinations

	Total (%)	Grade 1	Grade 2	Grade 3/4
Gastrointestinal disorders				
Nausea	1 (1.7%)	1	0	0
Toothache	1 (1.7%)	1	0	0
Infections and infestations				
Pharyngitis	2 (3.4%)	2	0	0
Investigations				
LDH increased	1 (1.7%)	1	0	0
Blood pressure increased	1 (1.7%)	1	0	0
Neoplasms benign, malignant, and unspecified				
Malignant glioma	2 (3.4%)	0	0	2
Musculoskeletal and connective tissue disorders				
Pain in extremities	1 (1.7%)	1	0	0
Skin and subcutaneous tissue disorders				
Seborrheic dermatitis	1 (1.7%)	1	0	0

Abbreviations: LDH, lactate dehydrogenase; PET, positron emission tomography.

PET is a promising approach. Administration of ^{18}F-FDG PET has been a precursor in this field,[26-28] but a number of drawbacks to ^{18}F-FDG PET imaging have been reported. In this study, the specificity of ^{18}F-FDG PET in tumor recurrence was better than that of ^{11}C-MET PET, but the overall sensitivity of ^{18}F-FDG PET in tumor recurrence was just 48.5%. This result indicates that the uptake of ^{18}F-FDG in the lesion was not apparent in a number of the recurrence cases, something which would lead to inaccurate diagnosis and delays in treatment. At the same time, the PPV of ^{11}C-MET PET in tumor recurrence was 84%, and the overall sensitivity was 97%, indicating that ^{11}C-MET PET would be able to identify tumor recurrence with the higher probability. As overlooking tumor recurrence could be fatal, we concluded that the diagnostic ability of ^{11}C-MET PET in the detection of tumor recurrence was superior to that of ^{18}F-FDG PET. In this regard, it is worth noting that the majority of previous clinical studies using ^{11}C-MET PET were retrospective, and that the recurrence was defined by clinical information;[16-19] this includes our previous study.[23] According to these retrospective studies, the sensitivities and specificities of ^{11}C-MET PET were 70%-90% and 70%-100%, respectively. This present prospective trial validates the previous retrospective studies.

There have only been few retrospective reports demonstrating the diagnostic accuracy of ^{11}C-MET PET in distinguishing between tumor recurrence and radiation injury based on histopathological information.[16,29,30] Kits et al investigated 30 patients who underwent surgical resection of suspected recurrent lesions after ^{11}C-MET PET.[29] As patients with primarily suspected radiation injuries

and low uptake of ^{11}C-MET were excluded from that study, the patient population could have been similar to our surgical cases. In the Kits et al study, 21 of 30 patients (70%) had histopathologically confirmed viable tumors. In our series, 32 out of 38 patients with ^{11}C-MET uptake (84%) were confirmed to have viable tumor cells. The remaining six cases, which were found to be free of viable tumor cells, were "false-positive" by the ^{11}C-MET PET. Our result was in line with the Kits et al retrospective study.[29]

An appropriate assessment method for tracer uptake is also an option that is under discussion. In this study, we adopted visual assessment to determine whether ^{11}C-MET and ^{18}F-FDG were taken up in the targeted lesions because visual assessment may be pertinent to daily clinical practice. However, a semiquantitative analysis is also important in clinical settings, and the T/N ratio is routinely applied to calculating the sensitivity and specificity in most retrospective studies; to control for this, we performed a semiquantitative analysis in the post hoc investigation. Upon the ROC analysis, the cutoff T/N ratio of 1.7 provided a sensitivity and specificity for recurrent tumors of 87.9% and 63.6%, respectively. Previous retrospective investigations suggest that the optimal cutoff value ranged from 1.4 to 1.62.[6,16,23,29,31] The optimal cutoff T/N ratio in our study is higher than the cutoffs in those retrospective studies, indicating that our study population included patients with radiation-induced necrosis with a high T/N ratio of ^{11}C-MET uptake. The calculated optimal cutoff values with specificity and sensitivity are significantly influenced by the study population. Our study population only included patients with suspected tumor recurrences that were difficult to distinguish from radiation-induced necrosis; patients with strongly suspected radiation injuries based on conventional MRI were not included in our study, and this could be a reason why the T/N ratio is higher here than in other studies. In addition, the T/N ratio is also affected by how the ROI was placed and whether SUVmax or SUVmean was used for ratio calculations. Basically, SUVmax has a higher interoperator reproducibility but is more sensitive to image noise than SUVmean. The SUVpeak, which is basically the SUVmean in a 1-mL spherical volume of interest, could be a good candidate to solve the noise issue. The way of the T/N ratio calculations will be optimized in a future study.

In addition, because we confirmed the histopathological diagnosis in all lesions with visually positive uptakes of ^{11}C-MET, this study also showed that radiation-induced necrosis occasionally induces a mild elevation in the ^{11}C-MET uptake. It is noteworthy that in these six false-positive cases, five cases were metastatic brain tumors. On the semiquantitative evaluation, the optimal cutoff value of the ^{11}C-MET uptake of metastatic brain tumors was higher than that of primary brain tumors. Although the mechanism of uptake of ^{11}C-MET in lesions without viable cells is poorly understood, some kind of biological reaction such as inflammation may tend to occur in metastatic tumors by radiotherapy,[32] in comparison with primary brain tumors.

The visual assessment procedure would correspond to a lower cutoff value of the T/N ratio. However, Minamimoto et al[25] reported that there was no significant difference between visual and (semi) quantitative assessments in terms of the diagnostic accuracy of ^{11}C-MET for distinguishing recurrent tumors from radiation-induced necrosis. It should be noted that in this study, both the sensitivity and specificity of the prospective visual assessment of ^{11}C-MET PET were superior to those of post hoc semiquantitative analysis. This study clearly demonstrated the visual assessment of ^{11}C-MET uptake for the determination of tumor recurrence is acceptable. Because the setting of the cutoff values depends on desired or acceptable false-positive rates, it is necessary to select the appropriate therapeutic approach on an individual patient basis.[29]

In this study, 10 adverse events occurred in 10 (16.9%) of the 59 patients who received the ^{11}C-MET PET examination. One was a minor event considered a drug-related complication. There were two severe adverse events, both of which displayed rapidly decreasing performance status after the ^{11}C-MET PET examination. It should be noted that patients with recurrent brain tumors are subject to potential risks of deteriorating clinical conditions due to rapid progress of the disease. Our present findings, together with the results of our previous ^{11}C-MET PET clinical trial for patients with primary gliomas, demonstrate that ^{11}C-MET is a sufficiently safe drug for daily clinical use.

There are limitations of the present study. First, this study had only a small number of enrolled patients and included patients with various pathological subtypes. Second, the patients in whom neither ^{11}C-MET nor ^{18}F-FDG uptake was observed in the examined lesions did not receive a surgical biopsy. Because such lesions were strongly suspected of radiation-induced necrosis in previous retrospective studies, we considered that the inclusion of a surgical intervention in these lesions in our study protocol would raise ethical concerns. Instead, follow-up MRI scanning 3 months after the PET examination was applied in the final diagnostic evaluation as an alternative approach. Third, regarding the follow-up period of the observation group, 3 months may be insufficient for definitive diagnosis. In fact, some patients here continued to receive chemotherapy during the follow-up period, and thus these patients are potentially confounders.

In conclusion, this prospective trial demonstrated the diagnostic superiority of ^{11}C-MET PET over ^{18}F-FDG PET in the discrimination between tumor recurrence and radiation-induced necrosis in patients with postirradiated brain tumors. In addition, we demonstrated that ^{11}C-MET PET is safe and does not cause severe examination-related adverse events. Because the findings of previous retrospective studies were validated in this trial, use of ^{11}C-MET PET should be developed for daily clinical application in patients with brain tumors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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