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ORIGINAL ARTICLE

Determining the extent of tumor resection at surgical planning with ^{18}F-fluciclovine PET/CT in patients with suspected glioma: multicenter phase III trials

Toshihiko Wakabayashi[1] · Yuichi Hirose[2] · Keisuke Miyake[3] · Yoshiki Arakawa[4] · Naoki Kagawa[5] · Tadashi Nariai[6] · Yoshitaka Narita[7] · Ryo Nishikawa[8] · Naohiro Tsuyuguchi[9] · Tadateru Fukami[10] · Hikaru Sasaki[11] · Takashi Sasayama[12] · Akihide Kondo[13] · Toshihiko Iuchi[14] · Hiroshi Matsuda[15] · Kazuo Kubota[16] · Ryogo Minamimoto[17] · Takashi Terauchi[18] · Yoichi Nakazato[19] · Kan Kubomura[20] · Masatoshi Wada[20,21]

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Abstract

Objective Glioma is the most common type of central nervous system tumor reported worldwide. Current imaging technologies have limitations in the diagnosis and assessment of glioma. The present study aimed to confirm the diagnostic efficacy and safety of *anti*-1-amino-3-[^{18}F]fluorocyclobutane carboxylic acid (^{18}F-fluciclovine; *anti*-[^{18}F]FACBC) as a radiotracer for patients undergoing combined positron emission tomography and computed tomography (PET/CT) for suspected glioma.

Methods Combined data from two multicenter, open-label phase III clinical trials were evaluated for this study. The two trials enrolled patients with suspected high- or low-grade glioma on the basis of clinical symptoms, clinical course, and magnetic resonance imaging findings, and who were scheduled for tumor resection surgery. Patients fasted for ≥ 4 h and received 2 mL of ^{18}F-fluciclovine (radioactivity dose 78.3–297.0 MBq), followed by a 10-min PET scan 10–50 min after injection. The primary efficacy endpoint was the positive predictive value (PPV) of the gadolinium contrast-enhanced T1-weighted image negative [Gd (–)] and ^{18}F-fluciclovine PET-positive [PET (+)] area of the scans, using the histopathological diagnosis of the tissue sampled from that area as the standard of truth. All adverse events reported during the study were recorded for safety analysis.

Results A total of 45 patients aged 23–89 years underwent ^{18}F-fluciclovine PET; 31/45 patients (68.9%) were male, and 30/45 patients (66.7%) were suspected to have high-grade glioma. The PPV of ^{18}F-fluciclovine PET in the Gd (–) PET (+) area was 88.0% (22/25 areas, 95% confidence interval: 70.0–95.8). The extent of planned tumor resection was modified in 47.2% (17/36 cases) after ^{18}F-fluciclovine PET scan, with an extension of area in 30.6% (11/36 cases) and reduction in 16.7% (6/36 cases). Furthermore, tissue samples collected from PET (+) areas tended to have a higher malignancy grade compared with those from PET (–) areas. Overall, ^{18}F-fluciclovine was well tolerated.

Conclusion ^{18}F-fluciclovine PET/CT is useful for determining the extent of tumor resection at surgical planning, and may serve as a safe and effective diagnostic tool for patients with suspected glioma.

Trial Registration These trials were registered in the Japan Pharmaceutical Information Center Clinical Trials Information (JapicCTI-152986, JapicCTI-152985).

Keywords ^{18}F-fluciclovine · Glioma · Phase III trial · Positron emission tomography · Surgical planning

Introduction

Glioma is one of the most frequent types of primary brain tumor, comprising 30.2% of brain tumors reported in Japan according to a nationwide survey [1]. The 5-year survival rate was 51.8% for patients with glioma and 16.0% for patients with glioblastoma (the most malignant type

✉ Masatoshi Wada
masatoshi_wada@nmp.co.jp

Extended author information available on the last page of the article

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of glioma) in Japan [1], indicating the need for newer and improved treatment methods.

The first-line treatment of choice for glioma is surgery, which involves resection of tumor to the maximum possible extent [2, 3]. It has been reported that the overall survival of patients with glioblastoma is significantly increased by removal of ≥ 78% of the tumor volume [4]. A survey conducted in Japan also indicated that the 5-year survival rate of patients with glioblastoma is proportional to the extent of resection [1].

Gadolinium contrast-enhanced T1-weighted magnetic resonance imaging (MRI) is widely used for the diagnosis of glioma. However, it contrasts the brain tissue after disruption of the blood–brain barrier and does not specifically visualize the tumor tissue. Because the tumor often infiltrates to the outside of contrast-enhanced area in patients with high-grade glioma, and tumor exists in non-enhancing areas in patients with low-grade glioma, this method has limited sensitivity and may not be sufficient to diagnose extent of glioma infiltration [5]. It is, therefore, desirable to develop a diagnostic method that can more precisely visualize the area covered by glioma [6, 7]. Combined positron emission tomography and computed tomography (PET/CT) using ^{18}F-fluorodeoxyglucose (FDG) or ^{11}C-methyl-L-methionine (MET) has been reported to be useful in the diagnosis of glioma [8, 9], and in determining the extent of resection needed during preoperative planning [10]. However, use of these PET/CT techniques presents the following challenges: ^{18}F-FDG has a high background level because of physiological accumulation in the brain, and ^{11}C-MET requires the use of a cyclotron, because this radiopharmaceutical has a short half-life (about 20 min) [11].

The synthetic amino acid *anti*-1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid (^{18}F-fluciclovine; *anti*-[^{18}F]FACBC) has been used widely as a PET tracer since its approval by the US Food and Drug Administration and European Medicines Agency for the assessment of patients with suspected recurrent prostate cancer [12, 13]. ^{18}F-fluciclovine shows high accumulation in glioma tissues and a low background level in normal brain tissue [14]. Compared with ^{11}C-MET, ^{18}F-fluciclovine has a lower standardized uptake value (SUV) in normal brain tissue and higher tumor/normal tissue ratio [15–17]. The early phase II clinical trial showed a high sensitivity and specificity and the late phase II clinical trial have reported a high positive predictive value (PPV) of ^{18}F-fluciclovine in the diagnosis of glioma not visualized by contrast-enhanced T1-weighted imaging [18, 19].

This paper reports verification of ^{18}F-fluciclovine PET/CT for visualizing the extent of glioma that cannot be visualized by contrast-enhanced MRI, using data from two multicenter phase III trials. An integrated analysis of data from these two studies was planned a priori. The hypothesis was that ^{18}F-fluciclovine PET/CT would be a useful diagnostic tool during surgical planning for determining the margins of tumor resection in patients with suspected glioma.

Methods

Study design

The diagnostic efficacy and safety of ^{18}F-fluciclovine were evaluated in two studies (NMK36-BT-P301 and NMK36-BT-P302, Fig. 1). The first was a multicenter, non-randomized, open-label phase III clinical trial (NMK36-BT-P301; JapicCTI-152986) conducted at six centers in Japan (Supplementary Table 1) from November 2015 to October 2016. The second was a multicenter, randomized, parallel-group, open-label phase III clinical trial (NMK36-BT-P302; JapicCTI-152985) conducted at eight centers in Japan (Supplementary Table 1) from October 2015 to August 2016. Patients in this study were randomized to tumor resection planning with ^{18}F-fluciclovine in addition to MRI or MRI alone; data from the group receiving ^{18}F-fluciclovine were used in this analysis.

The study protocols of the two trials were approved by the institutional review boards of each participating center before study initiation, and the studies were conducted in accordance with the approved protocols and the ethical principles contained in the Declaration of Helsinki as well as the Good Clinical Practice (GCP). All patients included in the two studies were well informed about the study design, and provided with written informed consent before participation in the study.

Patients

The main study inclusion criteria in both studies were: patients aged ≥ 20 years who were suspected of having high- or low-grade glioma on the basis of clinical symptoms, clinical course, and MRI findings (T1-weighted, gadolinium contrast-enhanced T1-weighted or fluid-attenuated inversion recovery [FLAIR]/T2-weighted images collected at the participating facility ≤ 30 days before the date of consent to participate in the studies), and who were scheduled to undergo open surgery for tumor resection. Patients who had received treatment for glioma (open surgery for tumor resection, chemotherapy or radiotherapy) or were receiving treatment (excluding therapy to relieve neurological symptoms associated with brain tumors) were excluded from the study. Patients were also excluded if they had undergone needle biopsy for diagnostic purposes; received chemotherapy for a malignant tumor ≤ 5 years before the study; were pregnant, possibly pregnant, or lactating; had hepatic or renal dysfunction diagnosed ≤ 30 days before the studies; had a Karnofsky Performance Status of ≤ 50; had a history

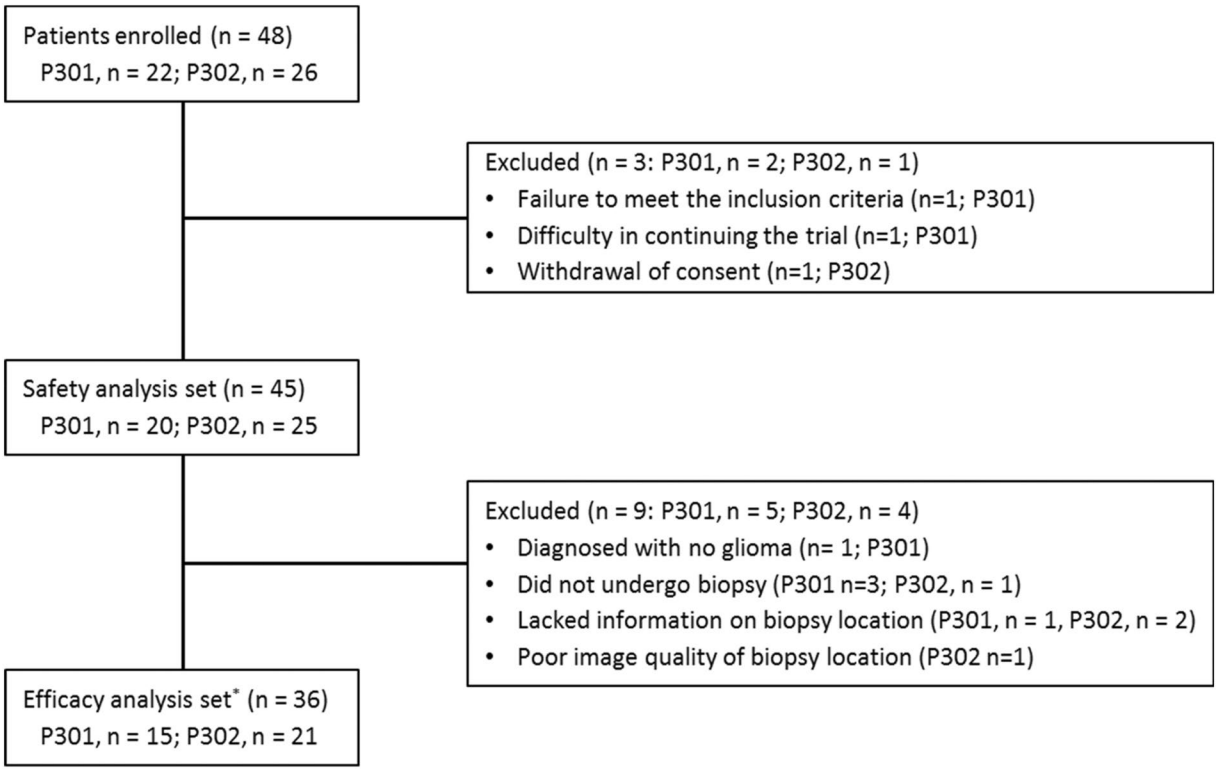

Fig. 1 Patient disposition during the study. *Pooled analysis of P301 and P302 trials. P301, NMK36-BT-P301 trial; P302, NMK36-BT-P302 trial

of severe drug allergy; had received ^{18}F-fluciclovine before the studies or had received treatment with any other investigational drugs ≤ 180 days before the date of consent for these studies. Patients were also excluded if they were judged as inappropriate for the study by the principal investigator.

The only difference in patient eligibility criteria between the two studies was that study NMK36-BT-P302 prohibited the use of ^{11}C-MET PET scanning from 180 days before inclusion to 270 days after tumor resection.

PET/CT imaging and tissue sampling

All patients in Study NMK36-BT-P301 underwent PET/CT with ^{18}F-fluciclovine; patients in Study NMK36-BT-P302 were randomized to PET/CT with ^{18}F-fluciclovine plus MRI or MRI alone. The use of ^{11}C-MET was permitted in Study NMK36-BT-P301.

In both studies, ^{18}F-fluciclovine was supplied by Nihon Medi-Physics Co., Ltd. (Tokyo, Japan) based on a previously reported method [20]. Patients fasted for ≥ 4 h and received an intravenous injection (2 mL; 185 MBq at the time of calibration) of ^{18}F-fluciclovine (radioactivity dose 78.3–297.0 MBq), followed by flushing with physiological saline. Head PET imaging (10 min) was started 10–50 min after injection, and a head computed tomography (CT) scan was conducted immediately before PET imaging to correct attenuation. Attenuation correction with an outside source of radiation was also permitted. The precision of the PET/CT devices was controlled at each facility using phantom test procedures with ^{11}C-MET, according to the specifications of the Japanese Society of Nuclear Medicine [21].

In both studies, the tissue collection site was determined by the local neurosurgeon by superimposing the MRI image and the ^{18}F-fluciclovine PET image on the navigation system and confirming whether there was an area that was negative for gadolinium contrast enhancement in T1-weighted images on MRI [Gd (–)] and positive on ^{18}F-fluciclovine PET images [PET (+)]. Since the accumulation area of ^{11}C-MET in brain tumor imaging is considered to be the same as that of ^{18}F-fluciclovine [16, 22], the biopsy site would not be affected by the use of ^{11}C-MET in study NMK36-BT-P301.

Efficacy endpoints

The procedure for evaluating the diagnostic efficacy of ^{18}F-fluciclovine was the same in the two studies, and pooled data from NMK36-BT-P301 and the group that received ^{18}F-fluciclovine in the NMK36-BT-P302 study were used for efficacy and safety analysis.

The primary efficacy endpoint was the PPV of the Gd (–) PET (+) area compared with histopathological findings, as judged by the central image evaluation committee (Supplementary Table 2). The secondary endpoints included: (i) PPV of the Gd (–) PET (+) area for each suspected malignancy at the time of enrolment, (ii) PPV of the Gd (+) PET (+) area, (iii) PPV of the PET (+) area, (iv) PPV of the Gd (–) PET (+) area analyzed by time of PET imaging, (v) negative predictive value (NPV) of the Gd (–) PET (–) area, (vi) sensitivity and specificity of ^{18}F-fluciclovine PET for all collected tissues, (vii) evaluation of the Gd (+) PET (–) area, (viii) percentage of cases yielding high-grade glioma from the PET (+) area among all cases of suspected low-grade glioma, (ix) percentage of patients for whom ^{18}F-fluciclovine PET imaging changed the extent of tumor resection, (x) comparison of histopathological findings between tissues collected from the PET (+) and PET (–) areas, (xi) inter-rater reliability of assessments of the ^{18}F-fluciclovine images.

Magnetic resonance imaging

Patients underwent an MRI scan 2–7 days after injection of ^{18}F-fluciclovine. The scans were performed at a magnetic field intensity of ≥ 1.5 T, and the following images were taken: (i) T1-weighted image (slice thickness ≤ 2 mm), (ii) gadolinium contrast-enhanced T1-weighted image (slice thickness ≤ 2 mm), and (iii) FLAIR/T2-weighted image (slice thickness ≤ 5 mm). T1-weighted imaging and gadolinium contrast-enhanced T1-weighted imaging were carried out using a 3D/2D gapless setting, and the setting was kept identical before and after the contrast medium infusion.

Tissue collection under the neuronavigation system

A tissue collection site was planned for each patient before tumor resection surgery at each institution by the local neurosurgeon. The ^{18}F-fluciclovine PET images, T1-weighted images and FLAIR/T2 images were matched with the gadolinium contrast-enhanced T1-weighted images to visually determine the extent of ^{18}F-fluciclovine accumulation in the tumors. One site from the Gd (–) PET (+) FLAIR/T2 (+) area was planned for tissue collection. In cases where no such areas could be selected, any one site of the Gd (+) PET (+) FLAIR/T2 (+) area was planned for tissue collection. If safe tissue collection was possible, another site from the Gd (–) PET (–) area was planned for tissue collection.

Tumor resection was carried out within 14 (for the group with suspected high-grade glioma) or 28 days (for those with suspected low-grade glioma) after the date of PET imaging. The effect of ^{18}F-fluciclovine PET imaging as an add-on to MRI for identifying the tumor resection area was determined using a method similar to the pattern classification by Pirotte and colleagues [10]. Before tumor resection, the dura mater was microincised within the range of craniotomy conducted for tumor resection to minimize brain shifts. Then biopsies were performed to collect tissues under the neuronavigation system (iPlan Cranial, Brainlab AG, Feldkirchen, Germany or StealthStation, Medtronic plc, Dublin, Ireland). The tissue collection site was displayed on three axes on the contrast-enhanced T1-weighted image, which was saved as a snapshot for use during central image evaluation.

Evaluation of tissue collection sites (central image evaluation)

The tissue collection sites were independently evaluated by members of the central image evaluation committee in charge of the MRI and PET (Supplementary Table 2) using the PMOD Program Version 3.402 (PMOD Technologies, Zurich, Switzerland).

First, one member in charge of MRI co-registered the T1-weighted image and the FLAIR/T2 image to the gadolinium contrast-enhanced T1-weighted image using automatic co-registration with PMOD software. The tissue collection sites were identified and the volume of interest (VOI) of 5 mm diameter on the gadolinium contrast-enhanced T1-weighted image was set based on the snapshots recorded at the biopsies under the navigation system.

Then, three members in charge of PET performed automatic co-registration of the PET image to the gadolinium contrast-enhanced T1-weighted image using PMOD software. PET (+) area was determined by displaying PET image under the following conditions using the Hot Iron for the lookup table. When the SUVmax of the tumor was 2.5 or more, the upper scale value was 50% of the SUVmax of the tumor and the lower scale value was twice the SUVmean of the normal region. When the SUVmax of the tumor was less than 2.5, the upper scale value was 75% of the tumor SUVmax (used 1.0 if less than 1.0) and the lower scale value was 1.5 times the SUVmean in the normal region. The SUVmax of the tumor was measured by setting a spherical VOI including the entire tumor. The SUVmean of the normal region was measured by identifying the center of the tumor in the sagittal image, then displaying the transaxial image at the specified center of the tumor and setting a VOI with a 10 mm diameter of normal tissue on the contralateral side of the tumor. Examples of the displaying PET image in cases of high and low SUVmax are illustrated in Fig. 2. The 5 mm-VOI of the tissue collection site was displayed on the PET image to judge whether the tissue collection site was within PET (+) area or not. The PET (+) area was defined as the PET accumulation area where the normal region could be clearly distinguished and which was consistent with the MR image. Care was taken not to include the physiological

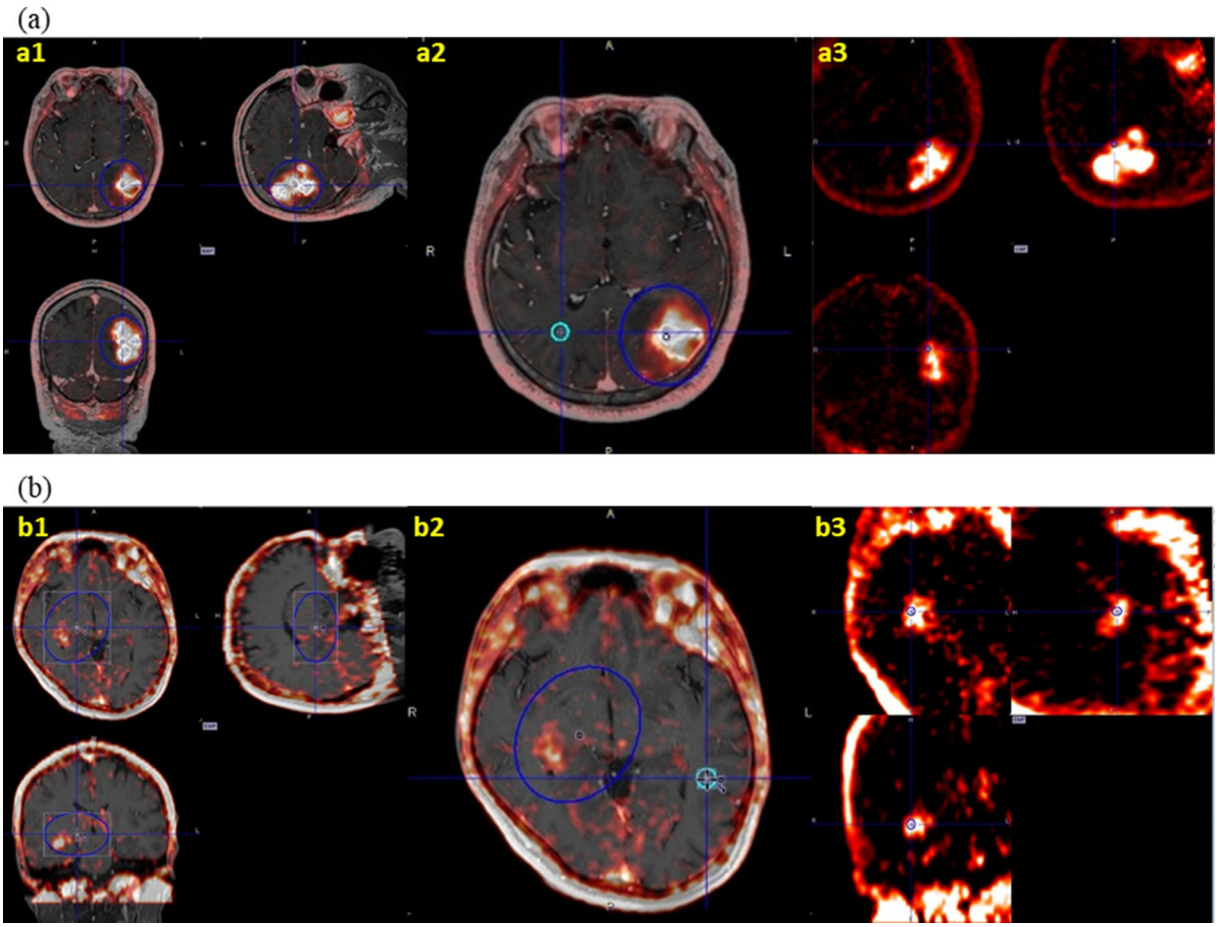

Fig. 2 Examples of the procedure for displaying PET (+) area. **a** Example case of SUVmax ≥ 2.5 (Patient 05H). The SUVmax of the tumor was measured by setting a spherical VOI including the entire tumor (blue VOI), and was 7.70 (**a1**). The SUVmean of the normal region was measured by identifying the center of the tumor in the sagittal image, then displaying the transaxial image at the specified center of the tumor and setting a VOI with a 10 mm diameter of normal tissue on the contralateral side of the tumor (light blue VOI), and was 0.19 (**a2**). Since the SUVmax of the tumor was more than 2.5, the upper scale value was set at 3.85 (50% of the SUVmax) and the lower scale value was set at 0.38 (twice the SUVmean of the normal region) (**a3**). **b** Example case of SUVmax < 2.5 (Patient 11L). The SUVmax of the tumor was measured by setting a spherical VOI including the entire tumor (blue VOI), and was 1.35 (**b1**). The SUVmean of the normal region was measured by identifying the center of the tumor in the sagittal image, then displaying the transaxial image at the specified center of the tumor and setting a VOI with a 10 mm diameter of normal tissue on the contralateral side of the tumor (light blue VOI), and was 0.26 (**b2**). Since the SUVmax of the tumor was less than 2.5, the upper scale value was set at 1.01 (75% of the SUVmax) and the lower scale value was set at 0.39 (1.5 times of the SUVmean of the normal region) (**b3**)

accumulation of blood vessels (especially when there was PET accumulation near the skull or brain surface) and the pituitary gland. Furthermore, the 5 mm-VOI of the tissue collection site was also displayed on the T1-weighted image, the contrast-enhanced T1-weighted image, and the FLAIR/T2 image, then the presence or absence of contrast enhancement and the signal intensity of FLAIR/T2 at the tissue collection site were determined, respectively. It was defined in the judgement of Gd (+) that it had an enhanced effect equal to or higher than the signal intensity of the cavernous sinus, that the contrast area was able to be contoured, and that the T1-weighted image indicated the higher signal intensity due to the contrast effect. The contrast effect due to blood vessels was not considered as Gd (+). The majority judgment was adopted as the final judgment.

Histopathological evaluation of tissues (central pathological diagnosis)

Each of the collected tumor tissue samples were fixed in formalin and embedded in paraffin. Thin sections were then stained with hematoxylin and eosin (HE), and underwent immunohistochemical analysis using antibodies against GFAP, Olig-2, NFP-MH, Nestin, MIB-1, IDH-1, p53 and, if needed, ATRX. The stained sections were evaluated for

malignancy grade, Ki-67 labelling indices, and content of tumor cells by the member of an independent central pathological diagnosis committee (Supplementary Table 2) according to the 2007 WHO classification [23].

Safety

The safety of ^{18}F-fluciclovine was evaluated before (on the day of injection) and 2–7 days after injection by recording the following parameters: patient's subjective symptoms/objective findings (measured also after PET imaging on the day of injection); 12-lead electrocardiogram (ECG) at rest; vital signs (blood pressure, heart rate); hematology (red blood cells, hemoglobin, hematocrit, white blood cells, differential leukocyte count [neutrophil, eosinophil, lymphocyte, monocyte, basophil]), platelet count; clotting tests (prothrombin time-international normalized ratio [PT-INR], activated thromboplastin time, fibrinogen); biochemistry (albumin, alkaline phosphatase, aspartate aminotransferase, alanine transaminase, γ-glutamyl transferase, lactate dehydrogenase, total bilirubin, urea nitrogen, creatinine, total creatine phosphokinase, total protein, triglyceride, total cholesterol, glucose, Na, K, Cl, Ca, P); and urinalysis (protein, glucose, occult blood). Additionally, the incidences of all adverse events (AEs) along with their outcomes, severity, seriousness, and causal relationship to ^{18}F-fluciclovine were also noted.

Statistical analysis

For determination of a target sample size, the expected PPV of the Gd (–) PET (+) area was assumed to be 95%, based on the results of the late phase II clinical trial [19]. The threshold PPV was set at 70% so that the sensitivity would be equal to or higher than the PPV of aminolevulinic acid hydrochloride (65.8%) [24]. Using the method described by Fleming and colleagues [25], the number of tissue samples needed to achieve this value was calculated to be 23. The target number of patients was set at 47 based on the following assumptions: 5% probability of being unable to collect tissue samples, 20% cases of deviation from the inclusion criteria during the study, ratio of 1.6 suspected high-grade gliomas for every one suspected low-grade glioma, and the percentage of patients enabling collection of Gd (–) PET (+) area being 50% in those with high-grade malignancy and 95% in those with low-grade malignancy.

Statistical analysis was performed using SAS Version 9.3 (SAS Institute, Japan). The mean ± standard deviation (SD) values of each parameter were used for analysis. The PPV of the Gd (–) PET (+) area was subjected to a one-sided binomial test through normal approximation for the population rate of 0.7 (threshold PPV 70%). The significance level was set at 2.5%. The 95% confidence interval (CI) was calculated by the Wilson method. The inter-rater reliability was evaluated by calculating the consistency rate and Kappa coefficient for all pairs of examiners (a-b, a-c and b-c).

Results

A total of 48 consenting patients were assigned to receive ^{18}F-fluciclovine in the two studies (P301: $n = 22$, P302: $n = 26$), of whom 45 patients (P301: $n = 20$, P302: $n = 25$) received ^{18}F-fluciclovine and were included in the safety analysis set (Fig. 1). The efficacy analysis set included 36 patients (P301: $n = 15$, P302: $n = 21$), excluding 9 patients from the safety analysis set who were not evaluable for efficacy (Fig. 1). Tissue samples were excluded from the analysis of PPV and NPV if they were collected from areas with discordant readings between the local neurosurgeon and central imaging committee, e.g. judged to be PET (+) by the local neurosurgeon but PET (–) by the central imaging committee or vice versa. The majority of patients included in the safety analysis set were male (P301: 65%, 13/20 cases; P302: 72%, 18/25 cases), with 66.7% suspected of having high-grade glioma (P301: 70%, 14/20 cases, P302: 64%, 16/25 cases) (Table 1). The mean ± SD radioactivity dose for the patients included in the safety analysis set was

Table 1 Baseline characteristics of patients included in the safety analysis set ($n = 45$)

Item	P301 ($n = 20$)	P302 ($n = 25$)
Age, years		
Mean ± SD	55.4 ± 14.0	54.3 ± 17.4
Range	23–76	31–89
Sex, n (%)		
Male	13 (65.0)	18 (72.0)
Female	7 (35.0)	7 (28.0)
Suspected grade, n (%)		
Suspected high-grade glioma	14 (70.0)	16 (64.0)
Suspected low-grade glioma	6 (30.0)	9 (36.0)
Comorbidity, n (%)		
Yes	14 (70.0)	16 (64.0)
No	6 (30.0)	9 (36.0)
Karnofsky performance status, n (%)		
100	6 (30.0)	7 (28.0)
90	11 (55.0)	9 (36.0)
80	0	4 (16.0)
70	2 (10.0)	2 (8.0)
60	1 (5.0)	3 (12.0)
≤ 50		0

P301 NMK36-BT-P301 trial, *P302* NMK36-BT-P302 trial, *SD* standard deviation

177.3 ± 62.8 MBq; two patients received a dose that was outside the planned range (303.6 and 64.8 MBq).

Diagnostic efficacy of ^{18}F-fluciclovine

All 63 tissues included in the efficacy analysis set were analyzed. Details of the areas of the tissue collection sites based on the central image evaluation were as follows: Gd (–) PET (–) FLAIR/T2 (–) on 2 tissues (1 tumor and 1 non-tumor), Gd (–) PET (–) FLAIR/T2 (+) on 27 tissues (20 tumors and 7 non-tumors), Gd (–) PET (+) FLAIR/T2 (+) on 31 tissues (26 tumors and 5 non-tumors), and Gd (+) PET (+) FLAIR/T2 (+) on 3 tissues (3 tumors) (Table 2). Of these, 6 tissues of Gd (–) PET (+) FLAIR/T2 (+) (4 tumors and 2 non-tumors) and 3 tissues of Gd (–) PET (–) FLAIR/T2 (+) (3 tumors) were excluded from the analysis of PPV and NPV, because the judgment of the presence or absence of PET accumulation was different between the local neurosurgeon and the central image evaluation.

Table 2 Details of the area of the tissue collection site based on the central image evaluation ($n = 63$)

Central image evaluation			Number of tissues	Central pathological diagnosis	
Gd	PET	FLAIR/T2		Tumor	Non-tumor
–	–	–	2	1	1
–	–	+	27	20	7
–	+	+	31	26	5
+	+	+	3	3	0
Total			63	50	13

Gd gadolinium-enhanced T1-weighted image, *PET* positron emission tomography, *FLAIR/T2* fluid-attenuated inversion recovery or T2-weighted image

The PPV of the Gd (–) PET (+) area was 88.0% (22/25 areas; 95% CI 70.0–95.8; Table 3), which was significantly higher than the threshold PPV of 70% ($p = 0.003$; one-sided binomial test). Representative true positives in a patient with suspected high-grade glioma and low-grade glioma are shown in Figs. 3 and 4, respectively. The PPV was 100.0% in the P301 study (11/11 areas; 95% CI 74.1–100.0) and 78.6% in the P302 study (11/14 areas; 95% CI 52.4–92.4). The PPV of the Gd (–) PET (+) area was 88.9% in the group with suspected high-grade glioma (16/18 areas; 95% CI 67.2–96.9) and 85.7% in the group with suspected low-grade glioma (6/7 areas; 95% CI 48.7–97.4; Table 3). Finally, the PPV of the Gd (+) PET (+) area was 100.0% (3/3 areas; 95% CI 43.9–100.0) and the entire PET (+) area was 89.3% (25/28 areas; 95% CI 72.8–96.3) for the two studies (Table 3). When analyzed by the time of initiation of PET scan after injection, the PPV of the Gd (–) PET (+) area was 89.5% when imaging was started 10– < 30 min after injection of ^{18}F-fluciclovine (17/19 areas; 95% CI 68.6–97.1), and 83.3% when the scan started 30–50 min after injection (5/6 areas; 95% CI 43.6–97.0).

The NPV of the Gd (–) PET (–) area was 30.8% (8/26 areas; 95% CI 16.5–50.0) overall, 44.4% (8/18 areas; 95% CI 24.6–66.3) in the group with suspected high-grade glioma and 0.0% in the group with suspected low-grade glioma (0/8 areas; 95% CI 0.0–32.4).

The sensitivity and specificity of ^{18}F-fluciclovine were 58.0% (29/50 tissues; 95% CI 44.2–70.6) and 61.5% (8/13 tissues; 95% CI 35.5–82.3), respectively (Table 4).

Of the 36 patients included in the efficacy analysis set, three patients had a Gd (+) PET (–) area and these patients showed ring-shaped enhancement on the contrast-enhanced MR images. None of the tissue samples collected from the PET (+) area of the suspected low-grade glioma patients ($n = 13$) were histopathologically diagnosed as showing high-grade glioma.

Table 3 Positive predictive value of ^{18}F-fluciclovine positron emission tomography for the diagnosis of glioma

Central pathological diagnosis	Central image evaluation					
	Gd (–), PET (+) area, n[a]					Gd (+), PET (+) area, n[a]
	All glioma	Trials		Suspected grade		
		P301	P302	Suspected high-grade glioma	Suspected low-grade glioma	
Tumor	22	11	11	16	6	3
Non-tumor	3	0	3	2	1	0
Total	25	11	14	18	7	3
PPV, % (95% CI)	88.0 (70.0–95.8)	100.0 (74.1–100.0)	78.6 (52.4–92.4)	88.9 (67.2–96.9)	85.7 (48.7–97.4)	100.0 (43.9–100.0)

CI confidence interval, *Gd* gadolinium-enhanced T1-weighted image, *P301* NMK36-BT-P301 trial, *P302* NMK36-BT-P302 trial, *PET* positron emission tomography, *PPV* positive predictive value

[a]Number of areas

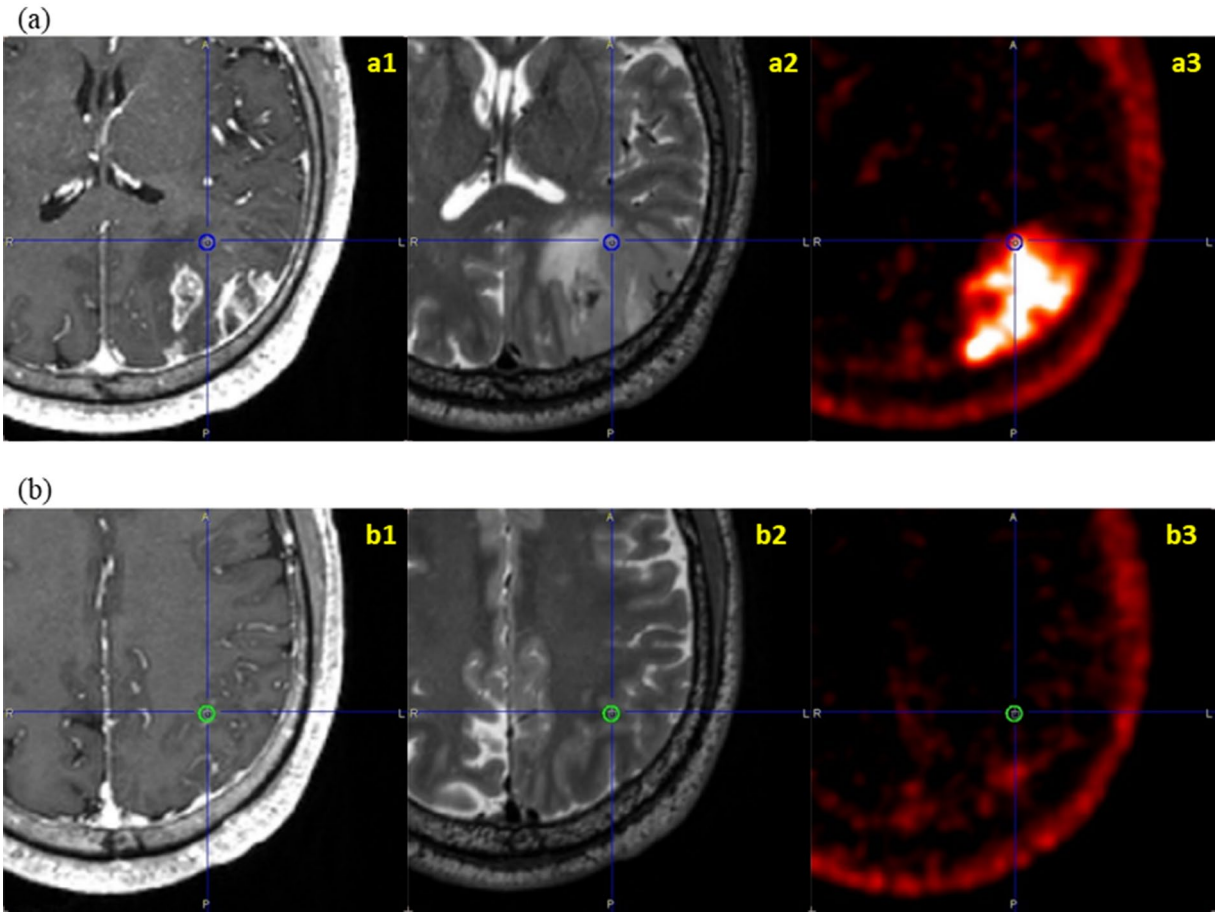

Fig. 3 Representative images of a true positive case in a patient with suspected high-grade glioma (Patient 05H). In each set, images a1 and b1 are the gadolinium contrast-enhanced T1-weighted magnetic resonance imaging (MRI) images, a2/b2 are the T2-weighted MRIs, and a3/b3 are the ^{18}F-fluciclovine-positron emission tomography (PET) images. The crosshair indicates the tissue collection site. In set (**a**), a tissue sample was collected from a gadolinium-enhanced T1-weighted image negative [Gd (–)] ^{18}F-fluciclovine PET positive [PET (+)] area (SUVmax = 4.23, SUVmean = 2.48) and histopathologically diagnosed as diffuse astrocytoma (World Health Organization [WHO] grade II) with 11.4% of Ki-67 and 25% of content of tumor cells, and in set (**b**) a tissue sample was collected from a Gd (–) ^{18}F-fluciclovine PET negative [PET (–)] area (SUVmax = 0.84, SUVmean = 0.42) and histopathologically diagnosed as no evidence of tumor with 1.7% of Ki-67 and 0% of content of tumor cells. The definitive diagnosis was glioblastoma (WHO grade IV). SUV, standardized uptake value

In the suspected high-grade glioma group, 29 of the 38 tissues collected from the Gd (–) FLAIR/T2 (+) area turned out to be tumors. Of the 29 tumor tissues, only 17 tissues were positive for ^{18}F-fluciclovine PET (sensitivity 65.5%), and some tumors could not be detected by PET. On the other hand, of the 38 tissues collected from the Gd (–) FLAIR/T2 (+) area, 9 resulted in non-tumor tissues. Of the 9 non-tumor tissues, 0 tissue was negative for FLAIR/T2 (specificity 0%), and 7 tissues were negative for ^{18}F-fluciclovine PET (specificity 77.8%).

Change in the extent of planned tumor resection after ^{18}F-fluciclovine PET scanning

Among the patients included in efficacy analysis ($n = 36$), the ^{18}F-fluciclovine PET scan modified the extent of planned tumor resection in 17 cases (47.2%) compared with MRI alone: tumor resection area was extended in 11 patients (30.6%) and reduced in six patients (16.7%; Table 5, Supplementary Table 3). ^{18}F-Fluciclovine PET imaging increased the tumor resection area in 11 of the 23 patients with high-grade glioma whose surgical goal is maximal safe resection of the contrast-enhanced area, and decreased the tumor resection area in 3 of the 13 patients with low-grade glioma whose surgical goal is maximal safe resection of the FLAIR/T2 hyper-intensity area (Table 5).

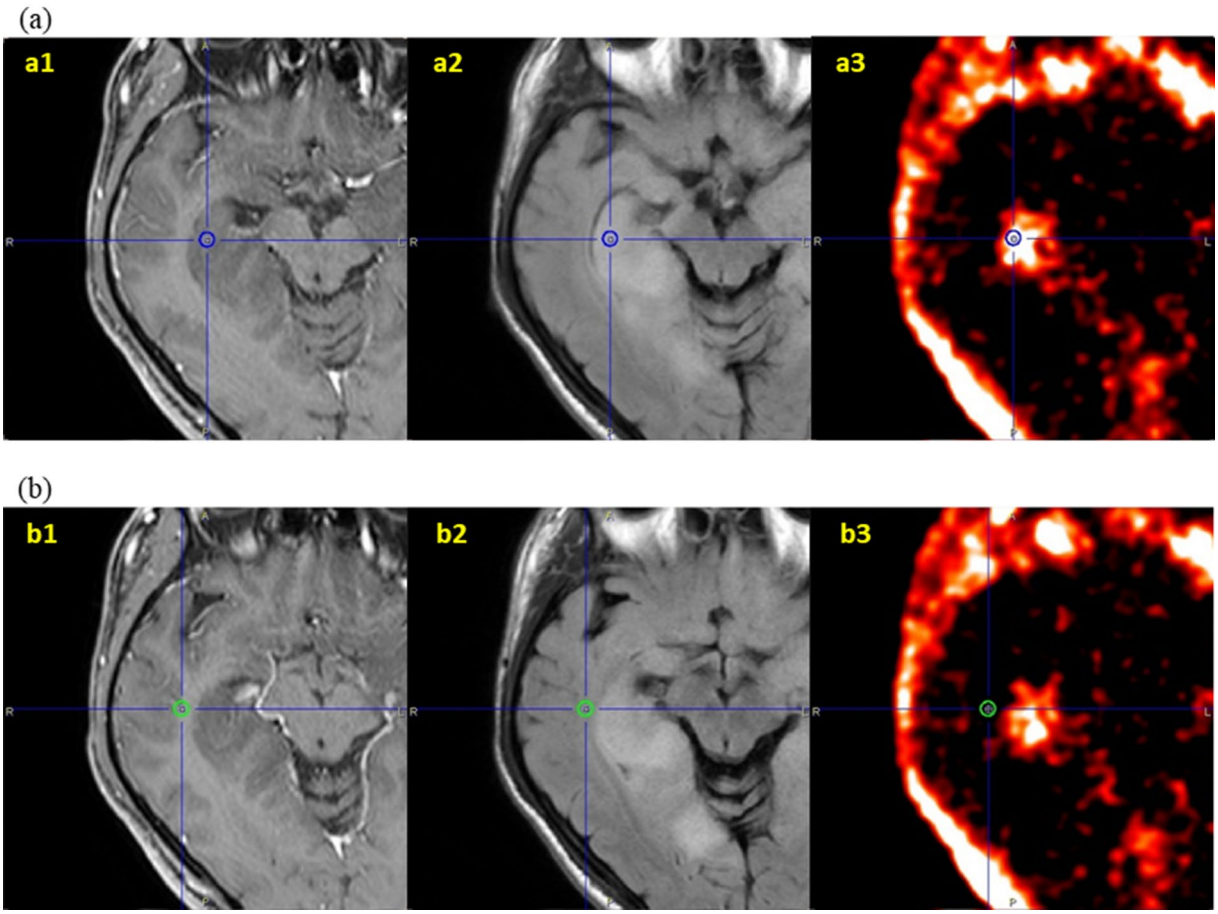

Fig. 4 Representative images of a true positive case in a patient with suspected low-grade glioma (Patient 11L). In each set, images a1 and b1 are the gadolinium contrast-enhanced T1-weighted magnetic resonance imaging (MRI) images, a2/b2 are the fluid-attenuated inversion recovery (FLAIR), and a3/b3 are the ^{18}F-fluciclovine- positron emission tomography [PET] images. The crosshair indicates the tissue collection site. In set (**a**), a tissue sample was collected from a gadolinium-enhanced T1-weighted image negative [Gd (–)] ^{18}F-fluciclovine PET positive [PET (+)] area (SUVmax = 1.35, SUVmean = 1.00) and histopathologically diagnosed as diffuse astrocytoma (World Health Organization [WHO] grade II) with 17.5% of Ki-67 and 60% of content of tumor cells, and in set (**b**), a tissue sample was collected from Gd (–) ^{18}F-fluciclovine PET negative [PET (–)] area (SUVmax = 0.51, SUVmean = 0.31) and histopathologically diagnosed as diffuse astrocytoma (WHO grade II) with 12.1% of Ki-67 and 10% of content of tumor cells. The definitive diagnosis was anaplastic astrocytoma (WHO grade III). SUV, standardized uptake value

Table 4 Sensitivity and specificity of ^{18}F-fluciclovine positron emission tomography for the diagnosis of glioma

Central pathological diagnosis	Central image evaluation, n^a (%)		Sensitivity, % (95% CI)	Specificity, % (95% CI)
	PET (+)	PET (−)		
Tumor	29 (46.0)	21 (33.3)	58.0 (44.2–70.6)	61.5 (35.5–82.3)
Non-tumor	5 (7.9)	8 (12.7)		
Total	34	29		

CI confidence interval, *PET* positron emission tomography

[a]Number of tissues

Degree of malignancy between the PET (+) and PET (–) areas

A subgroup of patients had evaluable tissue samples from both PET (+) and PET (–) areas (both areas showing FLAIR/T2 high signals), so we were able to compare the degree of malignancy in histopathological specimens between PET (+) and PET (–) areas from the same patient. Using the WHO classification, 9/17 patients (52.9%) had more malignant tissue in PET (+) areas than in PET (–) areas, 7/17 patients (41.2%) had similar malignancy grade in PET (+) and PET (–) areas, and 1 (5.9%) had less malignant tissue in the PET (+) than the PET (–) area. Similarly, the proportion of patients whose tissue in PET (+) areas was more malignant than in PET (–) areas was also highest when

Table 5 Effect of ^{18}F-fluciclovine positron emission tomography imaging on planning tumor resections

Resection planning	All patients ($n=36$)	Suspected high-grade glioma ($n=23$)	Suspected low-grade glioma ($n=13$)
Changed, *n* (%)	17 (47.2)	14 (60.9)	3 (23.1)
Extend resection area	11 (30.6)	11 (47.8)	0 (0.0)
Reduce resection area	6 (16.7)	3 (13.0)	3 (23.1)
Not changed, *n* (%)	19 (52.8)	9 (39.1)	10 (76.9)

Table 6 Histopathological comparison of the degree of malignancy between the tissue specimens from the positron emission tomography positive [PET (+)] and PET negative [PET (−)] areas among the same patients

Indices	Degree of malignancy, *n* (%)			
	n	PET (+) > PET (−)	PET (+) = PET (−)	PET (+) < PET (−)
WHO classification	17	9 (52.9)	7 (41.2)	1 (5.9)
Ki-67 labelling index	18	11 (61.1)	0 (0.0)	7 (38.9)
Content of tumor cells	18	11 (61.1)	2 (11.1)	5 (27.8)

PET positron emission tomography, *WHO* World Health Organization

using the Ki-67 labelling index or content of tumor cells as an index of malignancy (Table 6).

Inter-rater reliability

When analyzed by the tissue collection site, the mean inter-rater reliability for evaluation of ^{18}F-fluciclovine accumulation was as follows: 96.6–100.0% for Gd (−) PET (+) areas, 100.0% for Gd (+) PET (+) areas, 78.1–84.4% for Gd (−) PET (−) areas and 87.3–90.5% for all collected tissues (Table 7).

Safety

Among the patients evaluated for safety, one patient each from the P301 and P302 studies developed AEs (thirst, 1 case, P301; swelling of the punctured intravenous site, 1 case, P302). Both events were mild, with only one event (thirst) that was judged by the investigators as having a causal relationship with ^{18}F-fluciclovine. Both events were resolved quickly without any intervention.

Table 7 Inter-rater reliability during evaluation of ^{18}F-fluciclovine positron emission tomography imaging by the three central image evaluation committee members (a, b and c)

Inter-rater comparison	*n*	Inter-rater reliability, % (95% CI)	Kappa coefficient, (95% CI)
All tissues	63		
a–b		90.5 (80.7–95.6)	0.809 (0.644–0.954)
a–c		87.3 (76.9–93.4)	0.745 (0.583–0.907)
b–c		90.5 (80.7–95.6)	0.809 (0.666–0.952)
Gd (−) PET (+)	29		
a–b		96.6 (82.8–99.4)	0.838 (0.530–1.000)
a–c		96.6 (82.8–99.4)	0.838 (0.530–1.000)
b–c		100.0 (88.3–100.0)	1.000 (1.000–1.000)
Gd (+) PET (+)	2		
a–b		100.0 (34.2–100.0)	–
a–c		100.0 (34.2–100.0)	–
b–c		100.0 (34.2–100.0)	–
Gd (−) PET (−)	32		
a–b		84.4 (68.2–93.1)	0.355 (−0.092–0.801)
a–c		78.1 (61.2–89.0)	0.411 (0.073–0.748)
b–c		81.3 (64.7–91.1)	0.478 (0.157–0.799)

CI confidence interval, *Gd* gadolinium-enhanced T1-weighted image; PET, positron emission tomography

Discussion

A primary finding from this study is that the PPV of ^{18}F-fluciclovine PET imaging was statistically higher than the threshold PPV in the diagnosis of the tumor area not visualized by gadolinium contrast-enhanced T1-weighted imaging in patients with suspected glioma. This finding indicates that ^{18}F-fluciclovine can identify tumors infiltrating outside the gadolinium contrast-enhanced area in suspected high-grade glioma, and including ^{18}F-fluciclovine PET in the surgical planning is expected to maximize safe resection and contribute to better outcomes. In addition, for patients with suspected low-grade glioma, ^{18}F-fluciclovine PET can help to identify tumor within the FLAIR/T2 lesion, thereby helping to determine the site for preferential resection and enhancing accurate diagnosis. Although the PPV of ^{18}F-fluciclovine PET from the present study (88%) is slightly lower than that

reported in the late phase II clinical trial (100%) [19], it was significantly higher than the threshold PPV of 70%, and confirmed the effectiveness of ^{18}F-fluciclovine PET imaging in the diagnosis of glioma in the non-enhancing areas on MRI.

Three of the 25 tissue samples collected from a Gd (–) PET (+) area were pathologically rated as tumor-free in the present study. The reason for this discrepancy seemed to be a sampling error in two cases (a difference between the tissue collection site and the navigation image, and tissue shift at the time of biopsy), and a false-negative judgment of the histopathology (despite IDH-1 staining) due to the tumor being at an early stage in the other case. The PPV of the Gd (–) PET (+) area did not differ between the groups suspected to have high-grade or low-grade gliomas, suggesting that ^{18}F-fluciclovine PET has a high PPV for glioma regardless of the malignancy grade.

In this study, we had planned to set the radioactivity dose as 87–270 MBq and scan starting time as 10–50 min after injection. The reason for having planned to allow a wide range of injection dose was that ^{18}F-fluciclovine was developed as a single dose product of 185 MBq / 2 mL at the calibration time, and to be administered at the entire volume of 1 vial at any time from 1 h before (270 MBq) to 2 h after (87 MBq) the calibration time. In the late phase II study conducted by the same eligible patients and the same method as this study [19], the PPV of Gd (–) PET (+) area was 100.0% (13/13 area) in both of the low radioactivity group (87–127 MBq) and the high-dose radioactivity group (185–270 MBq), suggesting that good tumor imaging ability might be obtained (unpublished data). The reason why the starting time of PET scans was planned in such a wide range was that the early phase II trial demonstrated that the time activity curves of SUV and the tumor to normal ratio maintained a favorable status from a few minutes up to 60 min after injection in patients with high-grade glioma [18]. In addition, the late phase II study showed no difference in PPV of the Gd (+) PET (–) area between the images started scans from 10 to 20 min after injection (100.0%, 26/26 area [19]) and those from 40 to 50 min after injection (100.0%, 23/23 area, unpublished data). Furthermore, no difference between the starting time of 10– < 30 min and 30–50 min in the PPV of the Gd (−) PET (+) area was observed in this study. Therefore, we considered that there was no significant change in image quality that affected the achievement of the purpose of this study, although a wide range of scan starting time and radioactivity dose were set in this study.

The NPV of the Gd (–) PET (–) area was low overall (30.8%) and was 0.0% in suspected low-grade glioma. Of the 8 patients with suspected low-grade glioma, 6 had diffuse astrocytoma (WHO grade II) and 2 had oligodendroglioma (WHO grade II). As with methionine PET [26–28], the low accumulation of ^{18}F-fluciclovine in patients with diffuse astrocytoma was considered to have affected the NPV of ^{18}F-fluciclovine, so caution was required in the interpretation of the NPV findings in our study.

The sensitivity and specificity of ^{18}F-fluciclovine PET reported in the present study (58.0% and 61.5%, respectively) were lower than those reported in its early phase II trial (84.4–90.6% and 80.0%, respectively) [18]. The reason for the low sensitivity was considered that the sensitivity of the tissue collected from the area where the local neurosurgeon considered as the Gd (–) PET (–) FLAIR/T2 (+) area was low, and that the ratio of the number of tissues collected from that area was high (30/63 tissues). In the Gd (–) PET (–) FLAIR/T2 (+) area, since the infiltrating tumor cells might exist with low density, the tumor could be confirmed histopathologically but not detected by ^{18}F-fluciclovine PET due to insufficient accumulation. In fact, the sensitivity of the tissue collected from the area where the local neurosurgeon judged as Gd (–) PET (–) FLAIR/T2 (+) was 19.0% (4/21), which was lower than that of Gd (+) PET (+) FLAIR/T2 (+) [100.0% (2/2)] and that of Gd (–) PET (+) FLAIR/T2 (+) [88.5% (23/26)]. In addition, among the tumor tissues to be evaluated for the sensitivity, the ratio of the tissues collected from the Gd (−) PET (−) FLAIR/T2 (+) area (local neurosurgeon) to all the collected tissues in this study (21/50 tissues) was higher than that of the tissue collected from the Gd (−) PET (−) area (central image evaluation, FLAIR/T2 was not evaluated) in the early phase II (3–5 out of 32 tissues) [18]. The reduction in specificity might also be due to the three false-positive cases described above.

The sensitivity of ^{18}F-fluciclovine PET in the Gd (−) FLAIR/T2 (+) area in the suspected high-grade glioma group was 65.5%, indicating some tumors could not be detected by PET. On the other hand, the specificity of ^{18}F-fluciclovine PET in the Gd (−) FLAIR/T2 (+) area was 77.8% in that group, implying that it was possible to determine that the tissue was non-tumor despite FLAIR/T2 (+) with a certain degree of certainty. Therefore, although this drug is expected to provide information on the differentiation between tumors and non-tumors with a specificity of 77.8% in the Gd (−) FLAIR/T2 (+) area, considering the occurrence of false negatives to a certain extent in clinical use, it might be necessary to determine the extent of tumor resection appropriately without giving excessive importance to the PET results in patients with suspected high-grade glioma.

The results of this study showed that ^{18}F-fluciclovine PET imaging effectively modified the extent of planned tumor resection in 47.2% of the total number of patients undergoing surgery. The ability of ^{18}F-fluciclovine to visualize tumor present beyond the Gd (+) area is expected to increase the extent of tumor resection in patients suspected of having high-grade glioma. Also, ^{18}F-fluciclovine is expected to allow preferential resection within the FLAIR/T2 (+) PET (+) area, and is, therefore, expected

to obtain accurate definitive diagnosis in patients with suspected low-grade glioma. The extent of planned tumor resection in the present study increased in 47.8% of patients suspected of high-grade glioma and diminished in 23.1% of patients with suspected low-grade glioma. Furthermore, histopathological comparison between the PET (+) and PET (–) areas of the same patient showed higher malignancy grade in the PET (+) area compared with the PET (–) area. This tendency was also noted in the FLAIR/T2 high signal area, where edema is often present with the tumor, impairing the precision of clinical judgment about resection margins. These results suggest that ^{18}F-fluciclovine PET imaging can favorably influence preoperative resection planning and assist in identifying higher malignancy tumor areas, thus helping surgeons during decision-making regarding tumor resection.

The Kappa coefficient for the judgment of ^{18}F-fluciclovine accumulation was favorable for the Gd (–) PET (+) area but low for the Gd (–) PET (–) area. This was possibly due to the difficulty in distinguishing between tumor-associated accumulation and physiological accumulation of ^{18}F-fluciclovine, as some tissue samples collected from the Gd (–) PET (–) areas were in close proximity to the background area of ^{18}F-fluciclovine's accumulation.

Only two AEs were reported during the two studies; of these, mild thirst was the only AE judged to have a causal relationship with ^{18}F-fluciclovine. This event developed soon after administration of ^{18}F-fluciclovine and was, therefore, counted as a drug-related AE. However, it subsided quickly without the need for any intervention, and the laboratory parameters, vital signs, and ECG of the patient did not show any clinically significant changes after the occurrence of the AE.

The main limitation of this study is the method for evaluating the sensitivity and specificity, since this evaluation depends on the tissue collection site. Glioma infiltrates from the center of the tumor to the periphery, so the further from the center of the tumor that tissue samples are collected, the lower the tumor cell density and consequently accumulation of ^{18}F-fluciclovine are. This study was designed to collect each one tissue from PET (+) and PET (–) areas, and the PET (–) tissue samples were collected from the FLAIR/T2 hyper-intensity area as possible. Therefore, it is possible that the sensitivity decreases by collecting a large amount of tissue from a region that is likely to have low sensitivity. Furthermore, three tumor-negative samples were unexpectedly obtained from PET (+) areas, leading to a high proportion of three false-negative results and low specificity. Therefore, caution is required regarding the interpretation of the sensitivity and specificity of ^{18}F-fluciclovine.

Conclusion

^{18}F-fluciclovine PET had a high PPV in patients with clinically suspected low- and high-grade glioma, allowing visualization of glioma tissues that did not show gadolinium contrast enhancement in routine MRI scans. ^{18}F-Fluciclovine PET is useful for determining the extent of tumor resection at surgical planning, and may clinically serve as a safe and effective diagnostic tool for patients with suspected glioma.

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Declarations

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Authors and Affiliations

Toshihiko Wakabayashi[1] · Yuichi Hirose[2] · Keisuke Miyake[3] · Yoshiki Arakawa[4] · Naoki Kagawa[5] · Tadashi Nariai[6] · Yoshitaka Narita[7] · Ryo Nishikawa[8] · Naohiro Tsuyuguchi[9] · Tadateru Fukami[10] · Hikaru Sasaki[11] · Takashi Sasayama[12] · Akihide Kondo[13] · Toshihiko Iuchi[14] · Hiroshi Matsuda[15] · Kazuo Kubota[16] · Ryogo Minamimoto[17] · Takashi Terauchi[18] · Yoichi Nakazato[19] · Kan Kubomura[20] · Masatoshi Wada[20,21]

[1] Department of Neurosurgery, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan

[2] Department of Neurosurgery, School of Medicine, Fujita Health University, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan

[3] Department of Neurological Surgery, Kagawa University Faculty of Medicine, 1750-1 Ikenobe, Miki-cho, Kita-gun, Kagawa 761-0793, Japan

[4] Department of Neurosurgery, Kyoto University Graduate School of Medicine, 54 Shogoin-kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan

[5] Department of Neurosurgery, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan

[6] Department of Neurosurgery, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan

[7] Department of Neurosurgery and Neuro-Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

[8] Department of Neuro-Oncology/Neurosurgery, Saitama Medical University International Medical Center, 1397-1 Yamane, Hidaka, Saitama 350-1298, Japan

[9] Department of Neurosurgery, Osaka City University Graduate School of Medicine, 1-4-3 Asahi-machi, Abeno-ku, Osaka 545-8585, Japan

[10] Department of Neurosurgery, Shiga University of Medical Science, Seta-Tsukinowa-Cho, Otsu, Shiga 520-2192, Japan

[11] Department of Neurosurgery, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

[12] Department of Neurosurgery, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan

[13] Department of Neurosurgery, Juntendo Tokyo Koto Geriatric Medical Center, 3-3-20 Shinsuna, Koto-ku, Tokyo 136-0075, Japan

[14] Division of Neurological Surgery, Chiba Cancer Center, 666-2 Nitona-cho, Chuo-ku, Chiba 260-8717, Japan

[15] Integrative Brain Imaging Center, National Center of Neurology and Psychiatry, 4-1-1 Ogawa-Higashi-cho, Kodaira, Tokyo 187-8551, Japan

[16] Department of Radiology, Southern Tohoku General Hospital, 7-115, Yatsuyamada, Koriyama, Fukushima 963-8563, Japan

[17] Department of Nuclear Medicine, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan

[18] Department of Nuclear Medicine, Cancer Institute Hospital of Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan

[19] Department of Pathology, Hidaka Hospital, 886 Nakao-machi, Takasaki, Gunma 370-0001, Japan

[20] Clinical Development Department, Nihon Medi-Physics Co., Ltd, 3-4-10 Shinsuna, Koto-ku, Tokyo 136-0075, Japan

[21] Business Development and Project Department, Nihon Medi-Physics Co., Ltd, 3-4-10 Shinsuna, Koto-ku, Tokyo 136-0075, Japan