Clinical use of $^{11}$C-methionine and $^{18}$F-FDG-PET for germinoma in central nervous system

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Abstract

Objective The purpose of this study was to examine the $^{11}$C-methionine (MET) and $^{18}$F-fluorodeoxyglucose (FDG) positron emission tomography (PET) findings of central nervous system (CNS) germinoma and the diagnostic utility of these findings.

Methods We retrospectively evaluated the cases of 10 patients who were diagnosed with CNS germinoma according to their histopathological or clinical findings. All the patients underwent pretreatment MET and/or FDG-PET scans, and the resultant images were assessed qualitatively and quantitatively. In the qualitative assessments, we used 3- and 5-grade visual scoring systems for the MET- and FDG-PET images, respectively. In the quantitative assessments, the maximal standardized uptake value ($\text{SUV}_{\text{max}}$) and the ratio of the $\text{SUV}_{\text{max}}$ of the tumor ($T$) divided by the mean SUV for the normal white or gray matter [$T/N (\text{WM})$, $T/N (\text{GM})$], was calculated.

Results The mean and SD values of $\text{SUV}_{\text{max}}$, $T/N (\text{WM})$, and $T/N (\text{GM})$ were 1.9 ± 1.4, 2.5 ± 1.3, and 1.7 ± 0.9 on MET-PET and 5.8 ± 2.2, 1.6 ± 0.5, and 0.8 ± 0.2 on FDG-PET, respectively. On MET-PET, only one lesion was not detected. On the other hand, on FDG-PET all of the lesions exhibited uptake values that were intermediate between those of the normal white matter and gray matter.

Conclusion In terms of its tumor-contouring ability, MET is a good tracer for diagnosing CNS germinomas; therefore, MET-PET is considered to be useful for planning biopsies or surgery. Although FDG-PET is capable of detecting CNS germinomas, it produced insufficient image contrast in the present study. Further studies are needed before FDG-PET can be used in clinical examinations of CNS germinoma.

Keywords Germinoma · Positron emission tomography · $^{11}$C-methionine · $^{18}$F-FDG

Introduction

Germinoma, teratoma, choriocarcinoma, embryonal cell carcinoma, yolk sac tumor, and mixed tumors are all types of germ cell tumor (GCT). In the USA, GCT accounts for 0.5 % of all primary brain and central nervous system (CNS) tumors [1]. However, GCTs are more common in East Asia than in Western countries. For example, GCT accounts for 3.1 % of all primary brain tumors in Japan [2].

The prognosis of primary GCT varies depending on the histology and size of the tumor as well as its extent at the
initial diagnosis [3]. In general, intracranial GCTs are classified into three categories, i.e., those with good, intermediate, and poor prognoses [4]. Malignant GCT, such as embryonal carcinoma, yolk sac tumors, immature teratomas, teratomas exhibiting malignant transformation, and mixed tumors, generally exhibit poor prognoses [5–7]. On the other hand, CNS germinoma patients tend to display a good prognosis. Germinoma with syncytiotrophoblastic giant cells (STGC) is a subtype of CNS germinoma that is considered to have an intermediate prognosis. STGC produce β-HCG; therefore, the detection of β-HCG in serum or cerebrospinal fluid (CSF) is an indicator of germinoma with STGC [8]. CNS germinomas are generally sensitive to radiotherapy and chemotherapy, and their 10-year survival rate is approximately 90%; i.e., most of them are curable [9, 10].

CNS germinomas tend to develop in the midline structures of the brain, such as the pineal gland or the suprasellar region, and often occur as multifocal or disseminated lesions. In rare cases, CNS germinomas develop at ectopic sites such as the basal ganglia, thalamus, or internal capsule [11–16]. If germinoma is suspected, magnetic resonance imaging (MRI) is an essential diagnostic neuroimaging modality, and biopsy is recommended for achieving a final diagnosis [3, 10]. However, biopsies are sometimes omitted in cases in which the lesion exhibits a characteristic location and tumor markers such as β-HCG and alphafetoprotein (AFP) show appropriate expression patterns (tests for β-HCG are negative or slightly positive and those for AFP are negative) [17]. In germinoma patients in whom a biopsy would be a high-risk procedure, neoadjuvant therapy with very low-dose irradiation or chemotherapy might be helpful for confirming the presumed diagnosis [10]. In addition, non-invasive neuroimaging can also play an important role in pretreatment examinations.

Typical CNS tumors are easy to diagnose by conventional MRI; however, in some cases diagnosis is delayed due to the slow progression of the lesion or the tumor being located in the basal ganglia, in which it is difficult to detect tumors because lesions in this region only exhibit subtle signal changes on MRI during their early stages. On the other hand, many kinds of tumor can occur in the suprasellar region, e.g., craniopharyngioma, pituitary adenoma, glioma, hypophysitis, sarcoidosis, and germ cell tumor, all of which exhibit similar shapes and signal changes on MRI; therefore, the differential diagnosis of suprasellar tumors is often difficult.

The usefulness of $^{11}$C-methionine (MET)-positron emission tomography (PET) for tumor contouring and treatment planning has been extensively investigated in patients with brain tumors [18–20], and $^{18}$F-fluorodeoxyglucose (FDG)-PET is widely used for differential diagnosis, staging, histological grading, and prognostic evaluations in many kinds of tumor [21]. In typical cases of germinoma, PET imaging is considered to be of limited use; however, some difficult cases cannot be diagnosed by conventional MRI. Previous reports have indicated that MET-PET might facilitate the early diagnosis of CNS germinoma; however, these reports only assessed basal ganglia germinomas [9, 11, 12, 15, 16]. On the other hand, there have not been any systematic reports about the utility of FDG-PET in cases of CNS germinoma. Therefore, we elucidated the characteristic MET- and FDG-PET findings of germinomas that develop in the basal ganglia or the suprasellar or pineal region; i.e., the regions of the CNS that are most commonly affected by germinoma.

Specifically, we assessed the uptake of MET and FDG by CNS germinomas in the pineal gland, the suprasellar region, and the basal ganglia.

Materials and methods

Patients

Between November 2007 and March 2011, 10 CNS germinomas were initially diagnosed at our institution on the basis of their pathological findings or clinical features. All of these tumors were assessed by MET-PET and/or FDG-PET.

Pathological diagnoses (pure germinoma in all cases) were obtained from biopsy specimens in 5 cases. In the other 5 cases, we diagnosed the germinomas according to their clinical features. Based on the locations of the tumors; the patients’ age, sex, and tumor marker levels; and the fact that none of the patients exhibited positivity for AFP, which were suggestive of immature teratoma or mixed germ cell tumor, we administered a single course of chemotherapy and then assessed the treatment response. On the basis of the aforementioned clinical findings, the latter 5 tumors were diagnosed as germinomas.

Our study was approved by the Committee for Ethics of Nagoya University School of Medicine.

PET procedure

Positron emission tomography images were obtained using a Headtome-V PET camera (Shimadzu, Kyoto, Japan) with a spatial resolution of 4.5 mm (axial) and a full width at half maximum of 3.9 mm (transaxial) in the center of the field of view. The corrected data were reconstructed into 31 transaxial planes with a slice thickness of 6.25 mm and a 256 × 256 pixel image matrix. The effects of soft tissue attenuation on the scans were corrected using transmission scans that utilized a rotating 68 Ge/68 Ga line source. A 5-min transmission scan was performed before the PET
The uptake value (SUV max), the tumor-to-normal gray matter ratio, and the tumor-to-normal white matter ratio (T/N (GM)) ratio, and the tumor-to-normal white matter ratio (T/N (WM)) ratio. The T/N ratio was defined as the ratio of the SUV max of the tumor (T) ROI divided by the mean SUV (SUV mean) for the normal gray matter or white matter (contralateral frontal cortex) (N). The maximum SUV and mean SUV were calculated as follows: SUV max = maximum RI count (Bq/ml)/[MET dose (Bq)/body weight (g)]; SUV mean = mean RI count (Bq/ml)/[MET dose (Bq)/body weight (g)]. We measured the uptake values of all of the germinoma lesions.

The size of the normal brain tissue ROI differed from case to case. During the determination of the ROI for the GM, we carefully traced a gyrus reference from anatomical MRI and calculated the mean SUV. On the other hand, for the WM we first identified the ventricle and a GM reference on MRI and then drew the WM ROI so that it did not include the GM or ventricle and was as large as possible. Comparisons between the tracer uptake values for all patients and those for the patients with verified pathological diagnoses (No. 2, 4, 5, 9, and 10) were also made.

Statistical analysis

For each tumor type, the mean and standard deviation (SD) of the visual scores and the SUV values were calculated. These values were compared using an unpaired t test. P values of <0.05 were considered significant. All analyses were performed with SPSS 17.0.

Results

Patients

Ten germinoma patients (8 males and 2 females; mean age 13.4 ± 7.1) were involved in the present study. Eight of the 10 germinoma patients underwent both MET- and FDG-PET, and 2 only underwent FDG-PET. The patients’ age at diagnosis, sex, clinical presentation, and serum and CSF \( \beta \)-HCG and AFP levels; the duration of their symptoms; and information about the locations of the tumors and the administered treatments are summarized in Table 1.

One patient exhibited positivity for \( \beta \)-HCG in their serum alone (No. 1), two patients displayed positivity for \( \beta \)-HCG in their CSF alone (No. 4 and 7), and two patients showed positivity for \( \beta \)-HCG in both their serum and CSF (No. 3 and 10). Two out of 5 patients with elevated \( \beta \)-HCG levels were pathologically diagnosed with pure germinoma (No. 4 and 10). None of the patients displayed positivity for AFP in their serum or CSF.

We followed-up all of the patients (range 24–66 months; mean 41.6 months), and none of them suffered recurrence (as of February 2013).
| No | Age | Sex | Symptom                     | Location                  | Diagnosis | FDG | MET |
|----|-----|-----|-----------------------------|---------------------------|-----------|-----|-----|
|    |     |     |                             |                           |           | V.A. | SUV<sub>max</sub> | T/N (WM) | T/N (GM) | V.A. | SUV<sub>max</sub> | T/N (WM) | T/N (GM) | HCGs | AFPs | HCGc | APFc | Treatment | Follow-up (month) |
| 1  | 9   | M   | Left hemiparesis            | Right basal ganglia       | Clinical  | 3   | 4.3 | 1.9 | 0.8 | 2   | 2   | 3.3 | 1.4 | 9.6 | (-) | (-) | (-) | CBDCA + VP-16 (3 course) | 54 |
|    |     |     |                             |                           | Biopsy    | 3   | 4.6 | 1.8 | 0.8 | 3   | 0.6 | 2.8 | 2.4 | (-) | (-) | (-) | (-) | VP-16 (3 course) whole brain irradiation 30 Gy | 48 |
| 3  | 8   | M   | Left hemiparesis            | Right basal ganglia       | Clinical  | 4   | 6.8 | 1.7 | 1.1 | 3   | 2.2 | 2.4 | 1.8 | 4.6 | (-) | 19.4 | (-) | CBDCA + VP-16 (3 course) whole brain irradiation 30 Gy | 20 |
| 4  | 7   | M   | Left hemiparesis            | Right basal ganglia       | Biopsy    | 3   | 5.2 | 1.5 | 0.6 | 3   | 2.7 | 2.4 | 2.1 | (-) | (-) | 1.8 | (-) | CBDCA + VP-16 (3 course) whole brain irradiation 30 Gy | 48 |
| 5  | 10  | F   | Headache                   | Pineal                    | Biopsy    | 3   | 6.7 | 1.2 | 0.8 | NA  | NA  | NA  | NA  | (-) | (-) | (-) | (-) | CBDCA + VP-16 (3 course) whole ventricle irradiation 30 Gy | 42 |
| 6  | 13  | F   | Headache, DI               | Suprasellar               | Clinical  | 4   | 2.8 | 1.1 | 0.5 | 3   | 5.2 | 5.7 | 3.7 | (-) | (-) | (-) | (-) | CBDCA + VP-16 (3 course) whole ventricle irradiation 30 Gy | 24 |
| 7  | 29  | M   | Poor appetite, DI          | Suprasellar               | Clinical  | 2   | 2.2 | 0.7 | 0.4 | 1   | 0.9 | 1.2 | 0.9 | (-) | (-) | 3.5 | (-) | CBDCA + VP-16 (3 course) whole ventricle irradiation 30 Gy | 24 |
| 8  | 19  | M   | Vomit                      | Suprasellar, pineal       | Clinical  | 4   | (P, S) | 6.1 (S) | 6.9 (P) | 2.2 (S) | 2.5 (P) | 0.85 (S) | 0.96 (P) | NA  | NA  | NA  | NA  | (-) | (-) | (-) | (-) | CBDCA + VP-16 (3 course) whole ventricle irradiation 30 Gy | 66 |
| 9  | 20  | M   | Headache, visual disorder  | Suprasellar, pineal       | Biopsy    | 3   | (P) | 9.8 (S) | 1.6 (S) | 0.95 (S) | 3 (S, P) | 1.9 (S) | 1.7 (S) | 1.2 (S) | (-) | (-) | (-) | (-) | CBDCA + VP-16 (3 course) whole ventricle irradiation 30 Gy | 60 |

**Table 1** Patients characteristics and PET findings

FDG: Fluoro-2-deoxy-D-glucose; MET: Myeloestestone-1,2,4-triaxetate; V.A.: Volume of Abnormality; SUV<sub>max</sub>: Maximum Standardized Uptake Value; T/N: Tumor-to-Normal ratio; HCGs: Human chorionic gonadotropin; AFPs: Alpha fetoprotein; HCGc: Human chorionic gonadotropin; APFc: Alpha fetoprotein.
MRI results

All of the suprasellar and pineal tumors could be observed on Gd-enhanced T2-weighted images or T1-weighted MRI images. However, the tumors in the basal ganglia were not easy to detect or delineate because they had unclear boundaries and only produced slight signal changes. Therefore, it was difficult to measure the diameters of the basal ganglia germinomas. As for the suprasellar and pineal germinomas, their mean major diameter was $19 \pm 7.0$ (9–33) mm. The major diameter of tumor No. 7 was $10 \text{ mm}$, whereas those of the other tumors were more than 10 mm.

PET results

The visual score, SUV$_{\text{max}}$, $T/C$ (WM), and $T/C$ (GM) values for each case according to MET-PET and FDG-PET are summarized in Table 1. Representative images are shown in Fig. 1.

**MET-PET**

According to MET-PET, the mean and SD values of the visual score, SUV$_{\text{max}}$, $T/C$ (WM), and $T/C$ (GM) for all patients were $2.7 \pm 0.7$, $1.9 \pm 1.4$, $2.5 \pm 1.3$, and $1.7 \pm 0.9$, respectively (Table 2). On the other hand, the mean values and SD values of the visual score, SUV$_{\text{max}}$, $T/C$ (WM), and $T/C$ (GM) for the patients who were pathologically diagnosed with pure germinoma were $3.0 \pm 0$, $1.8 \pm 0.7$, $2.1 \pm 0.5$, and $1.6 \pm 0.6$, respectively. There were no significant differences in any parameter between the values for all patients and those for the patients who were pathologically diagnosed with pure germinoma. The tumors were generally well delineated by MET-PET, except in one patient (No. 7), who had a germinoma in the suprasellar region. As for the tumors in the basal ganglia, all of them presented with similar MET uptake levels. On the other hand, the MET uptake values of the suprasellar and pineal tumors displayed inter-lesional differences. In almost all cases, the tumor exhibited stronger MET tracer uptake than the normal white matter and gray matter tissue.

**FDG-PET**

According to FDG-PET, the mean and SD values of the visual score, SUV$_{\text{max}}$, $T/C$ (WM), and $T/C$ (GM) for all patients were $3.3 \pm 0.8$, $5.8 \pm 2.2$, $1.6 \pm 0.5$, and $0.8 \pm 0.2$, respectively (Table 2). On the other hand, the mean and SD values of the visual score, SUV$_{\text{max}}$, $T/C$ (WM), and $T/C$ (GM) for the patients who were pathologically diagnosed with pure germinoma were $3.1 \pm 0.7$, $6.7 \pm 2.1$, $1.6 \pm 0.2$, and $0.8 \pm 0.1$, respectively. There was no
significant difference in any parameter between the values for all patients and those for the patients who were pathologically diagnosed with pure germinoma. Similarly to MET-PET, the inter-lesion differences in SUV$_{\text{max}}$ were small in the basal ganglia; however, the SUV$_{\text{max}}$ values for the suprasellar and pineal tumors varied. In almost all cases, the tracer uptake of the tumor was intermediate between those of the normal white matter and normal gray matter.

Discussion

Germinomas do not necessarily have to be diagnosed pathologically. In fact, they are often diagnosed based on the patient’s background, the results of radiological imaging or cerebrospinal fluid tests, and/or the patient’s serum tumor marker levels. In addition, because of their sensitivity to chemotherapy a small dose of chemotherapy is often administered for diagnostic and therapeutic purposes. Accordingly, the present study was conducted to examine whether PET could be used as an additional diagnostic tool for germinoma.

There are few case reports about the FDG-PET findings of CNS germinomas. Sadamura et al. and Yu et al. reported a case of CNS germinoma that was diagnosed using FDG-PET [23, 24]. In addition, there have been some reports about the utility of MET-PET for diagnosing CNS germinoma; however, these reports were restricted to tumors...
Table 2  The uptake of PET at each region

|                | Total (12) | Suprasellar region (4) | Pineal region (4) | Basal ganglia | Pathological verified region (7) |
|----------------|------------|------------------------|-------------------|--------------|---------------------------------|
| **FDG**        |            |                        |                   |              |                                 |
| V.A.           | 3.3 ± 0.8  | 3.5 ± 1.0              | 3.0 ± 0.8         | 3.4 ± 0.5    | 3.1 ± 0.7                       |
| SUV<sub>max</sub> | 5.8 ± 2.2 | 5.2 ± 3.4              | 7.0 ± 1.8         | 5.4 ± 1.0    | 6.7 ± 2.1                       |
| T/N (WM)       | 1.6 ± 0.5  | 1.4 ± 0.6              | 1.7 ± 0.6         | 1.7 ± 0.2    | 1.6 ± 0.2                       |
| T/N (GM)       | 0.8 ± 0.2  | 0.7 ± 0.3              | 0.8 ± 0.1         | 0.8 ± 0.2    | 0.8 ± 0.1                       |
| **MET**        |            |                        |                   |              |                                 |
| V.A.           | 2.7 ± 0.7  | 2.3 ± 1.2              | 3.0 ± 0.0         | 2.8 ± 0.4    | 3.0 ± 0.0                       |
| SUV<sub>max</sub> | 1.9 ± 1.4 | 2.7 ± 2.3              | 1.7 ± 0.6         | 1.5 ± 1.2    | 1.8 ± 0.7                       |
| T/N (WM)       | 2.5 ± 1.3  | 2.9 ± 2.5              | 1.6 ± 0.4         | 2.6 ± 0.4    | 2.1 ± 0.5                       |
| T/N (GM)       | 1.7 ± 0.9  | 1.9 ± 1.5              | 1.1 ± 0.3         | 1.8 ± 0.4    | 1.6 ± 0.6                       |

Uptake of FDG-PET and MET-PET in suprasellar, pineal and basal ganglia regions. Uptake was evaluated by visual assessment (V.A.) SUV<sub>max</sub>, T/N (WM), and T/N (GM).

SUV standard uptake value, T/N ratio of tumor/normal, GM gray matter, WM white matter

Involving the basal ganglia [9, 11, 16]; therefore, little is known about the MET-PET and FDG-PET findings of germinoma and the effectiveness of these modalities for diagnosing germinoma in clinical practice.

Recently, Lee et al. [15] reported that MET-PET was useful for assessing the treatment responses of 3 basal ganglia germinomas Kawai et al. [11, 12] also reported that MET-PET is useful for response assessment and biopsy planning. Lee et al. assessed tracer uptake using the T/N ratio and SUV<sub>max</sub>, and Kawai et al. assessed it using SUV<sub>max</sub>. In these reports, SUV<sub>max</sub> values of 1.5–2.5 were observed in pretreatment examinations, and the T/N ratio ranged from 1.5 to 2.5, which were similar to our results.

In our study, all of the lesions except one were positively identified by MET-PET, suggesting that MET is a good tracer for detecting CNS germinoma. In particular, MET-PET is considered to be better than CT and MRI at detecting lesions in the basal ganglia, as such lesions only exhibit subtle signal changes or no mass effects on CT and MR images. In the present study, the lesion that produced a negative result on MET-PET measured less than 10 mm in diameter (the smallest tumor in the current study).

Furthermore, the germinoma lesions examined in the present study exhibited markedly higher MET uptake compared with the normal brain tissue, which enabled us to obtain a high level of contrast during tumor imaging. In the clinical setting, MET-PET is considered to be useful for tumor contouring and treatment planning.

For example, it is possible to conduct more accurate biopsies based on MET-PET, especially in the basal ganglia region. Radiation therapy is the standard treatment for germinoma, and the treatment field is chosen based on the contours of the tumor. Therefore, it is very important to accurately determine the location and borders of the tumor.

MET-PET is considered to be a good imaging tool for detecting germinoma.

Further studies should be conducted on other uses for MET-PET imaging, for example, its utility for differential diagnosis, tumor grading, or recurrence diagnosis, etc., in germinoma.

To the best of our knowledge, only case reports have described the use of FDG-PET to diagnose CNS germinoma, and there have not been any systematic studies of this issue; therefore, the tracer uptake values of CNS germinomas on FDG-PET are unknown. In the present study, the CNS germinomas generally showed uptake values that were intermediate between those of the gray and white matter. In addition, the visual appearance of the CNS germinomas differed depending on their location, even at similar uptake levels. Namely, the tumors in the suprasellar and pineal regions usually exhibited greater tracer uptake than the surrounding brain tissue or cerebrospinal fluid; on the other hand, those in the basal ganglia exhibited reduced tracer uptake compared with the surrounding normal basal ganglia in the normal hemisphere. Thus, we must be careful when evaluating FDG uptake visually.

In 1999, Utsuki et al. [25] reported the relationship between the serum level of β-HCG and the prognoses of various germinomas, including pure germinoma and germinoma with STGC. In the latter report, germinoma patients with serum β-HCG levels of <15 mIU/ml exhibited a high recurrence rate; however, the remaining patients did not suffer recurrence and achieved good outcomes. In 2002, the same group suggested that increased CSF β-HCG levels, but not increased serum β-HCG levels, are a favorable prognostic factor in cases of germinoma and that germinoma patients who exhibit such findings have similar
recurrence rates and prognoses to those with pure germi-
nomas [26]. In our study, 5 of 10 patients were diagnosed
based on their clinical features, rather than by biopsy;
therefore, there is a possibility that some of these patients
had germinoma with STGC. These patients demonstrated
increased β-HCG levels in their CSF (No. 4 and 7) or
serum (No. 1, 3, and 10); however, their serum β-HCG
levels were much <15 mIU/ml. Therefore, according to
previous reports it was expected that our patients would
exhibit a good prognosis, even if some of the lesions were
germinoma with STGC. In fact, in the present study there
was no difference in the uptake of MET or FDG between
the values for all germinoma patients and those for the
patients that were diagnosed pathologically. Subsequently,
all of the tumors exhibited good responses to therapy, and
none of the patients suffered recurrence during the obser-
vation period.

There were some limitations to this study. First, the sample
size was small, and the study had a retrospective design. In
addition, there were inter-individual variations in tumor size,
and the tracer uptake of small lesions is not easy to measure
accurately due to the partial volume effect. Second, it is
possible that the tumors examined in the present study
included some CNS germinomas with STGC.

Conclusion

In the present study, we demonstrated the FDG-PET and
MET-PET findings of CNS germinoma (possibly including
those of germinoma with STGC). On MET-PET, almost all
of lesions could be visualized; therefore, MET is consid-
ered to be a good tracer for diagnosing CNS germinoma,
especially for tumor contouring. Although the CNS ger-
minomas could be detected by FDG-PET, the image con-
trast was poor due to tracer uptake by the surrounding
normal brain tissue. We consider that further studies are
needed before FDG-PET can be used in clinical examina-
tions of CNS germinoma.

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