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A new diagnostic marker for differentiating multicentric gliomas from multiple intracranial diffuse large B-cell lymphomas on ^{18}F-FDG PET images

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Abstract

Intracranial gliomas and lymphomas may share similar radiological manifestations, while the treatment strategies for them are different. The aim of the study was to investigate the diagnostic value of fluorine-18-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission computed tomography (PET) for differentiation of multicentric gliomas and intracranial multiple diffuse large B-cell lymphomas (DLBCLs) as a study of diagnostic accuracy.

A total of 32 patients with multiple intracranial tumors visualized on contrast-enhanced magnetic resonance imaging (MRI) were retrospectively evaluated. Histopathological findings confirmed multicentric gliomas and multiple DLBCLs in 17 and 15 patients, respectively. All patients underwent ^{18}F-FDG PET with or without ^{11}C-methionine PET. Maximum standardized uptake values (SUV_{max}) and tumor-to-normal tissue (T/N) ratios were compared between the 2 tumors. The diagnostic value of ^{18}F-FDG PET for differentiating multicentric gliomas from multiple DLBCLs was evaluated by receiver operating characteristic (ROC) analysis.

The SUV_{max} of multiple DLBCLs was significantly higher than that of multicentric gliomas ($P = .009$). However, the percentage of maximum difference-value of SUV_{max} (or T/N ratio) of multiple DLBCLs was significant lower than that of multicentric gliomas ($P < .001$). The ROC curve demonstrated that the percentage of maximum difference-value of SUV_{max} (or T/N ratio) on ^{18}F-FDG PET images could effectively differentiate multicentric gliomas from multiple DLBCLs, with a cut-off value of 44.4%, sensitivity of 64.7%, and specificity of 100% ($P < .001$).

Percentage of maximum difference-value of SUV_{max} (or T/N ratio) on ^{18}F-FDG PET images might be a potential indicator for distinguishing multicentric gliomas from intracranial multiple DLBCLs, which might help determine the treatment strategy.

Abbreviations: ^{18}F-FDG = fluorine-18-fluoro-2-deoxy-D-glucose, DLBCLs = diffuse large B-cell lymphomas, D-value = difference-value, MET = methionine; PCNSLs = primary central nervous system lymphomas, PET = positron emission computed tomography, SUV = standard uptake value.

Keywords: 18F-FDG, differentiation, glioma, lymphoma, PET

1. Introduction

High-grade gliomas, including anaplastic gliomas and glioblastomas, primary central nervous system lymphomas (PCNSLs), and metastases are common malignant brain tumors in adults. These tumors may exhibit similar appearances on magnetic resonance (MR) images, which makes differential diagnosis challenging.[1,2] Although the standard treatment for patients with high-grade gliomas is maximal resection followed by radiation therapy and chemotherapy, in certain cases—for example in PCNSL—biopsy with the least invasive approach is recommended.[3,4] Therefore, accurate diagnosis is crucial because the treatment approach and prognoses of these tumors vary substantially.

As it is sometimes difficult to distinguish these tumors by MRI, fluorine-18-fluoro-2-deoxy-D-glucose (^{18}F-FDG) or ^{11}C-methionine (^{11}C-MET) positron emission computed tomography (PET) has been used to acquire additional information to assist differential diagnosis.[5] In brain metastases, whole-body ^{18}F-FDG PET might reveal the systemic site of the primary malignant lesion.[6] Consequently, it is often necessary to distinguish high-grade gliomas from lymphomas, especially diffuse large B-cell lymphomas (DLBCLs), in clinical practice. Previous studies have demonstrated that maximum standardized uptake value

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(SUV_{max}) and tumor-to-normal tissue (T/N) ratio on ^{18}F-FDG PET images are appropriate for distinguishing DLBCLs from glioblastomas and other malignant brain tumors.[5,7] In addition, ΔSUV_{max} on ^{11}C-MET PET images could be potentially useful for differential diagnosis of intracranial DLBCL and glioblastoma.[5]

Patients with brain tumors of glial origin often exhibit 2 or more brain lesions. Multicentric gliomas are widely separated lesions located in different lobes, which do not grow through dissemination along an established route. The most common pathologic type of PCNSL is DLBCL, which usually originates deep within the cerebral hemisphere. However, intracranial lymphomas could also present as multiple lesions separated from each other.[8] The similarities in conventional MRI features, including obvious edema, mass effect, and marked contrast enhancement, render differential diagnosis of multicentric gliomas and multiple DLBCLs challenging. ^{18}F-FDG and ^{11}C-MET are commonly used radiotracers that could help acquire additional information and improve the diagnostic accuracy of PET for distinguishing between these 2 tumors.[9] Although some previously reported indicators, such as SUV_{max} and T/N ratio, have been shown to be effective in differentiating solitary gliomas and lymphomas,[5,7,10] the diagnostic value of ^{18}F-FDG PET for distinguishing multicentric gliomas from multiple DLBCLs has not been well evaluated.

In the present study, we aimed to investigate the value of ^{18}F-FDG PET in differential diagnosis of multicentric gliomas and multiple DLBCLs and to establish a new and alternative PET marker for discriminating of these 2 malignant tumors, which might aid therapeutic decision making.

2. Methods

2.1. Participants

Fifth-three patients initially diagnosed with multiple intracranial tumors at our department between July 2014 and September 2016 were retrospectively enrolled. Patients were included if they met the following criteria: multiple intracranial tumors—supratentorial, infratentorial, or both, confirmed by contrast-enhanced T1-weighted MRI; histopathological diagnosis of multicentric gliomas or DLBCLs by neurosurgery or stereotactic biopsy according to the World Health Organization grading system for central nervous system tumors[11]; and presurgical ^{18}F-FDG PET data, with or without ^{11}C-MET PET, available for analysis. Patients were excluded if they had previously undergone neurosurgical resection or received radiotherapy or chemotherapy or exhibited blood sugar levels >150 mg/dL at the time of ^{18}F-FDG or ^{11}C-MET PET. The study has been approved by the institutional review board of Beijing Tiantan Hospital, and the need for written informed consent was waived due to the retrospective nature of the present study.

2.2. PET protocol

^{18}F-FDG and ^{11}C-MET PET images were acquired using a PET/CT scanner (Elite Discovery; GE Health Care, Fairfield, Connecticut), with a 5 mm axial resolution and 4 mm full-width half-maximum at the center of the field of view. Imaging data were reconstructed into 30 transaxial planes with 5 mm slice thickness and 256×256 image matrix.

All patients underwent ^{18}F-FDG or ^{11}C-MET PET according to the same protocol. ^{18}F-FDG was intravenously injected at a dose of 3.7 MBq/kg, and whole-brain image acquisition was started 60 minutes later. For ^{11}C-MET PET, 555 to 740 MBq of ^{11}C-MET was intravenously injected, and whole-brain imaging was started 10 minutes later. Subjects were positioned supine and instructed to remain absolutely quiet throughout the scanning procedure. Scanning times for both ^{18}F-FDG and ^{11}C-MET PET were maintained between 8 and 10 minutes.

The time interval between ^{18}F-FDG and ^{11}C-MET PET was at least 24 hours but less than a week. Patients were not administered any intervention between the 2 imaging sessions.

2.3. Analysis of PET images

Regional uptakes of ^{18}F-FDG and ^{11}C-MET were expressed as SUV, calculated according to the following equation: [tissue activity (Bq/mL) × (body weight, g)]/[injected radioisotope activity (Bq)].[7] The SUV_{max} of a tumor was sampled from a single pixel exhibiting the highest ^{18}F-FDG or ^{11}C-MET accumulation. The T/N ratio of ^{18}F-FDG PET images was defined as the ratio of SUV_{max} of the lesion to the contralateral normal white matter. The T/N ratio of ^{11}C-MET PET images was defined as the ratio of SUV_{max} of the lesion to the contralateral normal gray matter. For lesions located along the midline, such as the thalamus or brain stem, the average value of SUV_{max} of both sides of the gray (or white) matter was considered.

As all included patients exhibited multiple lesions in the brain, the following uptake features for ^{18}F-FDG and ^{11}C-MET in multicentric gliomas and multiple DLBCLs were evaluated. To be specific, the highest SUV_{max} among all lesions in multicentric gliomas (or multiple DLBCLs) was considered as the actual SUV_{max}. The maximum difference-value (D-value) of SUV_{max} among lesions in multicentric gliomas (or multiple DLBCLs) was calculated as the difference between the highest SUV_{max} and the corresponding lowest SUV_{max} among the tumors. A similar analysis method was applied for T/N ratios. The T/N $ratio_{max}$was defined as the ratio of the highest SUV_{max} to the SUV_{max} of the contralateral white (or gray) matter in ^{18}F-FDG (or ^{11}C-MET) PET images. The maximum D-value of T/N ratio among lesions in multicentric gliomas (or multiple DLBCLs) was calculated as the difference between the highest T/N ratio and the corresponding lowest T/N ratio among the lesions. The percentage of maximum D-value of SUV_{max} among lesions in multicentric gliomas (or multiple DLBCLs) for each patient was calculated as follows:

$$\text{Maximum D} - \text{value of SUV}_{max}\,(\%) = \frac{\text{highest SUV}_{max} - \text{lowest SUV}_{max}}{\text{highest SUV}_{max}} \times 100\%$$

The percentage of maximum D-value of T/N ratio among lesions in multicentric gliomas (or multiple DLBCLs) was also calculated according to the same formula. The uptake features mentioned above were assessed by 2 experienced nuclear medicine physicians (XBZ and QC, who have 8 and 10 years of experience, respectively) blinded to the patient clinical information.

2.4. Statistical analysis

All statistical analyses were performed using the SPSS Window version 16.0 (IBM, Armonk, NY) and Prism version 6.0 software (GraphPad Software, San Diego, CA). Patient age, SUV_{max}, maximum D-value of SUV_{max}, T/N $ratio_{max}$, maximum D-value of T/N ratio, and percentages of maximum D-values of SUV_{max}

Table 1

Clinical characteristics and positron emission computed tomography data of patients with multicentric gliomas.

			FDG PET				MET PET			
Gender	Age, y	Pathologic diagnosis	Uptake pattern	SUVmax	T/Nmax	Max D-value of SUVmax (or T/N) (%)	Uptake pattern	SUVmax	T/Nmax	Max D-value of SUVmax (or T/N) (%)
M	31	Astrocytoma	Heterogeneous	11.5	5.8	59.1	Heterogeneous	—	—	—
M	67	AA	Heterogeneous	6.8	3.2	42.6	Heterogeneous	—	—	—
F	47	AOA	Heterogeneous	9.6	3.3	57.3	Heterogeneous	4.7	2.8	61.7
M	59	AOA	Heterogeneous	14.5	4.7	54.5	Heterogeneous	—	—	—
F	59	Glioblastoma	Heterogeneous	16.5	6.1	24.8	Heterogeneous	—	—	—
M	28	OA	Heterogeneous	41.9	11.0	57.8	Heterogeneous	10.5	5.3	52.4
F	27	Astrocytoma	Heterogeneous	36.1	11.6	49.9	Heterogeneous	7.4	4.6	36.5
M	44	Astrocytoma	Heterogeneous	25.8	9.9	68.2	Heterogeneous	5.6	3.5	41.1
M	41	AOA	Heterogeneous	13.0	4.5	29.2	Heterogeneous	6.7	3.4	41.8
M	53	Glioblastoma	Heterogeneous	6.9	2.7	47.8	Heterogeneous	2.5	3.1	52.0
M	43	Astrocytoma	Heterogeneous	13.4	6.4	49.3	Heterogeneous	4.7	3.1	40.4
M	57	Astrocytoma	Heterogeneous	13.9	5.0	45.3	Heterogeneous	—	—	—
F	51	Glioblastoma	Heterogeneous	10.5	3.9	46.7	Heterogeneous	—	—	—
F	50	AA	Heterogeneous	18.9	9.5	27.5	Heterogeneous	—	—	—
F	50	AA	Heterogeneous	6.2	2.4	35.5	Heterogeneous	1.4	2.8	28.6
M	78	Glioblastoma	Heterogeneous	9.5	3.8	36.8	Heterogeneous	—	—	—
F	71	AA	Heterogeneous	17.9	5.6	45.8	Heterogeneous	—	—	—

AA = anaplastic astrocytoma; AOA = anaplastic oligodendroastrocytoma; D-value = Difference value; FDG = fluoro-2-deoxy-D-glucose; MET = methionine; OA = oligodendroastrocytoma; PET = positron emission computed tomography; SUV = standardized uptake value; T/N = tumor to normal tissue ratio.

and T/N ratio were expressed as mean value ± standard deviation. Differences in distribution of patients according to gender were evaluated by the Chi-square test. Comparison of mean values of parameters between patients with multicentric gliomas and multiple DLBCLs was performed with the 2-independent samples *t* test. Values of $P < .05$ were considered statistically significant. Optimal cut-off values for differential diagnosis of these 2 tumors were determined by receiver operating characteristics curves. The area under the curve, cut-off point, sensitivity, and specificity were calculated.

3. Results

3.1. Participants

Among all the 53 patients with multiple intracranial tumors between July 2014 and September 2016, a total of 32 patients were enrolled in the present study, with 17 harbored multicentric gliomas (mean age, 49.2 ± 16.6 years; male, 10; female, 7), while 15 exhibited multiple intracranial DLBCLs (mean age, 56.5 ± 15.3 years; male, 9; female, 6). All the enrolled patients underwent ^{18}F-FDG PET with or without ^{11}C-MET PET. Among the 17 patients with multicentric gliomas, 8 underwent both ^{18}F-FDG and ^{11}C-MET PET, while the other 9 patients only underwent ^{18}F-FDG PET. Among the 15 patients with multiple DLBCLs, all had undergone ^{18}F-FDG PET, and only 1 patient had undergone both ^{18}F-FDG and ^{11}C-MET PET. The clinical and imaging characteristics of patients with multicentric gliomas and multiple DLCBL are summarized in Tables 1 and 2, respectively. Moreover, patients harboring multicentric gliomas or DLBCLs are demonstrated in Figs. 1 and 2, respectively

3.2. Quantitative assessment of PET features

The mean age of patients with multicentric gliomas was lower than that of patients with multiple DLBCLs; however, the difference was not statistically significant ($P = .21$). The gender ratio between the 2 groups did not exhibit a significant difference either ($P = .94$).

The SUV_{max} of ^{18}F-FDG in patients with multiple DLBCLs (26.2 ± 10.5) was significantly higher than that in patients with multicentric gliomas (16.1 ± 10.0; $P = .009$). The difference in T/N $ratio_{max}$ of ^{18}F-FDG between multicentric gliomas and multiple DLBCLs was not significant (5.8 ± 2.9 vs 8.3 ± 4.0; $P = .06$). There were no statistically significant differences in maximum D-values of SUV_{max} or T/N ratio of ^{18}F-FDG between the 2 groups ($P = .39$ and $P = .18$, respectively). Notably, the percentage of maximum D-value of SUV_{max} (and T/N ratio) of ^{18}F-FDG in multicentric gliomas was significantly higher than that in multiple DLBCLs (45.8 ± 12.0% vs 22.6 ± 12.7%; $P < .001$; Table 3).

The SUV_{max}, T/N $ratio_{max}$, maximum D-values of SUV_{max} and T/N ratio, and percentages of maximum D-values of SUV_{max} and T/N ratio of ^{11}C-MET in patients with multicentric gliomas were all higher than those in patients with multiple DLBCLs (Table 3).

For ^{18}F-FDG PET data, receiver operating characteristic analysis demonstrated that percentages of maximum D-values of SUV_{max} and T/N ratio might be suitable markers for differentiating between multicentric gliomas and multiple DLBCLs (Fig. 3). The cut-off value, sensitivity, specificity, and area under the curve of ^{18}F-FDG PET for differential diagnosis between the 2 tumors were 44.4%, 64.7%, 100%, and 0.912, respectively. In other words, patients with multiple intracranial tumors exhibiting percentages of maximum D-values of SUV_{max} or T/N ratio ≥44.4% can be diagnosed with multicentric gliomas with a high degree of certainty. At percentages less than 44.4%, tumors may not be diagnosed as multicentric gliomas; instead, intracranial multiple DLBCL should be considered as a possible diagnosis after excluding metastasis by whole-body PET.

Table 2

Clinical characteristics and PET data of patients with multiple diffuse large B-cell lymphomas.

			FDG PET				MET PET			
Gender	Age, y	Pathologic diagnosis	Uptake pattern	SUVmax	T/Nmax	Max D-value of SUVmax (or T/N) (%)	Uptake pattern	SUVmax	T/Nmax	Max D-value of SUVmax (or T/N) (%)
M	24	DLBCLs	Homogeneous	33.4	7.8	12.3	—	—	—	—
F	73	DLBCLs	Homogeneous	20.7	6.9	21.7	—	—	—	—
M	56	DLBCLs	Homogeneous	21.6	7.0	8.8	—	—	—	—
M	40	DLBCLs	Homogeneous	33.3	11.1	42.6	—	—	—	—
F	66	DLBCLs	Homogeneous	21.3	7.3	19.2	—	—	—	—
M	72	DLBCLs	Homogeneous	43.8	19.9	18.5	—	—	—	—
M	50	DLBCLs	Homogeneous	30.2	7.7	41.4	—	—	—	—
F	65	DLBCLs	Homogeneous	43.0	9.6	20.2	—	—	—	—
M	63	DLBCLs	Heterogeneous	11.7	3.2	13.7	Heterogeneous	2.1	1.75	14.3
F	61	DLBCLs	Homogeneous	29.9	8.5	3.3	—	—	—	—
M	52	DLBCLs	Homogeneous	16.9	5.3	9.5	—	—	—	—
M	29	DLBCLs	Homogeneous	24.9	9.6	43.4	—	—	—	—
F	65	DLBCLs	Homogeneous	21.4	5.9	27.1	—	—	—	—
M	58	DLBCLs	Homogeneous	33.2	10.7	28.0	—	—	—	—
F	74	DLBCLs	Homogeneous	7.0	3.3	30.0	—	—	—	—

DLBCLs = diffuse large B-cell lymphomas; D-value = Difference value; FDG = fluoro-2-deoxy-D-glucose; MET = methionine; PET = positron emission computed tomography; SUV = standardized uptake value; T/N = tumor to normal tissue ratio.

4. Discussion

The present findings demonstrated that ^{18}F-FDG uptake in DLBCL is significantly higher than that in gliomas. Moreover, percentages of maximum D-values of SUV_{max} and T/N ratio of ^{18}F-FDG might be useful parameters for differentiating multicentric gliomas from multiple DLBCLs.

As the most widely used radiotracer for central nervous system lesions, ^{18}F-FDG has been employed for detection of brain tumors in clinical practice. ^{18}F-FDG uptake in gliomas is associated with tumor cell density and activity.[12,13] Specifically, increased tumor cellularity and decreased extracellular matrix are correlated with increased cell proliferation and glucose accumulation on ^{18}F-FDG PET images. In contrast,

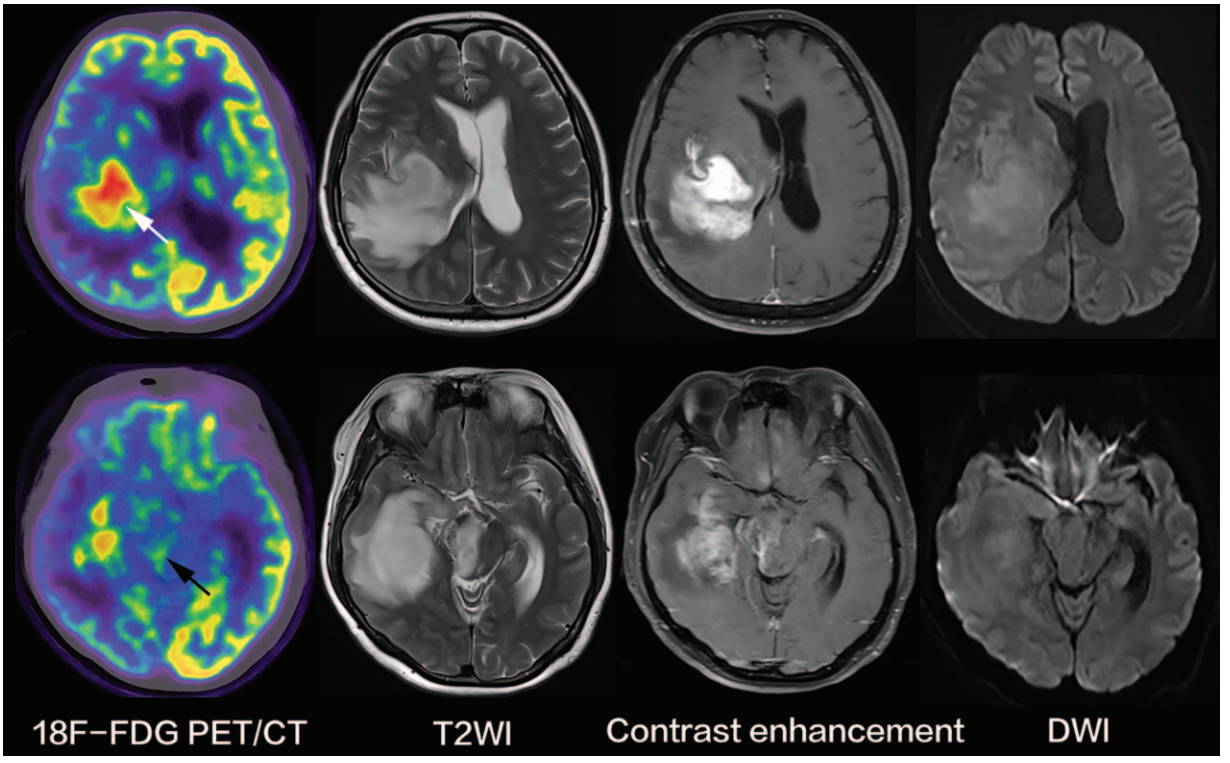

Figure 1. Multicentric gliomas. A lesion (white arrow) located at the junction of the right frontal and parietal lobes exhibited higher metabolism on ^{18}F-FDG PET findings than normal gray matter. The lesion exhibited hyperintensity on T2-weighted MR images and obvious inhomogeneous contrast enhancement and restricted diffusion on diffusion-weighted MR images (upper row). Another lesion in the mid-brain (black arrow) exhibited much lower metabolism than the above lesion on ^{18}F-FDG PET findings and similar manifestation on MR images (lower row).

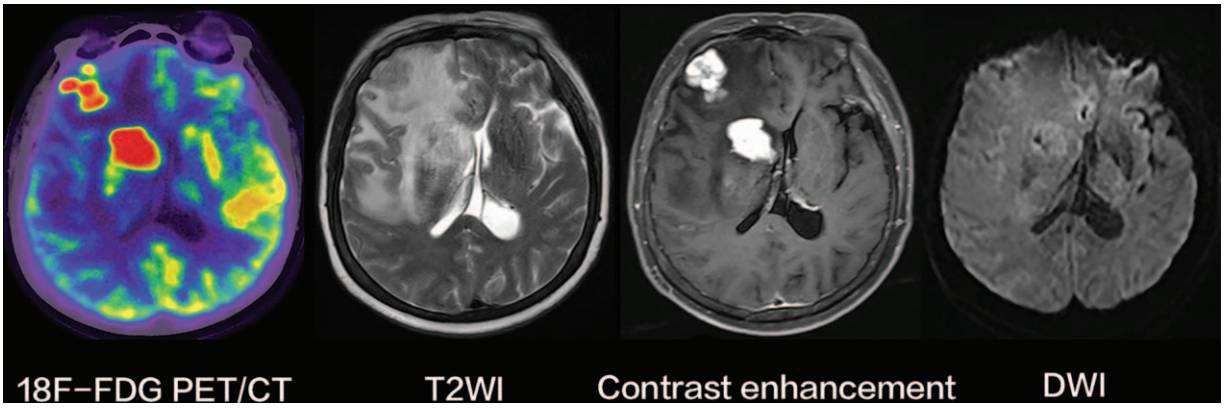

Figure 2. Multiple diffuse large B-cell lymphomas. Two lesions in the right frontal lobe and basal ganglion exhibited much higher accumulation of ^{18}F-FDG on PET images than normal gray matter. They exhibited iso to hyperintensities with edema on T2-weighted MR images, strong and relatively homogeneous enhancement on contrast-enhanced T1-weighted MR images, and slightly restricted diffusion on diffusion-weighted MR images.

scant cellularity and abundant extracellular matrix in gliomas correspond with decreased cell proliferation and low SUV of ^{18}F-FDG.[14] Therefore, SUV possibly indicates cellularity and tumor grading. Gliomas are generally heterogeneous and can present different histologic features and grades even within the same tumor. Patients with 2 or more gliomas in the brain are generally diagnosed with multiple or multicentric gliomas, which originate from different locations on the unilateral or bilateral cerebral hemisphere. Because of the heterogeneity of origin of gliomas, ^{18}F-FDG accumulation may vary among lesions or even within the same tumor. Therefore, differences in SUV_{max} as well as T/N ratio are relatively prominent, as ^{18}F-FDG uptake in the gray matter is generally constant.

Although PCNSL was previously regarded as a rare tumor, its incidence has been increasing over the past 2 decades.[15] Histologically, a majority of PCNSLs are DLBCLs. They consist of abundant tumor cells, which present as hyperintensities on diffusion-weighted images, suggesting high tumor cell density. Homogeneous and intense contrast enhancement is common, as intratumoral necrosis and hemorrhage rarely occur in DLBCL. Previous studies have reported that DLBCLs exhibit high ^{18}F-FDG uptake and can be detected by ^{18}F-FDG PET with relatively high sensitivity.[16] Besides, the mean T/N ratio of ^{18}F-FDG in lymphomas has been shown to be significantly higher than that in high-grade gliomas (2.0 vs 1.6).[17] The higher T/N ratio of ^{18}F-FDG in DLBCLs in comparison with that in gliomas may partially be due to the high cellularity and consumption rate of tumor cells in DLBCLs.[18] In addition to being solitary lesions in the brain, DLBCLs could also present as multiple lesions that could invade various anatomic structures of the brain, including the cerebral lobes, corpus callosum, and ventricles, in which case, some lesions may not be located deep within the cerebral hemisphere and, consequently, may not exhibit as high an ^{18}F-FDG uptake as typical DLBCLs. Although ^{18}F-FDG PET is regarded as a useful tool for diagnosing PCNSL,[9,19] the overall ^{18}F-FDG accumulation characteristics of multiple lymphomas have not been described well.

Table 3

Comparison of clinical data and positron emission computed tomography characteristics between patients with multicentric gliomas and multiple diffuse large B-cell lymphomas.

	Multicentric glioma (n=17)	Multiple DLBCLs (n=15)	*P*
Age (y, mean±SD)	49.2±16.6	56.5±15.3	.21
Gender (male/female)	10/7	9/6	.94
FDG PET (n=32)	(n=17)	(n=15)	
SUVmax	16.1±10.0	26.2±10.5	.009
Maximum D-value of SUVmax	7.7±6.2	6.0±4.3	.39
T/N $ratio_{max}$	5.8±2.9	8.3±4.0	.06
Maximum D-value of T/N ratio	2.8±1.8	1.9±1.5	.18
Maximum D-value of SUVmax (or T/N ratio) (%)	45.8±12.0%	22.6±12.7%	<.001
MET PET (n=9)	(n=8)	(n=1)	
SUVmax	5.4±2.9	2.1	—
Maximum D-value of SUVmax	2.5±1.5	0.3	—
T/N $ratio_{max}$	3.6±0.9	1.75	—
Maximum D-value of T/N ratio	1.6±0.6	0.25	—
Maximum D-value of SUVmax (or T/N ratio) (%)	44.3±10.5%	14.3%	—

Data are presented as mean±standard deviation.

DLBCLs=diffuse Large B-cell lymphomas; D-value=difference value; FDG=fluoro-2-deoxy-D-glucose; MET=methionine; PET=positron emission computed tomography; SD=standard deviation; SUV=standardized uptake value; T/N=tumor to normal tissue.

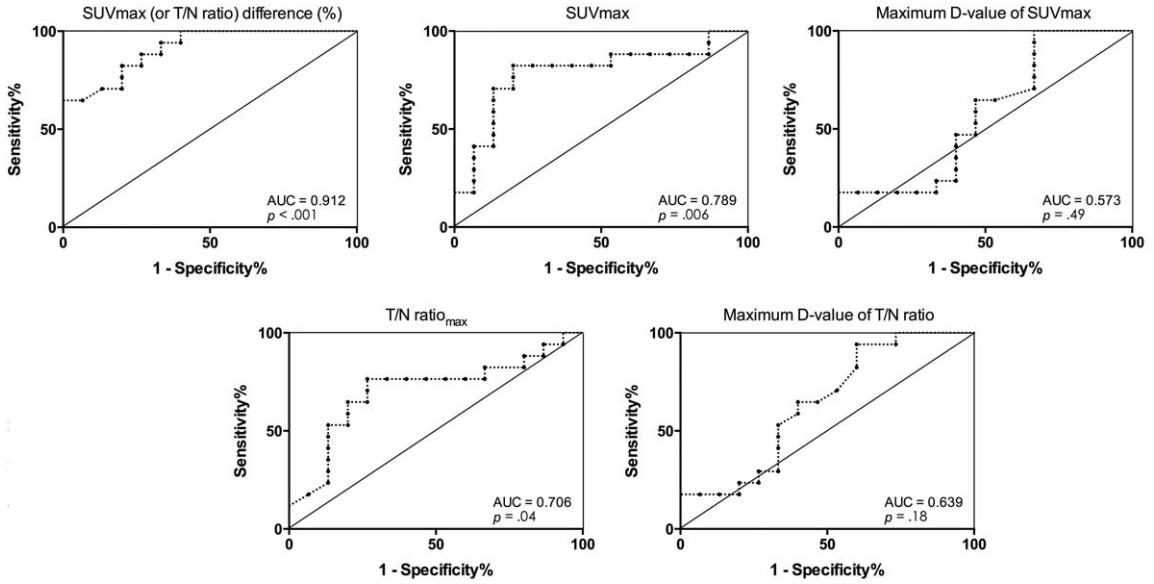

Figure 3. Receiver operating characteristic curves of different diagnostic markers for differentiating multicentric gliomas from multiple diffuse large B-cell lymphomas. In comparison with the other 4 diagnostic parameters, percentage of maximum difference-value of maximum standardized uptake value (or tumor to normal ratio) could better distinguish multicentric gliomas from diffuse large B-cell lymphomas (sensitivity and specificity, 64.7% and 100%, respectively).

Several studies have reported ^{18}F-FDG PET as sometimes demonstrating hypo or iso-metabolism in high-grade gliomas or lymphomas, which could be a limitation of this technique.[10,20] Other radioisotopes, such as ^{11}C-MET, have been proposed to overcome this limitation. High-grade gliomas and PCNSLs exhibit increased ^{11}C-MET uptake and good contrast, which might help locate PCNSLs.[21,22]

As the MR and ^{18}F-FDG and ^{11}C-MET PET features of multicentric gliomas and multiple DLBCLs might be similar, accurate differentiation of the 2 types of tumors is important for identifying the appropriate therapeutic strategy. In previous studies, the values of all ^{18}F-FDG PET parameters, including SUV_{max} and T/N ratio, in PCNSLs were found to be significantly higher than those in high-grade gliomas.[19] According to previous findings of receiver operating characteristic analysis, a SUV_{max} cutoff threshold of 12 (or 15) may be reliable for differentiation of PCNSLs and high-grade gliomas.[9,19] In addition, several studies have reported the cutoff thresholds of SUV_{max} for diagnosis of PCNSLs on FDG PET images.[9,19,23] However, SUVs of brain tumors may be influenced by various factors, including plasma glucose levels and steroid treatment.[17,24] In order to eliminate the effects of these confounding factors, previous studies have employed T/N ratio as a diagnostic indicator and have reported its superior accuracy in comparison with that of SUV_{max}. The mean T/N ratio of ^{18}F-FDG for distinguishing PCNSLs ranges from 2.36 to 2.79.[7,16,25] In ^{11}C-MET PET, the rate of ^{11}C-MET uptake—defined as ΔSUV_{max} (the ratio of SUV_{max} in the late and early phases of PET)—could enable clinicians to distinguish glioblastomas and DLBCLs.[5]

Although SUV_{max} and T/N ratio have been demonstrated to be useful for differential diagnosis of PCNSL and glioma, the targeted lesions in previous studies were confined to single tumors. In case of multiple lesions, however, previously established markers for differentiating multicentric gliomas and multiple DLBCLs might not be reliable. In the present study, we focused on a new indicator that could better distinguish these 2 types of multiple tumors. The present findings demonstrated that SUV_{max} and T/N $ratio_{max}$ of ^{18}F-FDG are useful for differentiating multicentric gliomas from multiple DLBCLs, with the former exhibiting better performance than the latter in terms of the area under the curve [0.789 ($P = .006$) vs 0.706 ($P = .04$)]. Irrespective of the type of tumor, accumulation of radioisotopes in each lesion was found to vary, which may be attributed to the heterogeneity of lesions, especially in multicentric gliomas; however, the same might also be true for multiple DLBCLs. In order to take greater advantage of the uptake data of each lesion, we compared the maximum D-values of SUV_{max} and T/N ratio of ^{18}F-FDG between lesions in multicentric gliomas and multiple DLBCLs. However, the diagnostic power of these 2 markers was inadequate for differentiating between the 2 types of tumors, which might possibly be because the absolute maximum D-values of SUV_{max} and T/N ratio of ^{18}F-FDG might not represent the actual degree of variation in radioisotope uptake among lesions in multicentric gliomas or multiple DLBCLs. Therefore, percentages of maximum D-values of SUV_{max} and T/N ratio among lesions in multicentric gliomas or multiple DLBCLs were evaluated and found to be more appropriate and accurate for distinguishing these 2 types of tumors than absolute maximum D-values (area under the curve, 0.912; $P < .001$). These new ^{18}F-FDG PET markers could better reflect the actual degree of variation in radioisotope uptake among lesions in multicentric gliomas or multiple DLBCLs than existing markers. Despite a cut-off value of 44.4% and specificity of 100%, the sensitivity of maximum D-value of SUV_{max} for diagnosing multicentric gliomas was only 64.7%, which might not be adequate for differential diagnosis. This suggests that the degree of radioisotope uptake varies substantially among lesions in multicentric gliomas, possibly because of their heterogeneity, including differences in histopathologic origin and tumor composition. In comparison, heterogeneity among lesions in multiple DLBCLs was relatively obscure.

Previous studies have reported that PET sometimes fails to detect atypical PCNSLs because of low ^{18}F-FDG or ^{11}C-MET uptake.[10,26,27] In the present study, only 1 patient (1/15) with multiple DLBCLs did not exhibit typical ^{18}F-FDG and ^{11}C-MET uptake; in addition, the SUV_{max} and T/N ratio in this patient were not as high as those among other patients. Although this atypical case was included for data analysis, it had no obvious effect on the present results. Therefore, in ^{18}F-FDG PET, the percentages of maximum D-values of SUV_{max} and T/N ratio among lesions might actually reflect the biological features of multicentric gliomas and multiple DLBCLs and thus exhibit better diagnostic performance than conventional markers such as SUV_{max} and T/N ratio.

There are some limitations to the present study. First, we retrospectively enrolled a limited number of patients from a single institution. Second, not all patients included in the present study underwent both ^{18}F-FDG and ^{11}C-MET PET. The diagnostic values of the new markers established in our study need to be validated in future prospective studies

5. Conclusion

The percentage of maximum D-values of SUVmax and T/N ratio on ^{18}F-FDG PET images might reflect the actual degree of variation among lesions in multicentric gliomas and multiple DLBCLs. These markers could potentially be used for further differentiation of these 2 tumors.

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References

[1] Sherman JH, Prevedello DM, Shah L, et al. MR imaging characteristics of oligodendroglial tumors with assessment of 1p/19q deletion status. Acta Neurochir (Wien) 2010;152:1827–34.
[2] Kleinschmidt-DeMasters BK, Aisner DL, Birks DK, et al. Epithelioid GBMs show a high percentage of BRAF V600E mutation. Am J Surg Pathol 2013;37:685–98.
[3] Wang S, Kim S, Chawla S, et al. Differentiation between glioblastomas, solitary brain metastases, and primary cerebral lymphomas using diffusion tensor and dynamic susceptibility contrast-enhanced MR imaging. AJNR Am J Neuroradiol 2011;32:507–14.
[4] Wang K, Wang Y, Fan X, et al. Radiological features combined with IDH1 status for predicting the survival outcome of glioblastoma patients. Neuro Oncol 2016;18:589–97.
[5] Okada Y, Nihashi T, Fujii M, et al. Differentiation of newly diagnosed glioblastoma multiforme and intracranial diffuse large B-cell lymphoma using (11)C-methionine and (18)F-FDG PET. Clin Nucl Med 2012; 37:843–9.
[6] Mohile NA, Deangelis LM, Abrey LE. The utility of body FDG PET in staging primary central nervous system lymphoma. Neuro Oncol 2008;10:223–8.
[7] Yamaguchi S, Hirata K, Kobayashi H, et al. The diagnostic role of (18)F-FDG PET for primary central nervous system lymphoma. Ann Nucl Med 2014;28:603–9.
[8] Younes A, Romaguera J, Fanale M, et al. Phase I study of a novel oral Janus kinase 2 inhibitor, SB1518, in patients with relapsed lymphoma: evidence of clinical and biologic activity in multiple lymphoma subtypes. J Clin Oncol 2012;30:4161–7.
[9] Makino K, Hirai T, Nakamura H, et al. Does adding FDG-PET to MRI improve the differentiation between primary cerebral lymphoma and glioblastoma? Observer performance study. Ann Nucl Med 2011;25: 432–8.
[10] Kawai N, Miyake K, Yamamoto Y, et al. 18F-FDG PET in the diagnosis and treatment of primary central nervous system lymphoma. Biomed Res Int 2013;2013:247152.
[11] Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 2016;131:803–20.
[12] Kaschten B, Stevenaert A, Sadzot B, et al. Preoperative evaluation of 54 gliomas by PET with fluorine-18-fluorodeoxyglucose and/or carbon-11-methionine. J Nucl Med 1998;39:778–85.
[13] Goldman S, Levivier M, Pirotte B, et al. Regional glucose metabolism and histopathology of gliomas. A study based on positron emission tomography-guided stereotactic biopsy. Cancer 1996;78:1098–106.
[14] Matsushima N, Maeda M, Umino M, et al. Relation between FDG uptake and apparent diffusion coefficients in glioma and malignant lymphoma. Ann Nucl Med 2012;26:262–71.
[15] Behin A, Hoang-Xuan K, Carpentier AF, et al. Primary brain tumours in adults. Lancet 2003;361:323–31.
[16] Palmedo H, Urbach H, Bender H, et al. FDG-PET in immunocompetent patients with primary central nervous system lymphoma: correlation with MRI and clinical follow-up. Eur J Nucl Med Mol Imaging 2006;33:164–8.
[17] Rosenfeld SS, Hoffman JM, Coleman RE, et al. Studies of primary central nervous system lymphoma with fluorine-18-fluorodeoxyglucose positron emission tomography. J Nucl Med 1992;33:532–6.
[18] Roelcke U, Leenders KL. Positron emission tomography in patients with primary CNS lymphomas. J Neurooncol 1999;43:231–6.
[19] Kosaka N, Tsuchida T, Uematsu H, et al. 18F-FDG PET of common enhancing malignant brain tumors. AJR Am J Roentgenol 2008;190: W365–369.
[20] Prat R, Galeano I, Lucas A, et al. Relative value of magnetic resonance spectroscopy, magnetic resonance perfusion, and 2-(18F) fluoro-2-deoxy-D-glucose positron emission tomography for detection of recurrence or grade increase in gliomas. J Clin Neurosci 2010;17:50–3.
[21] Kinoshita M, Arita H, Goto T, et al. A novel PET index, 18F-FDG-11C-methionine uptake decoupling score, reflects glioma cell infiltration. J Nucl Med 2012;53:1701–8.
[22] Yamamoto Y, Nishiyama Y, Kimura N, et al. 11C-acetate PET in the evaluation of brain glioma: comparison with 11C-methionine and 18F-FDG-PET. Mol Imaging Biol 2008;10:281–7.
[23] Kawai N, Zhen HN, Miyake K, et al. Prognostic value of pretreatment 18F-FDG PET in patients with primary central nervous system lymphoma: SUV-based assessment. J Neurooncol 2010;100: 225–32.
[24] Hustinx R, Smith RJ, Benard F, et al. Can the standardized uptake value characterize primary brain tumors on FDG-PET? Eur J Nucl Med 1999;26:1501–9.
[25] Karantanis D, O'Eill BP, Subramaniam RM, et al. 18F-FDG PET/CT in primary central nervous system lymphoma in HIV-negative patients. Nucl Med Commun 2007;28:834–41.
[26] Garcia-Garzon JR, Villasboas-Rosciolesi D, Baquero M, et al. A false-negative case of primary central nervous system lymphoma on 11C-methionine PET and intense 18F-FDG uptake. Clin Nucl Med 2016;41: 664–5.
[27] Kawai N, Okubo S, Miyake K, et al. Use of PET in the diagnosis of primary CNS lymphoma in patients with atypical MR findings. Ann Nucl Med 2010;24:335–43.