

FDG PET/CT Assessment of the Biological Behavior of Meningiomas

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Objective : We investigated the pattern of glucose uptake in meningiomas using ¹⁸F-fluoro-2-deoxy-D-glucose(FDG) PET/CT. It was hypothesized that the degree of glucose uptake in each tumor could predict the histologic grade.

Methods : In 19 patients with meningiomas, the Ki-67 proliferative index, standardized uptake values(SUV) of FDG uptake, tumor to contralateral gray matter ratio(TGR) of SUV, tumor size, edema grade, vascular endothelial growth factor(VEGF) expression, histopathologic grade and the blood supply pattern were assessed.

Results : Of the 19 meningiomas, 8 were meningothelial, 1 fibrous, 2 transitional, 1 psammomatous, 2 angiomatous, and 5 atypical. The tumor proliferative index of Ki-67, tumor size, and peritumoral edema were larger in the histopathologic grade-2 meningiomas than in the grade-1 meningioma group. There were no significant differences in SUV and TGR between two groups. Tumor size and peritumoral edema were significantly larger in VEGF-positive tumors than in negative tumors. Conventional angiography was performed in 12 patients. Dural supply was noted predominantly in 2 patients. Four patients had mainly pial cortical supply patterns. In tumors with more pial supply, VEGF was more frequently positive. There was a significant relation between SUV and Ki-67 and between SUV and peritumoral edema.

Conclusion : We found FDG uptake in meningiomas is associated with proliferative potential, however, no clear limits of SUV and TGR can be set to distinguish between grade-1 and grade-2 meningiomas, which makes the assessment of malignancy grade using PET scan metabolic imaging difficult in individual cases.

KEY WORDS : Positron emission tomography · 2-[¹⁸F] fluoro-2-deoxy-D-glucose · Meningiomas · Proliferation · Ki-67.

Introduction

Despite similar benign histological appearances, the proliferative activity of meningiomas varies from tumor to tumor, and even from region to region within a tumor¹¹. Preoperative prediction of proliferative potential of meningiomas is gaining importance considering the rate of incidental detection of meningiomas, the existence of mimicking lesions such as dura-based metastatic tumors, and the trend toward radiosurgical treatment without pathologic verification. There have been several efforts to estimate the biological behaviors of meningiomas using positron emission tomography(PET), however no consensus has been reached^{3,5,11,26}.

¹⁸F-fluoro-2-deoxyglucose(FDG) has been a standard tracer

for tumor detection, grading, discrimination between radiation necrosis and tumor recurrence, and evaluating response to therapy^{1,2,9}. ¹⁸F-FDG accumulates not only in neoplastic cells but also in inflammatory cells^{10,14} and vascular endothelial growth factor(VEGF) significantly stimulates endothelial ¹⁸F-FDG uptake¹⁷. The expression of VEGF positively relates to the formation of peritumoral brain edema in patients with meningiomas²¹ and there was a report that a high level of expression of VEGF constituted the most useful predictor of recurrence²⁸. Tumor infiltration into adjacent brain parenchyma and a pial-cortical blood supply are critical factors for the development of peritumoral brain edema among patients with meningiomas²⁵.

Based on these relationships, we compared regional uptake

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of ¹⁸F-FDG with the histological index of tumor proliferative activity, peritumoral edema, tumor size, histologic grade, VEGF activity and the blood supply pattern, to predict the proliferative potential of meningiomas before surgery.

Materials and Methods

From August 2004 to January 2006, 19 patients with meningiomas were included. There were 13 female and 6 male patients. Mean age was 57 years (range 32~77 years).

Uptake of FDG into meningiomas was assessed by PET/CT preoperatively and was quantified by the standardized uptake value(SUV) and the tumor-to-contralateral gray matter SUV ratio(TGR). SUV was determined as the ratio of the tissue concentration of tracer in the tumor divided by the injected tracer dose and body weight (mean ROI activity (mCi/mL)/ injected dose (mCi/body weight [kg])). The comparative variables were as follows: the proliferative index of a tumor based on Ki-67 immunostaining, tumor size presented as the maximum diameter of a tumor, peritumoral edema represented as the maximum length of high signal area on T2 WI of MR imaging, the degree of VEGF expression, the pattern of blood supply to tumors, histological subtype, and tumor

Table 1. Comparison of tumors based on histopathological grades

	Grade I (n=14)	Grade II (n=5)	P-value
	Mean ± SD	Mean ± SD	
SUV	3.578 ± 1.744	5.100 ± 3.535	0.487
TGR	0.806 ± 0.451	0.749 ± 0.534	0.459
Ki-67	0.650 ± 0.581	4.300 ± 2.683	0.003
Size	3.657 ± 1.753	5.240 ± 1.101	0.026
Edema	1.578 ± 2.289	4.120 ± 1.098	0.013
VEGF	9/14 (64.3%)	4/5 (80%)	ns*

SD : standard deviation, SUV : standardized uptake value, TGR : tumor to contralateral gray matter ratio, VEGF : vascular endothelial growth factor. * ns : no statistical calculation due to small patient population

Table 2. Differences between VEGF-positive and -negative groups

	VEGF + (n=13)	VEGF - (n=6)	P-value
	Mean ± SD	Mean ± SD	
SUV	4.469 ± 2.537	2.916 ± 1.475	0.203
TGR	0.895 ± 0.500	0.566 ± 0.266	0.219
Ki-67	1.953 ± 2.473	0.866 ± 0.895	0.464
Size	4.646 ± 1.761	2.833 ± 0.811	0.043
Edema	2.900 ± 2.206	0.833 ± 2.041	0.022

VEGF : vascular endothelial growth factor, SD : standard deviation, SUV : standardized uptake value, TGR : tumor to contralateral gray matter ratio

Table 3. The pattern of blood supply

Blood supply pattern	No. of cases (n=12)	VEGF +
Only dural	2	1
Pial < dural	3	2
Pial = dural	3	2
Mainly pial	4	3

VEGF : vascular endothelial growth factor

Table 4. Correlation between FDG uptake and tumor parameters

		Ki-67	VEGF	Edema	Tumor size
		SUV	r*	0.536	0.091
	p†	0.018	0.712	0.050	0.984
TGR	r	0.020	0.289	0.386	0.160
	p	0.935	0.230	0.102	0.513

FDG : fluoro-2-deoxyglucose, SUV : standardized uptake value, TGR : tumor to contralateral gray matter ratio, VEGF : vascular endothelial growth factor. *r : correlation coefficient. † p : probability value

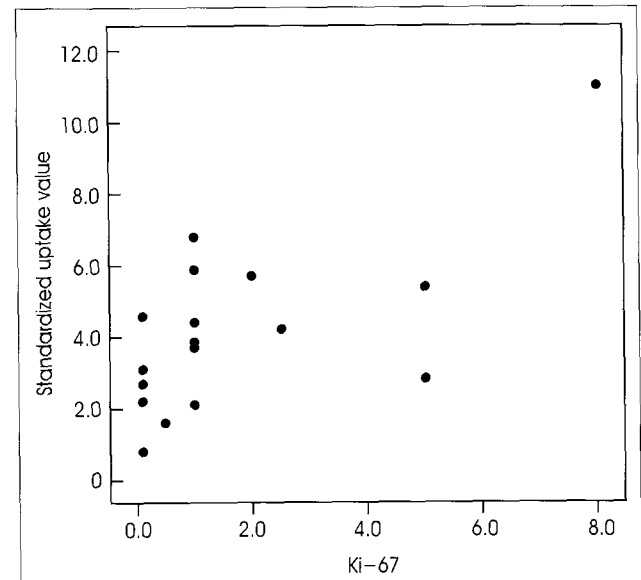


Fig. 1. Scatter plot showing the association between fluoro-2-deoxyglucose standardized uptake values and Ki-67 (r=0.536, p=0.018).

grade. VEGF immunoreactivity was graded as grade 0, no detectable immunoreactivity; grade 1, trace of positive cells; grade 2, moderate amount of diffuse staining or sparsely intensive positive staining and grade 3, the largest amount of diffuse staining. Grades 2 and 3 were considered to be positive. The extent of pial blood supply was graded in a semi-quantitative way. Grade 1 was only dural supply, grade 2 pial supply smaller than dural supply, grade 3 pial supply equal to dural supply, and grade 4 pial supply greater than dural supply.

Because hyperglycemia in non-fasting patients and in diabetic patients may lead to the overestimation of meningioma grading⁴⁾, patients were asked to fast for at least 4 hours before undergoing the examination. All patients had glucose levels below 150mg/dL. The patients received an intravenous injection of 370-666 MBq (10-18mCi) of ¹⁸F-FDG. Data were acquired 60-120 min after injection using an integrated in-line PET/CT system (Discovery LS; GE medical system). Data acquisition was as follows : non-enhanced CT scanning was performed first, from the head to the pelvic floor, with 140kV, 80mA, a tube rotation time of 0.5s, a pitch of 6, and a 5-mm section thickness, which matched the PET section thickness. Immediately after CT scanning, a PET scan was obtained that covered the identical transverse field of view.

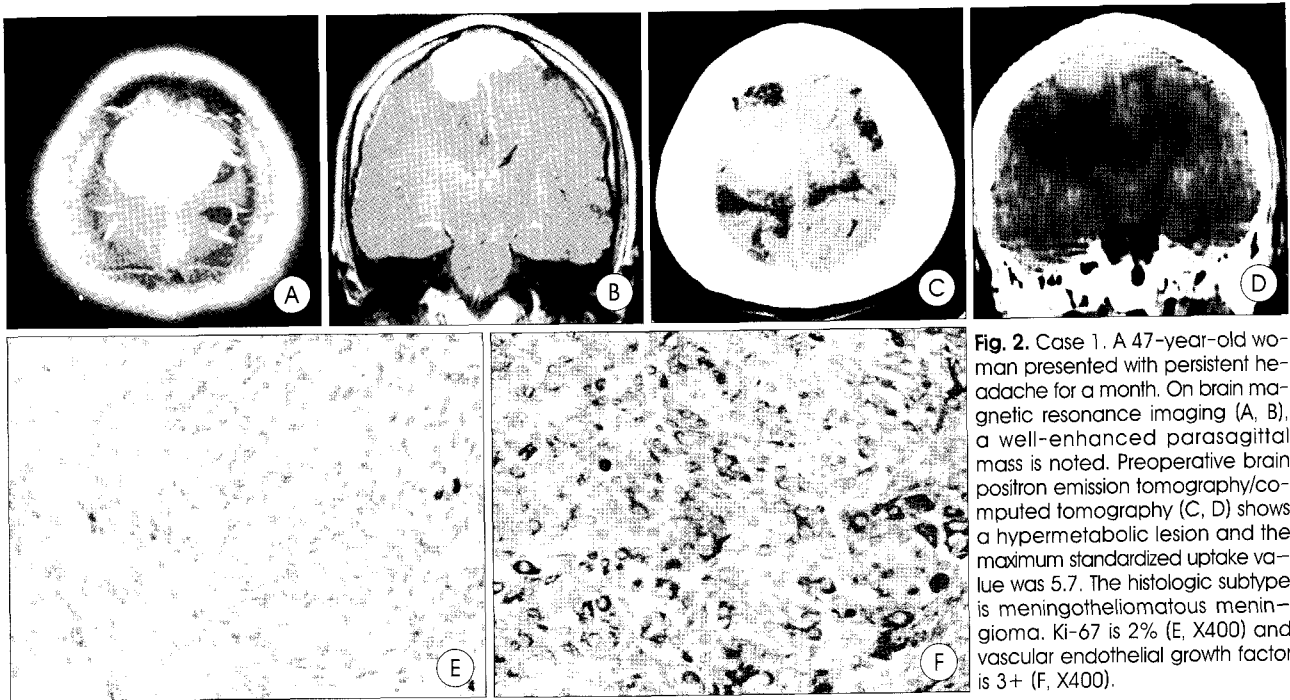


Fig. 2. Case 1. A 47-year-old woman presented with persistent headache for a month. On brain magnetic resonance imaging (A, B), a well-enhanced parasagittal mass is noted. Preoperative brain positron emission tomography/computed tomography (C, D) shows a hypermetabolic lesion and the maximum standardized uptake value was 5.7. The histologic subtype is meningotheiomatous meningioma. Ki-67 is 2% (E, X400) and vascular endothelial growth factor is 3+ (F, X400).

The acquisition time was 5 minutes per table position. PET image datasets were reconstructed iteratively using CT data for attenuation correction, and co-registered images were displayed on a workstation (CTI molecular image -Reveal-MVS Viewer).

Spearman's correlation coefficients were calculated for the SUVs in tumors and for tumor-to-contralateral gray matter SUV ratios in relation to each other and to immunohistologic parameters. For group comparisons between malignancy grades, patients were divided into low-grade (WHO grade I) and high-grade tumor (WHO grade II) groups. Between VEGF positivities, patients were divided into positive and negative groups. Group comparisons were performed with the Mann-Whitney test. All statistical analyses were performed using the SPSS software (SPSS, Chicago, IL). The results are expressed as mean \pm the standard deviation of the mean. Two-sided P values less than 0.05 were statistically significant.

Results

Of the 19 meningiomas, 8 were meningotheial type, 1 fibrous, 2 transitional, 1 psammomatous, 2 angiomatous, and 5 were atypical. Twelve tumors were convexity located, 2 falx, 2 parasagittal, 2 sphenocavernous, and 1 tuberculum sellae.

When the tumors were divided into two groups as grade 1 meningiomas and grade 2 atypical meningiomas, the tumor proliferative index of Ki-67, tumor size, and peritumoral edema were larger in grade 2 tumors than in grade 1

meningiomas. There were no significant differences in SUV and TGR between the two groups (Table 1). VEGF positivity was more frequently noted in grade 2 tumors (4 of 5, 80%) than in grade 1 tumors (9 of 14, 64.3%).

VEGF positivity was detected in 13 tumors (68.4%). When the tumors were divided into two groups as VEGF-positive and -negative, the tumor size and peritumoral edema were significantly larger in the positive group than in the negative group (Table 2).

Conventional angiography was performed for 12 patients. Predominantly dural supply was noted in 2 patients. Four patients had mainly pial cortical supply patterns. VEGF was more frequently positive in tumors with more pial supply, however, the numbers of patients were too small to draw a statistical conclusion (Table 3).

In the correlation study of the degree of FDG uptake and other factors, there were significant correlations between SUV and Ki-67 ($p=0.018$, $r=0.0536$, Fig. 1) and between SUV and peritumoral edema ($p=0.050$, $r=0.0456$, Table 4).

Case illustration

Case 1

A 47-year-old woman presented with persistent headache for a month. On brain MR imaging, a well-enhanced parasagittal mass was noted. Preoperative brain PET/CT showed a hypermetabolic lesion and the maximum SUV was 5.7. The tumor was resected and the histologic subtype was meningotheiomatous meningioma. Ki-67 was 2% and VEGF was 3+ (Fig. 2).

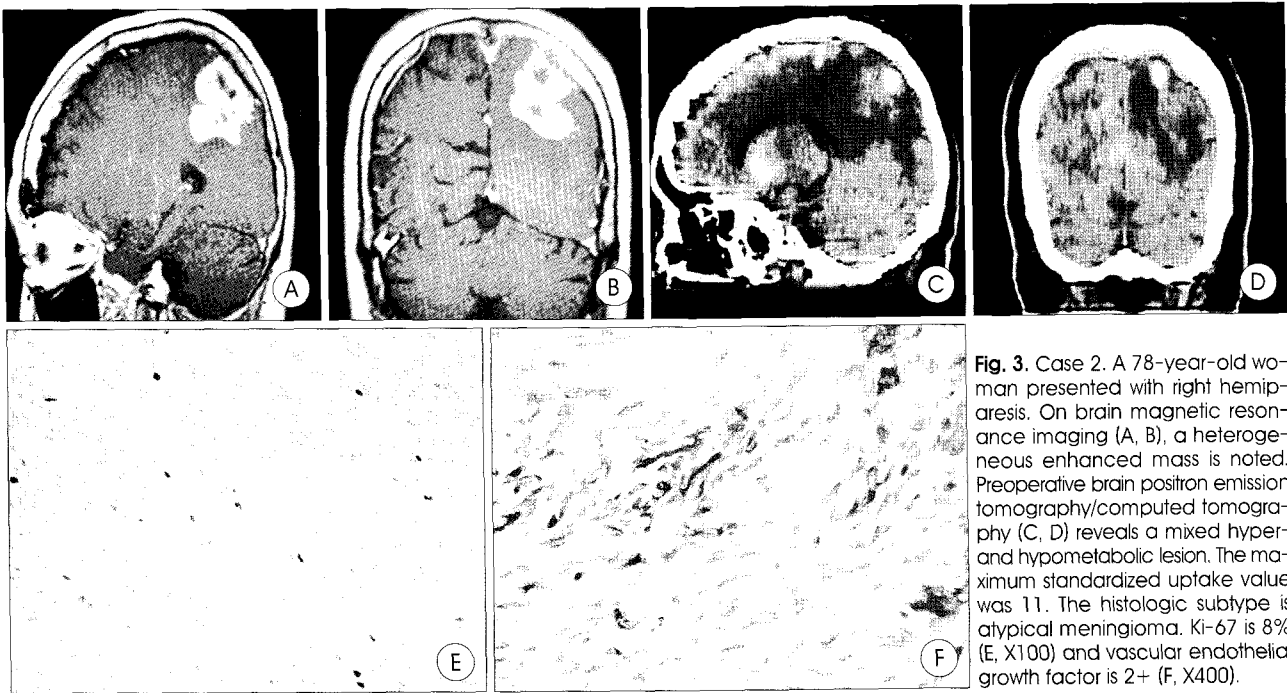


Fig. 3. Case 2. A 78-year-old woman presented with right hemiparesis. On brain magnetic resonance imaging (A, B), a heterogeneous enhanced mass is noted. Preoperative brain positron emission tomography/computed tomography (C, D) reveals a mixed hyper- and hypometabolic lesion. The maximum standardized uptake value was 11. The histologic subtype is atypical meningioma. Ki-67 is 8% (E, X100) and vascular endothelial growth factor is 2+ (F, X400).

Case 2

A 78-year-old woman presented with right hemiparesis. On brain MR imaging, a heterogeneous enhanced mass was noted. Preoperative brain PET/CT revealed a mixed hyper- and hypometabolic lesion. The maximum SUV was 11. The tumor was resected and the histologic subtype was atypical meningioma. Ki-67 was 8% and VEGF was 2+ (Fig. 3).

Discussion

Although FDG PET has been proven to play some role in assessing the degree of malignancy, predicting survival in malignant brain tumors^{8,22,23}, and forecasting the aggressiveness of benign tumors²⁰, the utility of FDG PET in meningiomas is still not clear.

Di Chiro et al. reported significantly lower glucose metabolic utilization rates in non-recurrent meningiomas than in recurrent or regrowing meningiomas in a study of 17 meningiomas that had been surgically treated⁶. Histopathologically, atypical meningioma had the highest glucose utilization rate. Di Chiro et al. insisted that glucose utilization rate appears to be at least as reliable as histologic classification for predicting the behavior and recurrence of intracranial meningiomas⁶. Cremerius et al. reported that ¹⁸F-FDG PET correctly identified 8 out of 9 atypical or malignant meningiomas and 58 out of 66 grade 1 meningiomas using tumor to contralateral gray matter ratio⁴. In another study Iuchi, et al. found that uptake of methionine significantly correlated with a histological index of protein synthesis and Ki-67 index

in meningiomas¹¹. In our study, SUVs significantly correlated with Ki-67 but had no discriminating power to distinguish atypical meningiomas from benign meningiomas. This is probably because of the wide range of SUV within a tumor (data not shown) or among the tumors (Table 1). The marked differences between these tumor types in glucose metabolism despite their similar microscopic appearances have been published in another report⁶.

The high concentration of FDG in normal brain makes diagnosis difficult in some malignant tumors. Owing to its low uptake in normal brain tissue, C-Methyl-L- and D-Methionine (MET) is a frequently used tracer. Cho et al. studied MET- and FDG-PET to differentiate the grade of gliomas³. In this report, authors suggested the MET-PET showed superior sensitivity and specificity to FDG-PET for detecting recurrence of gliomas. Although their study included four cases of meningiomas, there made no mentions of the findings about meningiomas. Iuchi et al. compared regional uptake of FDG and MET with tumor proliferative activity in 17 meningioma specimens which had been obtained by PET guided stereotactic biopsies¹¹. They suggested MET-PET was a useful tool for predicting tumor proliferative potential in meningiomas rather than FDG-PET. Besides, 1-(11)C-acetate¹⁶, (14)C-choline²⁹, (111)indium-octreotide¹⁹ and others have been tried as feasible tracers of PET to assess the cell proliferation in brain neoplasms. Uptake into inflammatory cells after radiation therapy is also perplexing when differentiating a tumor recurrence from radiation necrosis⁷. Murakami et al. performed a quantitative kinetic analysis of

meningiomas and gliomas using dynamic PET¹⁸). The vascular surface area was significantly larger in meningiomas than in gliomas and atypical meningiomas had higher values than benign meningiomas for both permeability and surface area. The synergistic interaction of the high permeability and the large vascular surface area yields conditions conducive to glucose metabolism and tumor proliferation¹⁸). The high vascularity of meningiomas could cause confusion when estimating the proliferative activity of meningiomas with FDG PET. In a recent in vitro study, Maschauer et al. published that VEGF significantly stimulated endothelial ¹⁸F-FDG uptake¹⁷). Yamasaki et al. analyzed the recurrence of supratentorial convexity meningiomas which had undergone Simpson grade I resection and reported high levels of expression of VEGF constituted the most useful predictor of recurrence²⁸). The formation of peritumoral brain edema in meningiomas is also thought to be related to VEGF expression^{12,13,21}) and pial cortical blood supply^{15,24,25}). In a very logical study about the vascular density of tumors using von Willebrand factor (vWF) as a marker for endothelial cells, no significant associations were observed between SVU and vWF²⁷). Considering these relationships, glucose uptake in meningiomas would reflect not only the tumor proliferation potential, but also the vascular density.

Despite the concordant results of our study, significant greater edema size in grade 2- than in grade 1 meningiomas and significant association between VEGF and peritumoral edema, SUVs did not associate with the expression of VEGF directly. SUVs showed the marginal significance with the size of peritumoral edema (p=0.050). To further delineate these relationships, a study based on a larger number of patients would be needed.

Conclusion

FDG uptake in meningiomas seems to reflect the proliferative potential rather than vascularity of tumors. We have found FDG uptake in meningiomas is associated with proliferative potential, however, no clear limits of SUV and TGR can be set to differentiate between grade 1- and grade 2 meningiomas, making the assessment of malignancy grade using PET scan metabolic imaging difficult in individual cases. Further clarification of these issues can be provided through studies involving expanded patient population, using other surrogate markers of proliferative indices of meningiomas, or using other PET tracers.

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