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ORIGINAL RESEARCH

The Diagnostic Value Of Using ^{18}F-Fluorodeoxyglucose Positron Emission Tomography To Differentiate Between Low- And High-Grade Meningioma

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Objective: This study aims to evaluate the potential role of ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) in detecting high-grade meningiomas and predicting the prognosis of patients after meningioma surgery.

Patients and methods: A total of 124 patients met the final inclusion criterion. Tumor to gray ratio (TGR) was compared with Ki-67 labeling index, and its correlations with pre-operative neurological function and treatment status were also evaluated. Receiver-operating characteristic (ROC) curve was drawn to determine a cut-off value which could discriminate meningioma of different grades. Prognostic factors including TGR were analyzed using Kaplan-Meier survival curve and cox proportional model.

Results: The TGR of higher World Health Organization (WHO) grade meningioma was significantly higher than that in lower grade ($p < 0.001$), and it was correlated with the Ki-67 labeling index ($p < 0.001$, $r = 0.1545$). The TGR of 1.30 was the best cutoff value for the detection of high grade (WHO grade II&III) meningioma from low grade (WHO grade I) according to ROC analysis, with a sensitivity of 61.5%, the specificity of 86.7%, and accuracy of 81.5%. The TGR ($p < 0.001$), treatment status ($p = 0.035$), tumor grade ($p < 0.001$) and Ki-67 labeling index ($p < 0.001$) were significantly associated with progression-free survival (PFS). Cox proportional hazards model demonstrated that TGR ($p = 0.013$) was an independent prognostic factor for PFS.

Conclusion: A high uptake of FDG was correlated with a more proliferative biological behavior and is a risk factor for tumor recurrence.

Keywords: meningioma, ^{18}F-FDG PET, molecular imaging, clinical characteristic, prognosis

Introduction

Meningioma is one of the most common intracranial tumors, constituting approximately 36.4% of primary neoplasms.[1] These tumors arise from the leptomeninges covering the cerebrum and the spinal cord, and have been classified into three grades and 15 histological subtypes since WHO 2000 grading criterion for central nervous system (CNS) tumors.[2–4] The majority of meningiomas are benign with an inherent biological behavior and a satisfying prognosis. However, there still exists a subset of tumors showing more aggressive biological behavior, usually accompanied by higher pathologic grade.[5] Standard-of-care management typically involves

surgical resection and often radiation therapy for high-grade (grade II-III) tumors. The biological behavior and prognosis of high-grade meningioma is quite different from that of a low-grade meningioma, which makes pre-operative accurate assessment of proliferative potential quite important for management decisions.[6] Currently, reliable parameters do not exist that can predict tumor grade and the associated clinical course. Non-invasive and early predictors of meningioma grade may enhance clinical decision-making by providing prognostic information that could guide the decision of whether to observe or to treat.[7]

One typical biological characteristic of tumors is that they depend more on aerobic glycolysis and the increased aerobic glycolysis accompanied by accelerated glucose uptake is known as the Warburg effect.[8] ^{18}F-FDG is an analogue of glucose, which is absorbed, phosphorylated, and trapped in the cytosol of the cells. The use of ^{18}F-FDG clinically is based on the increase in glucose metabolism of malignant cells.

Although morphological imaging by means of computed tomography (CT) and magnetic resonance (MR) imaging is still the gold standard in the preoperative diagnosis of intracranial tumors, molecular imaging still has its values in predicting the nature of the tumor.[9] Over the last two decades, PET has developed quickly and has been applied especially in oncology.[10] Currently, ^{18}F-FDG is the most used radiotracer for metabolic imaging; therefore, ^{18}F-FDG PET has been widely used in patients with neoplasms, especially in the diagnosis of metastases and in discriminating malignancies from benign tumors. Studies have indicated that ^{18}F-FDG PET has the ability to distinguish tumor from radiation necrosis, predict tumor grade or even evaluate the prognosis.[11]

Here, we enrolled the largest number of meningioma patients so far to thoroughly analyze the potential role of ^{18}F-FDG PET in the assessment of meningioma grade, subtype, biological behavior and prognosis.

Materials And Methods

Patients

We performed a retrospective database review of patients who underwent pre-operative ^{18}F-FDG PET scanning in the Department of Nuclear Medicine and PET Center as well as surgical resection of meningioma in the Department of Neurosurgery, Huashan Hospital, Fudan University in a time period between March 2008 to December 2015. A total of 124 patients who had been surgically diagnosed with meningioma were collected from March 2008 to December 2015 by searching the database of the Department of Nuclear Medicine and PET Center of Huashan Hospital, Fudan University. All patients underwent pre-operative ^{18}F-FDG PET scanning. Pregnant women were strictly prohibited from taking 18F-FDG PET scanning in our institution due to potential radiation exposures. Patient consent was not required since our study did not include any usage of personal information or collection of patient samples. This clinical study was approved by the Human Subjects Institutional Review Board at Huashan Hospital, Fudan University (KY-2017-09).

Seventeen of them were recurrent patients who had a history of meningioma resection in other hospitals, and were admitted to our department when tumor recurred during follow-up. None of the patients in our series had other intracranial lesions except meningioma.

The extent of tumor resection was evaluated according to the Simpson grading scale. Simpson grade I&II was regarded as gross total resection (GTR) while grade III-IV was considered subtotal resection (STR). Follow-up was conducted through the out-patient department. The last follow-up date was March 1st, 2017.

^{18}F-FDG PET Imaging

PET studies were performed using an eminence system (Siemens Biograph Sensation 16 PET/CT, Siemens Healthcare, Erlangen, Germany). The ^{18}F-FDG was synthesized according to the protocol provided by the manufacturer and under the inspection of the State Food and Drug Administration (SFDA). The mean interval between the 18F-FDG PET scan and surgical treatment of the meningioma was 16.0 ± 12.2 days (range: 1–53 days). All patients were normoglycemic and were asked to fast for at least 6 hrs to keep the blood glucose level at 3.9–6.1 mmol/L before whole-body FDG PET scans. A mean dose of 5.55 MBq/kg (0.15 mci/kg) of ^{18}F-FDG was administrated intravenously to each patient. Subsequently, the patients were asked to rest quietly for 30 mins in a waiting room and 800–1000 mL water was administrated to dilate the gastrointestinal tract. Imaging started after an FDG uptake period of 60 min. Each patient underwent a total body scan which contained two steps: brain and body scanning. Brain images were acquired from corona capitis to inferior maxilla plane for 15 min. Body images were acquired from the base of the skull to the upper thighs for

about 2.5–3.0 min per bed position, and a total of 5–6-bed positions were used.

Imaging Interpretation

All PET scan results were evaluated by two experienced nuclear physicians (Dr. FC Hua and Dr. YH Guan) independently. All lesions were confirmed by pre-operative T1WI enhanced MR images. Standardized uptake value (SUV) of ^{18}F-FDG was calculated automatically by drawing the region of interest (ROI), the median SUV was defined as the mean concentration of FDG uptake in the ROI, both FDG uptakes of the contralateral cerebrum and the ipsilateral cerebellum were used as controls. If the tumor was located in the cerebellum, FDG uptake of contralateral cerebellum was used as a control instead. Tumor to gray ratio (TGR) was defined as the ratio of the mean SUV of the tumor to the uptake of the normal gray.

Histopathological Analysis

All surgical specimens were reviewed and re-confirmed by two board-certified neuro-pathologists (Dr. Y Wang and Dr. HX Li) according to the 2007 WHO meningioma grading criterion. The data were additionally reviewed according to the newest 2016 WHO classification system to assess any potential impact that the inclusion of brain invasion as a formal diagnostic criterion for grade II meningiomas might have on their association with imaging features. In this study, low and high grade refers to grade I and grade II/III, respectively.

Statistical Analysis

All statistical analysis was performed using Stata 13.3 software (STATA 13.3 for windows; Stata Corp). The correlation coefficients between the TGR and the Ki-67 labeling index were analyzed with linear regression. Variance analysis and Mann–Whitney *U*-test were used in determining the ^{18}F-FDG uptake of different subgroups. For skewed distribution, Wilcoxon's rank-sum test was used for continuous data. Fisher's exact tests were applied for categorical data. A receiver operating characteristics (ROC) curve was drawn to confirm the best cutoff value of the TRG for distinguishing different grades. Factors including age (<60 years or ≥60), gender (male or female), preoperative KPS (<80 or ≥80), Ki-67 labeling index (<5% or ≥5%), tumor location (skull base or non-skull base), treatment status (newly diagnosed or recurrent), tumor grade (grade I or grade II&III), Simpson grade of resection (GTR or STR) and TGR level were used for prognostic analysis. Survival curves were generated using the Kaplan–Meier method; differences were evaluated through the log rank tests and cox proportional hazards model was used to analyze possible prognostic factors. A p-value <0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 124 patients (79 females and 45 males) eligible for inclusion criterion were finally enrolled in our study (Figure 1), of which 98 patients were diagnosed with WHO grade I meningioma, 13 with grade II, and 13 with grade III. Among them, 17 patients were recurrent. Convexity (n = 56) is the most common location followed by falx and parasagittal (n = 16) (Table 1). The mean pre-operative Karnofsky Performance Score (KPS) was 89.8 ± 6.0 (range, 70–100).

TGR And Tumor Factors

The mean Ki-67 labeling index was 4.0% ± 5.4% (range 1–25%). The mean TGR (tumor to contralateral cerebral) was 1.2 ± 1.2 (range 0.3–9.0) and was 1.1 ± 1.1 (tumor to ipsilateral cerebellum, range 0.3–10.3). The results were similar either with contralateral cerebrum or ipsilateral cerebellum as normal SUV controls (p = 0.488). The FDG uptake of tumor to contralateral cerebrum was used for further analysis. TGR was significantly different between WHO grade I, grade II and grade III meningiomas (p < 0.001). The TGR of grade I meningioma was significantly lower than grade II (p < 0.001) and grade III (p < 0.001), and the TGR of grade II was lower than grade III (p = 0.038). The Ki-67 labeling index was also different within the three grades (p < 0.001), further analysis showed that the Ki-67 labeling index in higher grade was higher than that in lower grade (grade I vs II, p <0.001; grade I vs III, p < 0.001; grade II vs III, p = 0.035) (Table 2). No significant difference was observed on age (p = 0.601) and tumor location (p = 0.725) between three WHO grades in our series.

The Ki-67 labeling index was well known to be associated with the proliferative ability of the tumor. In our series, we found that the TGR was significantly correlated with the Ki-67 labeling index, although the correlation was quite weak (p < 0.001, r = 0.1545, Figure 2). The TGR was not associated with the pre-operative KPS either (p = 0.622,

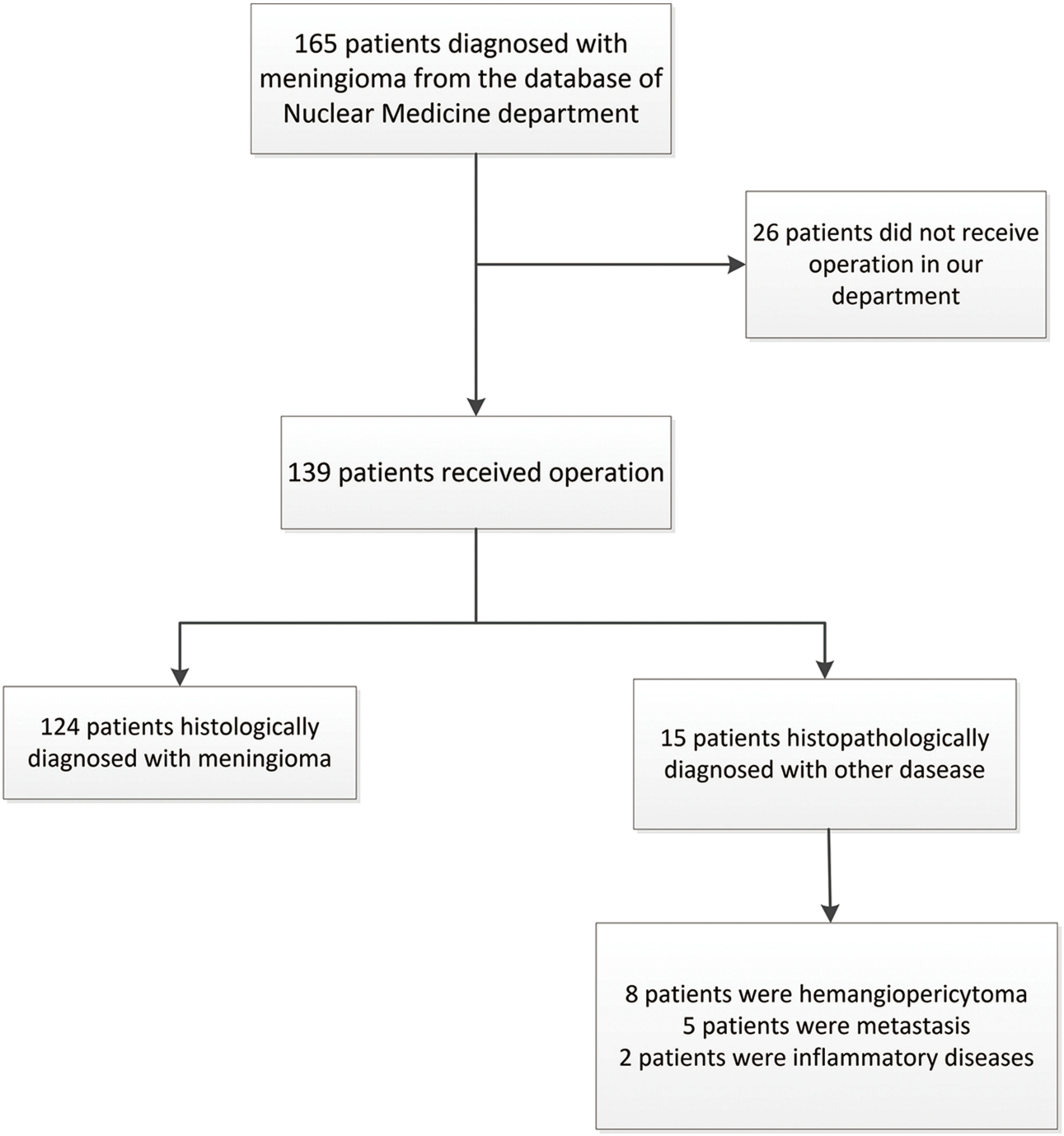

Figure 1 Analysis of meningioma patients using 18F-FDG PET from the database.

r = 0.0020). We further evaluated the ^{18}F-FDG uptake of different histological subtypes using Bonferroni *t*-test and no significant difference was observed between the subtypes within the same grade.

The mean TGR of the 17 recurrent meningioma cases was 2.2 ± 2.3 (range 0.4–9.0) and the mean Ki-67 labeling index was 8.8% ± 8.3% (range 1–25%). Both the ^{18}F-FDG uptake ($p < 0.001$) and the Ki-67 labeling index ($p < 0.001$) of recurrent meningioma were significantly higher than that of newly diagnosed meningiomas.

ROC Curve Analysis

To determine a cut-off value of TGR to discriminate tumor grades, ROC curve was drawn for analysis. The area under ROC curve (AUC) between grade I and grade II was 0.91

Table 1 Clinical Features Of Enrolled Patients

Characteristics		Number
Mean age		58.8 ± 10.8 years
Gender		
	Male Female	45 (36.3%) 79 (63.7%)
Tumor grade		
Grade I (n = 98)	Meningethelial Fibrous Angiomatous Microcystic Psammomatous Secretory Transitional Metaplastic	32 (25.7%) 40 (32.3%) 5 (4.0%) 3 (2.4%) 4 (3.2%) 8 (6.5%) 5 (4.0%) 1 (0.8%)
Grade II (n = 13)	Atypical Clear cell Chordoid	7 (5.6%) 2 (1.6%) 4 (3.2%)
Grade III (n = 13)	Anaplastic Rhabdoid Papillary	7 (5.6%) 4 (3.2%) 2 (1.6%)
Tumor location	Non-skull base Skull base	72 (58.1%) 52 (41.9%)
Recurrent meningioma		17 (13.7%)
Preoperative KPS		89.8 ± 6.0 (range, 70–100)
Ki-67 labeling index		4.0% ± 5.4% (range 1% - 25%)
TGR of FDG uptake		
	Tumor to contralateral cerebral Tumor to ipsilateral cerebellum	1.2 ± 1.2 (range 0.3–9.0) 1.1 ± 1.1 (range 0.3–10.3)

Abbreviations: KPS, Karnofsky performance scale; TGR, tumor to grey ratio; FDG, fluorodeoxyglucose.

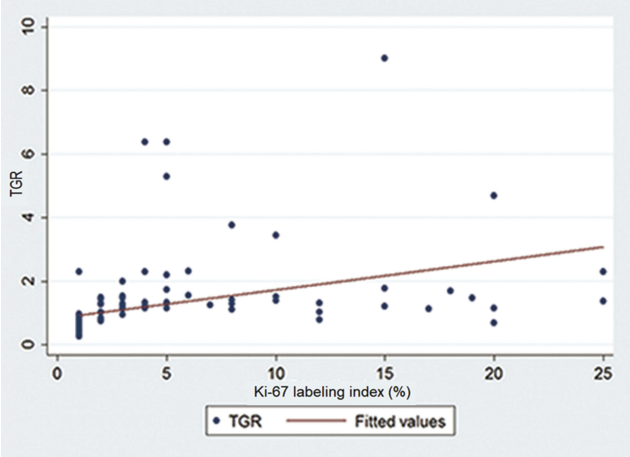

Figure 2 Scatter plot showing the association between the TGR on FDG PET and the tumor proliferative behavior (Ki-67 labeling index).

(95% CI: 0.85–0.96), while it was 0.74 (95% CI: 0.82–0.95) between grade II and grade III. Using a cut-off value 1.52 to distinguish between grade I and grade II, the sensitivity, specificity and accuracy was 69.2%, 91.8% and 89.2%, respectively. The best cut-off value for distinguishing grade II and grade III meningioma was 1.42; with the sensitivity, specificity and accuracy were 76.9%, 76.9% and 76.9%, respectively. After combining the grade II and grade III meningiomas as the high-grade group, the AUC between low grade (grade I) and high grade (grade II and III) was 0.85 (95% CI: 0.78–0.92). When the cut-off value was defined at 1.30, the sensitivity, specificity and accuracy was 61.5%, 86.7% and 81.5%, respectively (Figure 3). Ten (10/26) high-grade meningioma patients were mistakenly diagnosed with low-grade meningioma, and only 10 (10/98) grade I meningioma patients were misdiagnosed with high-grade meningioma.

In high-grade meningioma, the Ki-67 labeling index of those whose TGR was higher than 1.30 was compared to those lower than 1.30. There exists a significant difference between the two groups ($p < 0.001$), indicating that true positive patients diagnosed with TGR ≥ 1.30 had a significant

Table 2 Comparison Of Characteristics Of Patients By Different WHO Grades (Grade I Vs Grade II Vs Grade III)

Characteristics	WHO Grade I (n=98)	WHO Grade II (n=13)	WHO Grade III (n=13)	P value
Mean age (years)	58.2 ± 1.2 (95% CI:55.8–60.5)	59.5 ± 3.2 (95% CI: 52.4–66.5)	60.8 ± 3.0 (95% CI:54.2–67.5)	0.6009[a]
TGR of FDG uptake	0.9 ± 0.8 (95% CI:0.8–1.1)	1.6 ± 0.2 (95% CI: 1. 2–1.9)	2.0 ± 2.3 (95% CI: 0.6–3.4)	0.0001[a]
Ki-67 labeling index	1.5 ± 0.8 (95% CI:1.3–1.7)	11.8±7.2 (95% CI: 8.9–14.7)	15.0 ± 1.5 (95% CI: 11.7–18.3)	0.0001[a]
Tumor location (non-skull base/skull base)	55/43	8/5	9/4	0.725[b]

Notes: [a]Kruskal–Wallis test; [b]Fisher's exact test.

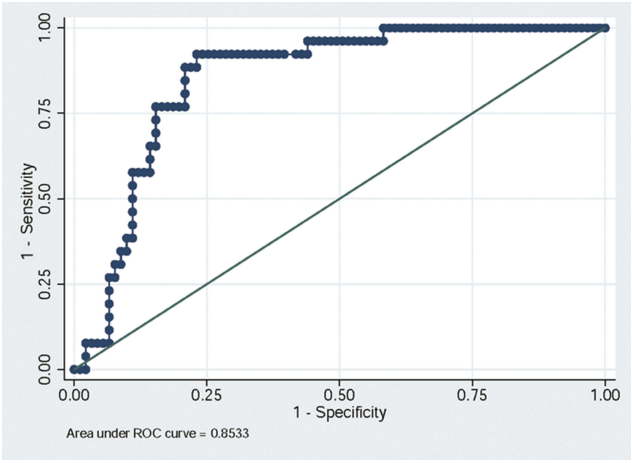

Figure 3 ROC curve of the TGR of meningioma. AUC of the TGR between low grade (WHO grade I) and high grade (WHO grade II&III) was 0.8533. The optimal cut-off value was 1.30. The sensitivity and specificity were 69.23% and 91.84%, respectively.

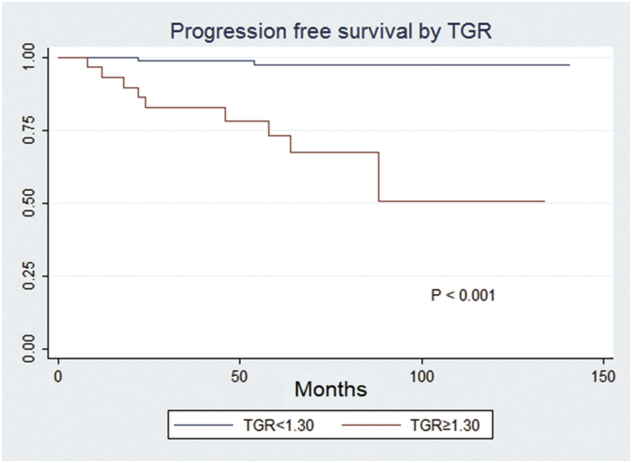

Figure 4 Kaplan-Meier survival curve. Progression-free survival of patients by TGR (<1.30 vs ≥1.30).

higher proliferative ability than those false negative patients. In low-grade meningioma, the Ki-67 labeling index of those with TGR lower than 1.30 was significantly lower than those with TGR ≥ 1.30 ($p < 0.001$), which was similar with that of high-grade meningiomas.

Prognostic Value Of FDG PET

The mean follow-up period was 68.9 ± 32.7 months (range, 24–141 months). One patient died of tumor recurrence 26 months after surgery; another one died due to severe intracranial infection 6 months after surgery. The mean PFS was 66.3 ± 32.7 months (range, 8–141 months). Twelve patients recurred during the follow-up, with significantly higher TGR (3.1 ± 2.7; range, 0.9–9.0) than primary patients (1.0 ± 0.8; range, 0.3–5.3) ($p < 0.001$). The mean post-operative KPS was 90.8 ± 16.1 (range, 0–100). A number of 17 patients experienced post-operative neurological function deterioration, and the TGR was not associated with the deterioration of the neurological function ($p = 0.676$).

TGR ($p < 0.001$), treatment status ($p = 0.048$), tumor grade ($p = 0.001$) and Ki-67 labeling index ($p = 0.001$) were found to be significantly associated with PFS (Figure 4). In addition, TGR ($p = 0.013$) was the only independent prognostic factor for PFS through cox proportional hazards model (Table 3).

Discussion

For the past two decades, PET with ^{18}F-FDG as a tracer has been accepted as a useful tool for diagnosis, grading, and

Table 3 Univariate And Multivariate Analysis Of Prognostic Factors In Patients With Meningioma In Our Series

Variable	Univariate Analysis		Multivariate Analysis	
	PFS		PFS	
	p	HR (95% CI)	p	HR (95% CI)
Age (<60/≥60)	0.716	1.24 (0.39–3.90)		
Gender (male/female)	0.399	0.57 (0.15–2.11)		
Preoperative KPS (<80/≥80)	0.612	1.70 (0.22–13.19)		
Extent of resection (GTR/STR)	0.982	1.02 (0.27–3.76)		
Location (skull base/non-skull base)	0.118	3.36 (0.73–15.33)		
Ki-67 index (<5%/≥5%)	0.001*	9.88 (2.67–36.52)		
TGR (<1.30/≥1.30)	0.000*	17.46 (3.82–79.76)	0.013*	9.63 (1.62–57.17)
Treatment status (newly diagnosed/recurrent)	0.048*	2.37 (1.01–11.24)		
Tumor grade(grade I vs grade II&III)	0.001*	7.64 (2.30–25.42)		

Note: *P<0.05 considered statistically significant.

Abbreviations: KPS, Karnofsky performance score; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; GTR, gross total resection; STR, subtotal resection; TGR, tumor to grey ratio.

therapeutic monitoring of intracranial neoplasms.[12–15] Previous studies have shown that ^{18}F-FDG PET can be applied to discriminate the meningioma grade, predict the biological behavior and even the prognosis.[7,16–23] Cremerius et al analyzed a total of 75 patients using SUV and TGR of FDG uptake and demonstrated high sensitivity (89%) and specificity (88%) of FDG PET for detection of high-grade meningioma by using a threshold TGR value of 1.05 in primary meningioma and 0.85 in recurrent tumors.[24] Similarly, Lee et al reported that ^{18}F-FDG PET was a useful surrogate for grading meningioma and that the best threshold TGR to discriminate between a low and high-grade meningioma was 1.0.[7] However, Iuchi et al reported that the FDG uptake of meningioma showed no significant correlation with the Ki-67 labeling index or clinical malignancy.[25] Also, Liu et al found ^{18}F-FDG was useful in differentiating benign from malignant meningioma, but was not useful to evaluate the response to radiosurgical treatment.[26] The potential role for predicting histological grading or the proliferative potential was still controversial and need to be validated.

Our study enrolled a total of 124 meningioma patients, which is the largest series to date. Histopathological results showed that patients in our series covered 14 of all 15 subtypes of meningioma, except the lymphoplasmacyte-rich subtype. Similar to previous results, our study revealed that the TGR uptake correlates well with the proliferative behavior of the tumor, and we for the first time separated meningioma into three groups based on WHO grades for analysis. We found that the TGR was different in each tumor grade, with grade III the highest and grade I the lowest, which correlated well with the biological behavior of the tumor. The TGR of each subgroup was compared with each other and showed no difference between the subtypes within the same WHO grade. We tried to find the best cut-off value to distinguish three WHO grades apart, but analysis of AUC in the ROC could not separate out three distinct groups. It was more accurate if we combined the grade II and grade III tumors into a high-grade group and found that the best cut-off value was 1.30 to distinguish low grade (WHO Grade I) and high grade (WHO Grade II and III). For patients who had previous meningioma resection(s), the TGR tended to be higher than those who were newly diagnosed, indicating that the metabolism was higher in recurrent meningioma.

We conducted a relatively long-term follow-up with a mean of 68.86 months. Factors including tumor grade, TGR, treatment status, and Ki-67 labeling index were significant prognostic factors for PFS, while the extent of resection was not. However, the extent of resection has been shown to be a significant factor for PFS in prior studies.[27,28] This was perhaps partly due to the short period of follow-up, since the majority of patients were grade I and nearly half of the patients were followed-up for less than 5 years. In addition, the limited patient population may also weaken the statistical powers. We for the first time analyzed the correlations between TGR and neurological outcomes, and no association between them. The TGR of those who recurred during the follow-up was significantly higher. In addition, the TGR was the only prognostic factor for PFS in our series, indicating that TGR is a valuable factor to predict the prognosis. If further validated, it provided neurosurgeons and patient choices that if tumor TGR<1.3, after tumor partial removal, a wait and see policy may be appropriate for these patients.

Conclusions

Our study revealed that the uptake of FDG was correlated with the biological behavior and it was different between the three tumor grades. However, FDG uptake was similar between different subtypes within the same grade. The TGR, treatment status, tumor grade, and Ki-67 labeling index were correlated with PFS for meningioma patients, while TGR is the only independent prognostic factor.

Abbreviations

^{18}F-FDG PET, ^{18}F-fluorodeoxyglucose positron emission tomography; TGR, tumor to gray ratio; ROC, receiver-operating characteristic; WHO, World Health Organization; PFS, progression-free survival; CNS, central nervous system; CT, computed tomography; MR, magnetic resonance; GTR, gross total resection; STR, subtotal resection; T1WI, T1 weighted imaging; SUV, Standardized uptake value; ROI, region of interest; EMA, epithelial membrane antigens; Vim, vimentin; KPS, Karnofsky Performance Score.

Research Involving Human Participants

All procedures performed in studies involving human participants were in accordance with the ethical standards of Huashan Hospital, Fudan University and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was not required since our study did not include any usage of personal information or collection of patient samples. This clinical study was approved by the Human Subjects Institutional Review Board at Huashan Hospital, Fudan University (KY-2017-09).

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Disclosure

The authors report no conflicts of interest concerning the materials or methods used in this study or the findings specified in this paper.

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