Role of ^{18}F-fluoro-ethyl-tyrosine Positron Emission Tomography in Investigation and Management of Suspected Gliomas

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- BACKGROUND: **This study aims to investigate the utility of ^{18}F-fluoro-ethyl-tyrosine (^{18}F-FET) positron emission tomography in surgical decision making in suspected glioma.**
- METHODS: **A retrospective review of patients undergoing ^{18}F-FET positron emission tomography was performed. Previously published thresholds for maximum tumor background ratios (TBRs) were used for quantitative analysis. Forty-seven patients were included in the study, of whom 15 had confirmed glioma and 7 had a confirmed alternative diagnosis.**
- RESULTS: **^{18}F-FET showed significantly higher uptake in high-grade glioma than in nonglioma.**
- CONCLUSIONS: **Lesions with TBR_{max} >2.5 should be considered suspicious for glioma and biopsy considered. Threshold TBR_{max} >3.0 is useful for differentiating high-grade glioma from low-grade glioma. This may be a particularly useful tool for directing management in eloquent areas, such as brainstem glioma.**

INTRODUCTION

With increasing availability of neuroimaging, in particular magnetic resonance imaging (MRI), the neurosurgeon is more frequently presented with a patient whose imaging shows an asymptomatic abnormality, the exact nature of which may be difficult to determine on structural imaging alone. The best management for these patients poses a dilemma, particularly when asymptomatic of the lesion. The risks of craniotomy may outweigh the benefits in patients with benign lesions such as cortical dysplasia. However, early surgery is recommended in patients with neoplastic disease.

The approach to management of low-grade gliomas has changed significantly in recent years. Previously, a conservative approach with serial imaging was common practice. Recent guidelines support surgery, with the aim of resection rather than biopsy, as evidence suggests this improves progression-free survival, overall survival, and seizure control.[1] Resection may also increase accurate pathologic diagnosis compared with biopsy alone.[1]

^{18}F-Fluoro-deoxyglucose (FDG) is unfavorable for use in the central nervous system due to high background glucose metabolism.[2] It has been the predominant tracer used in positron emission tomography (PET) for assessment of highly metabolic high-grade gliomas but is typically not helpful in low-grade gliomas, which have a similar or reduced glucose metabolism compared with brain.[2] ^{18}F-FDG also has limited utility in differentiating disease progression from treatment-induced necrosis.[3] Increasingly, amino acid tracer PET imaging, in particular ^{18}F-fluoro-ethyl-tyrosine (^{18}F-FET) PET, has been used in high-grade glioma to differentiate tumor progression from treatment-induced necrosis, as it has lower uptake than ^{18}F-FDG in inflammatory cells.[2,4] There is increasing investigation into the utility of amino acid tracers including ^{18}F-FET for the investigation of suspected low-grade lesions.[2]

In 2016 the Neuro-Oncology Working Group and European Association for Neuro-Oncology published guidelines for the use of PET imaging in glioma.[5] They recommend that amino acid PET is superior to ^{18}F-FDG-PET in differentiating glioma from non-neoplastic tissue. However, negative amino acid PET does not exclude glioma as more than one third of low-grade gliomas do not show amino acid tracer uptake.[5]

Several criteria for interpretation of ^{18}F-FET-PET have been described. In the literature TBR_{max} (maximum uptake of lesion

Key words
- Glioma
- ^{18}F-fluoro-ethyl-tyrosine
- Positron emission tomography

Abbreviations and Acronyms
^{18}F-FET: ^{18}F-fluoro-ethyl-tyrosine
^{18}F-FDG: ^{18}F-fluoro-deoxyglucose
PET: Positron emission tomography
TBR: Tumor background ratio
TBR_{max}: Maximum tumor background ratio
SD: Standard deviation

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divided by mean uptake of contralateral brain) and TBR mean (mean uptake of lesion divided by mean uptake of contralateral brain) are often used for quantitative analysis. However, there are no clearly defined criteria for interpretation.

This study aims to investigate the utility of ^{18}F-FET-PET in suspected glioma in a single-center cohort. Thresholds for quantitative analysis are considered.

MATERIAL AND METHODS

Patients were identified through the nuclear medicine database. All patients who had ^{18}F-FET-PET performed during the study period, from commencement of ^{18}F-FET scanning at Royal North Shore Hospital to December 2016, were identified. Exclusion criteria were positive ^{18}F-FDG PET or surgery before ^{18}F-FET-PET scanning.

Patient files were reviewed to ascertain demographics, date, and indication for first neuroimaging and nuclear medicine specialist report of PET studies. For patients undergoing biopsy, pathology results were collected. Latest follow-up information was reviewed for patients without definitive diagnosis, and length of follow-up from first abnormal imaging was calculated.

All PET scans were performed on the Siemens Biograph mCT PET/computed tomography scanner. Patients received a 3-minute ^{18}F-FET infusion (median dose 161.7MBq). Image acquisition was performed at 10 minutes.

^{18}F-FET PET, FDG, and MRI were reviewed on the Siemens Syngo Fastview system. Standard uptake value was measured in an elliptical region of interest within the lesion and in gray and white matter of the contralateral hemisphere for each patient. TBR_{max} was calculated for each patient. Patients were divided into subgroups for analysis: glioma, nonglioma, or unconfirmed. The mean TBR_{max} and standard deviation were calculated for each group. The groups were compared using a paired Student's *t*-test.

RESULTS

Sixty-two patients underwent ^{18}F-FET PET during the study period. Nine patients were excluded because they had undergone surgery before PET being performed. Five patients were excluded because they had positive or indeterminate ^{18}F-FDG-PET. One patient was excluded because MRI was not available for review. The remaining 47 patients were included in the study as shown in Figure 1.

Glioma Group

Fourteen patients had histologic confirmation of glioma. One patient was treated as brainstem glioma on the basis of initial imaging and subsequently showed radiologic response to treatment with temozolomide. All of these patients had qualitatively positive

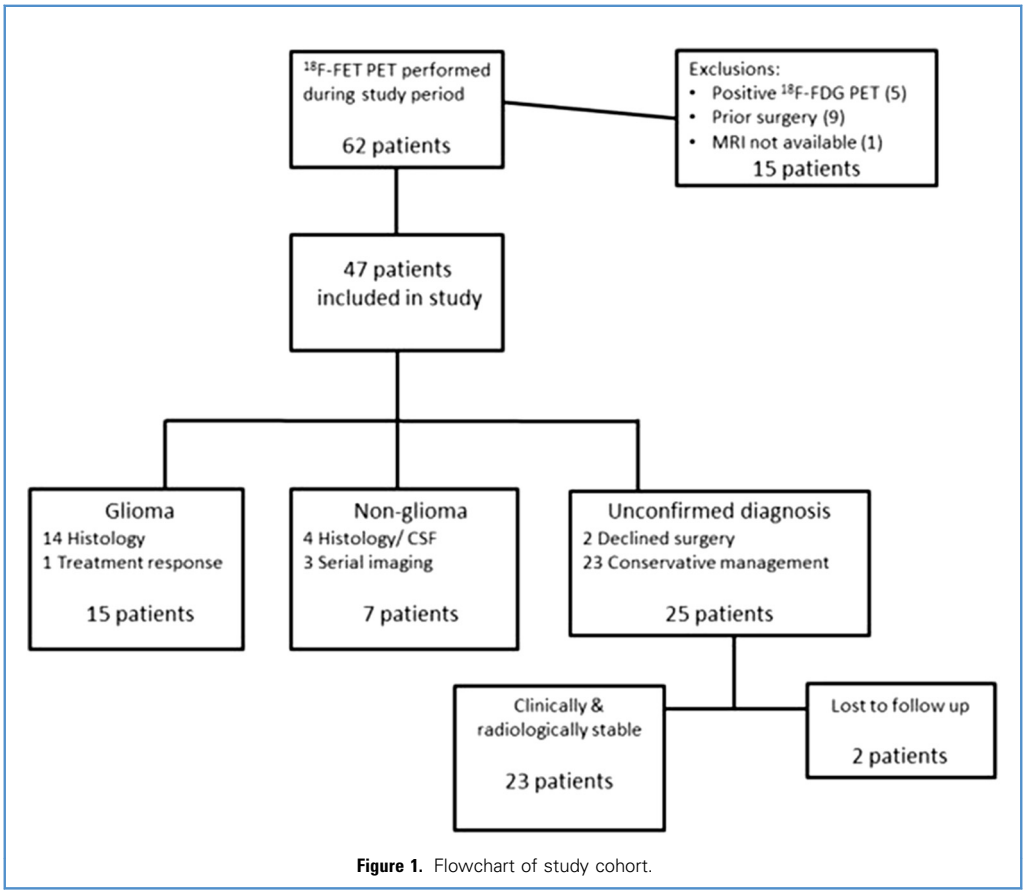

Figure 1. Flowchart of study cohort.

^{18}F-FET-PET as reported by a nuclear medicine specialist. The mean TBR_{max} for this group was 4.36 (standard deviation [SD] ± 3.35).

Four patients had World Health Organization grade I or II tumors. The mean TBR_{max} for this group was 2.48 (SD ± 0.21). Ten patients had World Health Organization grade III or IV tumors. The mean TBR_{max} for this group was 5.38 (SD ± 3.68). The difference between the high-grade glioma and low-grade glioma groups was not significant ($P = 0.149$).

Nonglioma Group

Seven patients had confirmed alternative diagnosis as shown in Table 1. Six of these patients had qualitatively negative ^{18}F-FET-PET as reported by a nuclear medicine specialist. One patient with neurosarcoid was reported as indeterminate, with patchy ^{18}F-FET uptake. The mean TBR_{max} for this group was 2.56 (SD ± 0.76). Patients with confirmed inflammatory conditions had high ^{18}F-FET uptake (mean TBR_{max} 3.26). Other diagnoses including infarction and demyelination showed lower ^{18}F-FET uptake (mean TBR_{max} 2.04).

The glioma group had higher ^{18}F-FET uptake (mean 4.36 ± 3.35) than the nonglioma group (mean 2.56 ± 0.76), but this did not reach significance ($P = 0.117$). Uptake in the low-grade glioma group (mean 2.48 ± 0.21) was similar to patients in the nonglioma group. The high-grade glioma group had significantly higher uptake than the nonglioma group ($P = 0.05$).

Follow-up Group

Twenty-five patients with lesions on MRI did not have a definitive diagnosis at the time of data collection. Two patients had positive ^{18}F-FET-PET on qualitative review and were recommended for surgery but declined. The TBR_{max} for these patients was 4.38 and 3.80. Both patients remained clinically stable, without progressive changes on MRI, at 18 months and 2 months, respectively.

Two patients were lost to follow-up, both with negative qualitative reports and TBR_{max} of 2.73 and 1.99.

The remaining 21 patients all had negative qualitative reports with a mean TBR_{max} of 1.91 (range 1.22–4.38). Median follow-up for this group was 17 months (1–85 months). Nineteen patients were asymptomatic or had well-controlled symptoms, as shown in Table 2. No patients had documented clinical deterioration or radiologic progression.

DISCUSSION

This retrospective cohort study investigates the role of ^{18}F-FET-PET in suspected glioma in a single center. Forty-seven patients were included in the study, of which 15 had confirmed diagnosis of glioma. In our cohort ^{18}F-FET-PET was useful in determining glioma grade but less useful in differentiating low-grade glioma from nonneoplastic disease.

Quantitative Analysis

Dunet et al[4] performed a meta-analysis of ^{18}F-FET-PET for the differential diagnosis of primary brain tumors. TBR_{max} 2.1 was used as a threshold for determining glioma versus alternative diagnosis.[4] The researchers included 180 patients from 5 studies in the analysis. In their study, ^{18}F-FET-PET demonstrated 65% sensitivity and 56% specificity for diagnosis of glioma using threshold

Table 1. Patients with Confirmed Nonneoplastic Diagnosis

Indication	TBR_{max}	Diagnosis
Seizure	1.84	Epilepsy (resolution of changes post seizure)
Headache and dysphasia	1.92	Infarction
Right hemiparesis and headache	2.03	Infarction
Headache and right-sided paresthesia	2.35	Demyelination
Memory loss and confusion	2.74	Hashimoto encephalopathy/ autoimmune thyroiditis
Seizure	2.85	Encephalitis
Memory loss, nystagmus, seizures	4.19	Neurosarcoid (biopsy)

TBR_{max} of 2.1. In our cohort of patients with definitive diagnosis, this gives a sensitivity of 86.7% with specificity of only 37.5%. TBR_{max} threshold 2.1 is sensitive for glioma but has poor specificity.

TBR_{max} 2.5 has also been used.[6] Rapp et al[6] performed a retrospective review of 174 patients with suspected glioma. In their cohort they found TBR_{max} 2.5 to be the optimal threshold for differentiating neoplastic from nonneoplastic disease with sensitivity of 57% and specificity of 92%. However, they did not differentiate glioma from other neoplastic disease in the analysis.[6] In our cohort, TBR_{max} >2.5 gives a sensitivity of 60% and specificity of 62.5% for differentiating glioma from nonneoplastic disease. Rapp et al[6] also found 2.5 to be the optimal threshold for differentiating high-grade glioma from low-grade glioma.[6] This suggests TBR_{max} >2.5 does not differentiate low-grade glioma from nonneoplastic lesions.

In our series high-grade gliomas showed higher ^{18}F-FET uptake than low-grade gliomas, as reported in previous studies. Dunet et al[7] performed a meta-analysis to investigate the utility of ^{18}F-FET-PET in

Table 2. Indication for Imaging and Clinical Status of Patients with Negative ^{18}F-FET PET and No Definitive Diagnosis

Indication	Number of Patients	Clinical Status at Last Review
Seizure	5	3 Well controlled 2 Not specified
Headache	5	4 Asymptomatic 1 Stable
Sensory disturbance	2	1 Asymptomatic 1 Stable
Motor weakness	1	Asymptomatic
Syncope	1	Asymptomatic
Tinnitus	1	Asymptomatic
Mood disturbance	1	Stable (psychiatric review)
Not specified	5	5 Asymptomatic

grading glioma. Five studies were included in their analysis with 119 patients in total. They found that TBR_{max} >3.0 was optimal for differentiating high-grade glioma from low-grade glioma, with sensitivity of 80% and specificity of 82%. In our cohort TBR_{max} >3.0 has a sensitivity of 70% and specificity of 91.7% for differentiating high-grade glioma from low-grade glioma.

Qualitative Analysis

The nuclear medicine specialist report had 100% sensitivity and 85.7% specificity in our cohort of patients with confirmed diagnosis.

Sarcoid

One patient in our cohort had biopsy-proven sarcoidosis after positive ^{18}F-FET PET (TBR_{max} 4.19). Sarcoidosis exhibits neurologic involvement in 5%–27% of cases,[8] and up to 16% of patients with sarcoid initially present with neurologic symptoms.[8] Our patient presented with memory loss, nystagmus, and seizures in the absence of systemic symptoms. On MRI, a neurosarcoid can appear as an intraparenchymal T2 hyperintense mass with variable enhancement.[8] Sarcoidosis is an inflammatory condition and is therefore positive on ^{18}F-FDG-PET due to high glucose metabolism.[9] Our patient did not undergo FDG PET. Chae et al[10] demonstrated that uptake of the amino acid tracer ^{18}-F-FSPG is significantly higher in sarcoid than nonsarcoid inflammatory lesions, consistent with our case of high ^{18}F-FET uptake.

Limitations

In our cohort a large proportion of patients with qualitatively negative ^{18}F-FET-PET did not go on to biopsy. The median follow-up for this group was 17 months. However, low-grade glioma often remains clinically and radiologically stable for many years. Longer-term follow-up data will be useful in determining the sensitivity of ^{18}F-FET-PET in those patients for whom histologic diagnosis has not occurred.

Given this is a retrospective cohort study, there is inherent bias in patient selection. This is a reflection of current practice, whereby the majority of patients undergoing ^{18}F-FET-PET are cases in which there is diagnostic uncertainty based on clinical presentation and MRI findings. Preoperative ^{18}F-FET-PET is not routinely used in patients in whom glioma is the main differential and is surgically accessible. This means a small number of patients fulfill the criteria for inclusion in the study. Furthermore, it means few patients have histologic diagnosis in the negative group.

CONCLUSION

In our cohort, previously published TBR_{max} thresholds are not reliable for diagnosis of low-grade glioma. Lesions with TBR_{max} >2.5 should be considered suspicious for glioma and biopsy considered. Lesions with TBR_{max} >2.1 should be closely monitored.

^{18}F-FET shows significantly higher uptake in high-grade glioma than in nonglioma lesions. Threshold TBR_{max} >3.0 is useful for differentiating high-grade glioma from low-grade glioma. This may be a particularly useful tool for directing management in eloquent areas, such as brainstem glioma.

Interpretation of ^{18}F-FET-PET should be made in consultation with a nuclear medicine specialist.

Although amino acid tracer PET may be a useful adjunct in the investigation of cerebral lesions, surgery for tissue diagnosis remains the gold standard.

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