O-(2-(18F)fluoroethyl)-L-tyrosine PET for the differentiation of tumour recurrence from late pseudoprogression in glioblastoma

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INTRODUCTION

Pseudoprogression (PsP) in glioblastoma presents a significant obstacle in distinguishing genuine tumour recurrence from treatment-induced contrast enhancement on MRI. Only retrospectively identifiable, PsP is believed to be at least partly a result of radiochemotherapy-based alterations in the blood–brain barrier (BBB). Radiation-induced hypoxia has been suggested to upregulate vascular endothelial growth factor, which then mediates blood vessel permeability and fosters BBB dysregulation.

Typically understood to occur within the first 12 weeks following radiotherapy, PsP has recently been demonstrated to also appear significantly later ('late pseudoprogression').[1]

Given its ability to mimic true tumour development, late PsP can lead to interference with treatment course or unwarranted surgical intervention. Thus, its prompt and definitive detection serves a critical role in glioblastoma management.

Positron emission tomography (PET) using radiolabelled amino acids such as O-(2-(^{18}F)fluoroethyl)-L-tyrosine ((^{18}F) FET) has proven a useful tool in the differentiation of true tumour progression from treatment-induced changes, as tracer uptake reflects amino acid transport rather than inflammatory processes. The purpose of this study was to further substantiate the available data on the suitability of ^{18}F)FET-PET in suspected late PsP.

MATERIALS AND METHODS

Subjects

This retrospective study included 36 consecutive patients (22 males and 14 females, ages ranging from 24 to 75 years, with a mean of 54±14) with histopathologically confirmed glioblastoma. Between April 2010 and August 2016, patients were referred to (^{18}F)FET-PET/CT due to suspicion of recurrence/disease progression as determined by the Response Assessment in Neuro-Oncology (RANO) working group criteria.[2] The interval between cessation of radiotherapy and subsequent PET imaging was >12 weeks in all cases.

Imaging

All patients fasted for at least 12 hours prior to PET imaging. Twenty minutes following intravenous injection of (^{18}F) FET (217±13 MBq), patients were scanned for 10 minutes using a dedicated PET/CT scanner (Siemens Biograph mCT 64, Siemens, Knoxville, USA). Detailed information on the PET/CT imaging protocol can be found in the online Supplementary materials.

Image analysis

Images were analysed according to Fueger *et al*.[3] Scan slices were first inspected visually and, upon identification of the axial image slice presenting the maximum tumour uptake, regions of interest were selected. The first region consisted of a 10 mm diameter circle centred on the area of highest activity and allowed for derivation of maximum (SUV_{max}) and mean (SUV_{mean}) standardised uptake values . A 50 mm reference region containing white and grey matter was selected in an area of normal-appearing brain tissue on the contralateral hemisphere. Tumour values were then divided by mean background SUVs to calculate maximum and mean tumour-to-background ratios (TBR_{max} and TBR_{mean}).

Diagnosis of true progression

Diagnosis of genuine tumour progression was done by histopathological proof (details available in the online Supplementary materials), clinical deterioration, or further radiological progression in follow-up MRI at least 4 weeks following initial assessment.[2]

Late pseudoprogression was diagnosed when histopathology was negative, the clinical condition of the patient remained stable for at least 6 months (with no treatment changes), or follow-up MRI (>4 weeks following initial assessment) showed stabilisation or regression of the contrast-enhancing lesions.[4]

Statistical analysis

All analyses were conducted in IBM SPSS Statistics V.22.0 software. Descriptive statistics were reported as mean±SD. Optimal cut-off values for tumour-to-background ratios indicative of genuine recurrence were determined by receiver operating characteristic curve analysis. P values of 0.05 and below were considered to be significant. No correction of p values was applied to adjust for multiple tests.

RESULTS

Patient characteristics

All patients underwent imaging either after radiotherapy alone (n=2) or while receiving first-line treatment consisting of temozolomide-based radiochemotherapy with adjuvant temozolomide according to Stupp *et al* (n=34). Individual patient data, including O-6-methylguanine-DNA methyltransferase promoter status, is shown in the online Supplementary table 1.

Diagnosis of true tumour progression versus late PsP

Diagnosis of true tumour progression versus late PsP was established by histological analysis of surgical tumour samples in 16/36 patients and by clinical and radiological examination in the remainder. In total, genuine tumour progression was diagnosed in 28/36 cases and late PsP in the remaining eight (examples are given in figure 1 and online Supplementary figure 1). Patients with late PsP presented with reactive astrogliosis and/or postradiation necrosis in histopathology (online Supplementary figures 1 and 2).

PET imaging results

TBR_{mean} and TBR_{max} were significantly higher in patients with tumour progression when compared to patients with late PsP (TBR_{mean} 3.61±0.74 vs 2.75±0.50, p<0.01; TBR_{max} 4.50±1.01 vs 3.28±0.60, p<0.01; online Supplementary table 2).

A TBR_{max} threshold of 3.52 generated the best discrimination between true tumour progression and late PsP with an accuracy of 86% (sensitivity 89%, specificity 75%, area under the curve (AUC) 0.87±0.07; 95% CI 0.73 to 1.0, p=0.002). TBR_{mean} calculation rendered comparable results with an AUC of 0.84±0.08 (95% CI 0.69 to 0.99, p=0.004, accuracy 83%, sensitivity 82%, specificity 87.5% for optimal cut-off of 2.98).

DISCUSSION

This study affirms the general suitability of (^{18}F)FET-PET in discriminating between genuine tumour progression and late PsP, with an optimal TBR_{max} cut-off threshold of 3.52. Our findings corroborate those of numerous other studies, demonstrating the value of amino acid PET/CT in differentiating vital tumour from unspecific (treatment-related) changes at all disease stages.[1 5 6]

Despite differences in both tumour delineation and tracer uptake analysis, we were able to confirm recently published data, attesting to the robustness of amino

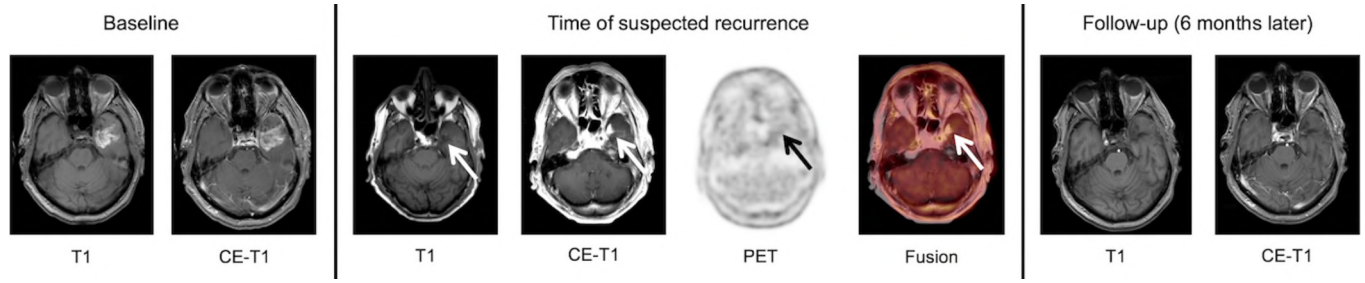

Figure 1 Display of a patient with late pseudoprogression. Transaxial native MR (T1), contrast-enhanced MR (CE-T1), positron emission tomography (^{18}F) FET-PET), and fused (Fusion) images of patient #8 with radiological suspicion of glioblastoma recurrence 24 weeks after cessation of external radiation (due to new contrast enhancement). (^{18}F)FET-PET demonstrated a maximum tumour-to-background ratio of 2.37, consistent with late pseudoprogression, which was confirmed by clinical and radiological follow-up.

acid PET and supporting the suitability of alternative methods for tracer uptake quantification.[1] Despite ongoing research, standardisation of image analysis and data processing in (^{18}F)FET-PET remains to be accomplished. Selection of a single approach could facilitate comparisons between study centres as well as potentially establish an optimal technique for future research. In fact, the need for standardisation is strongly emphasised in the current RANO/European Association for Neuro-Oncology (EANO) recommendations for the clinical use of PET imaging in gliomas and might be achieved through the anticipated release of technical guidelines for glioma PET imaging protocols by the RANO, EANO, and European Association of Nuclear Medicine.

Limitations of this study include its retrospective nature and small sample size. Scans were performed at a single time point and were therefore static. Regardless, our results were able to successfully differentiate PsP from tumour recurrence, relativising the additional information acquired through the use of dynamic scans.

In conclusion, this study confirms (^{18}F) FET-PET as a robust means for distinguishing late PsP from genuine tumour progression. It is less sensitive to artefacts than MRI and can be easily read due to high tumour-to-background contrasts, which makes it an attractive tool for brain tumour assessment.

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Contributors MIM, OK, ML, R-IE, AKB and CL were involved in the conception and design. HH, CMM, IK, SS, AFK, TL and CL were involved in the development of methodology. MIM, OK, CMM, IK, AFK, TL and CL were responsible for the acquisition of data. MIM, OK, HH, ML, CMM, IK, AFK, TL and CL contributed to the analysis and interpretation of data. HH, CMM, SS, TL, R-IE and AKB were involved in the administrative, technical, or material support. ML, R-IE, AKB and CL supervised the study. All authors contributed to the writing, review, and/or revision of the manuscript.

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