The University of Manchester
Wolfson Molecular Imaging Centre

Salford Royal NHS Foundation Trust

Imperial College London

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In Vivo Imaging of Translocator Protein Expression in Low-Grade Gliomas by Positron Emission Tomography

Su ZJ[1], Gerhard A[1], Hinz R[1], Coope DJ[2], Thompson G[1], Karabatsou K[2], Janczar K[3], du Plessis D[4], Roncaroli F[3], Turkheimer FE[3], Jackson A[1], Herholz K[1]

1. Wolfson Molecular Imaging Centre, University of Manchester
2. Department of Neurosurgery, Salford Royal NHS Foundation Trust
3. Department of Clinical Neuroscience, Imperial College London
4. Neuropathology Unit, Salford Royal NHS Foundation Trust

Introduction

Astrocytomas and oligodendrogliomas account for more than 70% of all primary neoplasms in the brain. Therapeutic management and outcome differ in these two commonest types of gliomas due to their different biological characteristics. Translocator protein (TSPO), previously termed as peripheral benzodiazepine receptor (PBR), is an 18 kDa molecule located on the outer mitochondrial membrane (Fig 1). It has been detected in gliomas and appears to be closely correlated with tumour proliferation, histological type and grade of malignancy: astrocytic type and high-grade tumours express significantly more TSPO than oligodendroglial type and low-grade ones. In the tumour, TSPO is prominently expressed in neoplastic cells instead of activated microglia, the main cells over-expressing TSPO in various other brain diseases. PET studies using TSPO-specific ligand PK11195 in glioma patients were sparse with variable results [1-3], and none of them had been conducted on oligodendroglioma patients. We are investigating the *in vivo* expression of TSPO in low-grade gliomas, whether PK11195 can be utilised as an imaging marker to distinguish between astrocytomas and oligodendrogliomas, and how such PET scanning can be applied in guiding biopsy.

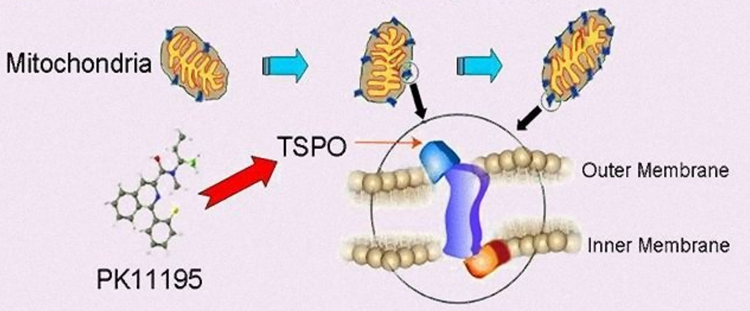


Figure 1. TSPO expression in mitochondria and PK11195 binding to the TSPO (modified after [4])

Methods

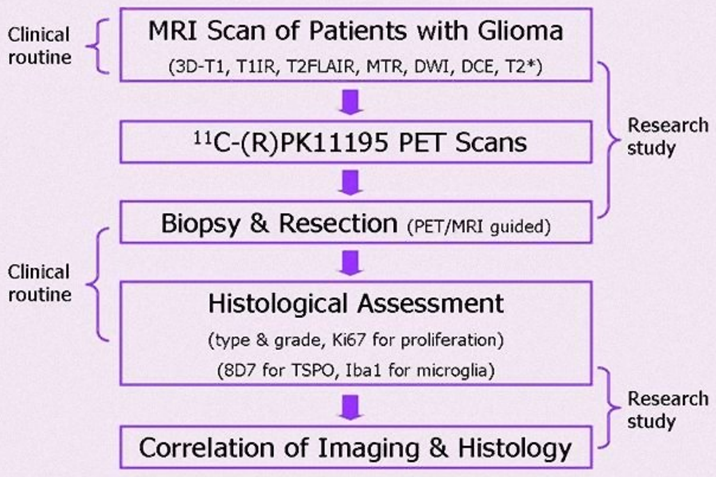
•4 patients (mean age 36, male : female = 3 : 1) with low-grade gliomas and 5 healthy volunteers (mean age 50, male : female = 2 : 3) recruited

•MRI to detect brain tumours the cerebral blood volume (CBV), followed by PET scans with the radiotracer ^{11}C-(R)PK11195 (injected activity 467±78MBq) for specific binding to the TSPO

•Reference tissue input function obtained from the grey matter of ipsilateral cerebellum and the supervised cluster analysis [5]; regions of interest (ROIs) drawn on the tumours with high and low PK11195 uptake; co-registered PET/MRI to guide biopsies.

•Parametric maps of binding potential (BP_{ND}) calculated using the simplified reference tissue model (SRTM)[5]

•Tumour tissue assessed using H&E and immunohistochemical staining to determine the histotype and grade, cell proliferation, TSPO expression and microglial activation



•HRRT

- Dedicated brain scanner
- Dual layer LSO crystals
- Larger FOV (250mm)
- 2.2mm spatial resolution

Figure 2. High Resolution Research Tomograph (HRRT) for PET scans

Results

Imaging

The ^{11}C-(R)PK11195 uptake in most parts of the tumours was lower than that in the unaffected cortex in glioma patients. High uptake foci were found in the margin and within the generally low uptake tumour regions, from which biopsies were taken (Fig 3, 4).

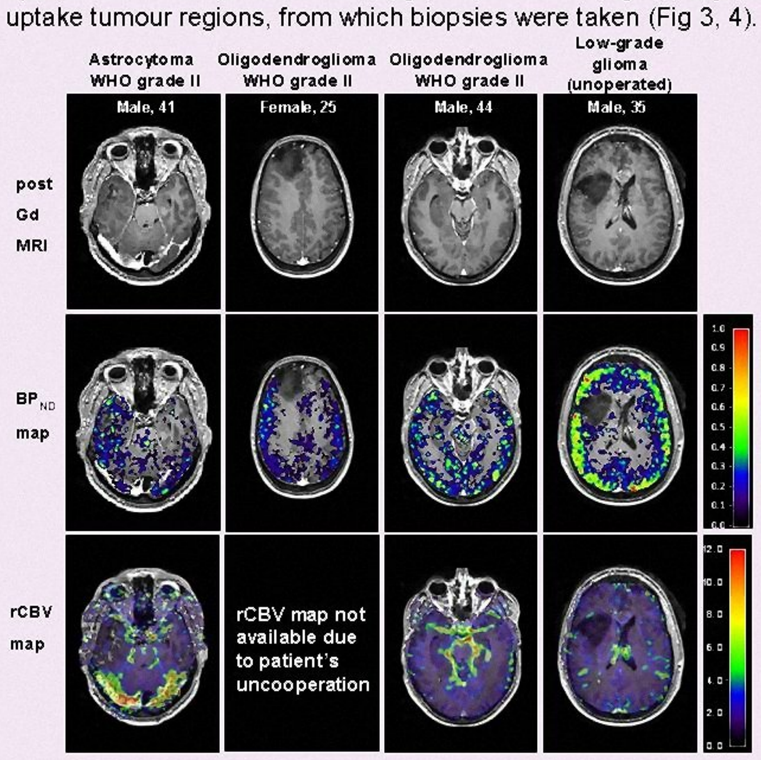


Figure 3. Co-registered MR/PET images in 4 glioma patients

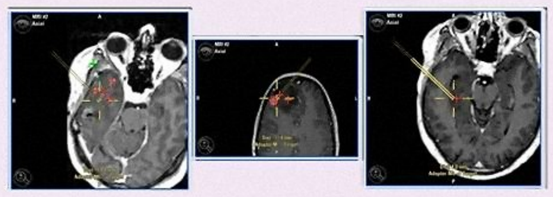


Figure 4. Biopsy sites from high PK11195 uptake foci within the tumours.

The relatively fast washout of the tracer in the normal brain tissue (ipsilateral cerebellum and the cluster of pure grey matter) appeared to be slower in the tumour regions (Fig 5).

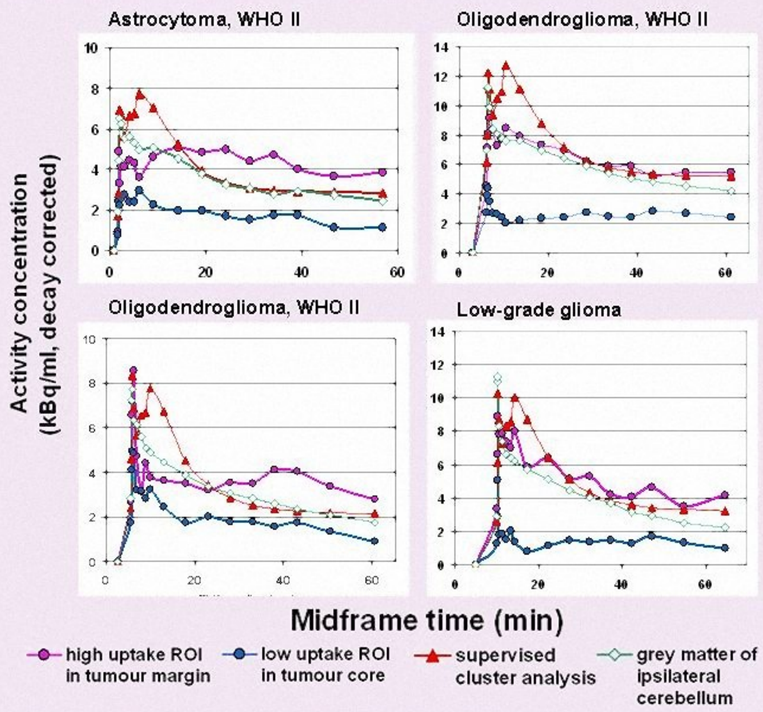


Figure 5. Time-activity curves from PK11195 PET scans in 4 glioma patients

The binding of ^{11}C-(R)PK11195 in the grey matter of unaffected hemispheres in glioma patients seemed higher than that in the healthy volunteers (Fig 6), but the difference was not statistically significant ($p>0.05$), possibly due to limited number of cases.

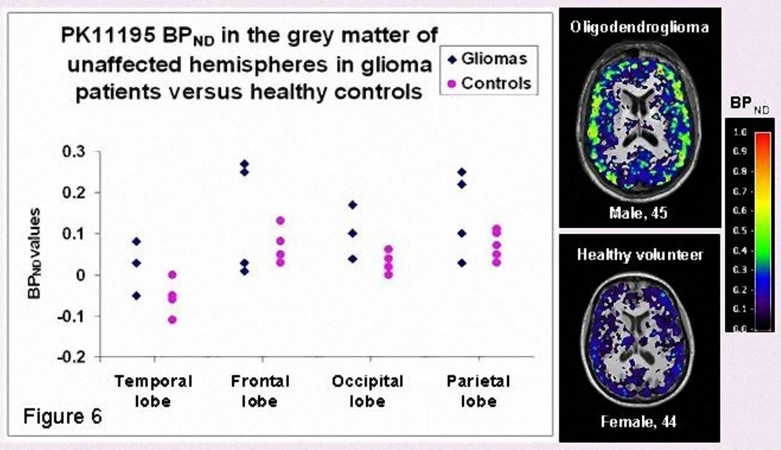


Figure 6

Histology

Table 1. Histology results of the 3 low-grade gliomas biopsied

	Astrocytoma	Oligodendroglioma	Oligodendroglioma
grade	WHO II	WHO II	WHO II
TSPO	25%	23%	16%
microglia	20%	6%	8%
Ki 67	1.77%	4.8%	2%
1p 19q	N/A	intact	deleted

Discussion

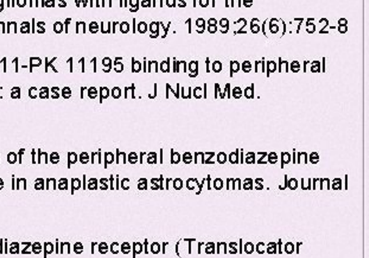
The variable results in previous PET studies investigating TSPO expression in astrocytoma patients (Table 2) [1-3] highlight the complexity of *in vivo* TSPO expression in gliomas and question the generally accepted view of TSPO over-expression in activated microglia: is it still the case in gliomas?

Table 2. Previous PK11195 PET studies in astrocytoma patients

Authors	Patients	Radiotracer	Main findings
Junck *et al.*, 1989	n=10 astrocytomas (WHO II-IV)	^{11}C-PK11195	increased radioactivity in the late images in 8 out of 10 patients
Pappata *et al.*, 1991	n=1 GBM (WHO IV)	^{11}C-PK11195	2-fold higher binding in the tumour; 30% binding was displaced by a large excess of unlabelled ligands
Takaya *et al.*, 2007	n=2 anaplastic astrocytomas (WHO III)	^{11}C-(R)PK11195	markedly lower binding in tumours; activated microglia failed to express TSPO

Our preliminary findings show generally lower PK11195 uptake and slightly different tracer kinetics in low-grade gliomas compared with the unaffected grey matter. The unaffected brain tissue in the patients may not be normal due to increased TSPO expression in activated microglia although such change may be suppressed in the tumour. More cases are needed to verify the imaging pattern and the correlation between PK11195 uptake and TSPO expression.

Recent histology studies by our colleagues (KJ and FR) showed significantly higher TSPO expression in astrocytomas than oligodendrogliomas (Fig 7), which is in keeping with our PET results and indicates that PK11195 may be used as a biomarker to distinguish them.



Conclusion

TSPO expression in low-grade gliomas may be suppressed with differences between astrocytomas and oligodendrogliomas. PK11195 PET may be useful for distinguishing these two histotypes and guiding biopsy.

Acknowledgement

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References

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zhangjie.su@mmic.man.ac.uk