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PET imaging in glioma: techniques and current evidence

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Abstract

Positron Emission Tomography (PET) holds potential to provide additional information about tumour metabolic processes, which could aid brain tumour differential diagnosis, grading, molecular subtyping and/or the distinction of therapy effects from disease recurrence. This review discusses PET techniques currently in use for untreated and treated glioma characterisation and aims to critically assess the evidence for different tracers (FDG, choline and amino acid tracers) in this context.

Keywords: PET, glioma, FDG, Choline, Amino acid tracers, IDH, molecular typing, pseudoprogression, radiation necrosis

Abbreviations

Blood-brain-barrier	BBB
Choline kinase	CK
Diffuse B cell lymphoma	DBCL
Glucose transporter	GLUT
High-grade glioma	HGG
Isocitrate dehydrogenase	IDH
IDH wild type	IDH_{wt}
IDH mutant	IDH_{mut}
L amino acid transporter	LAT
Low-grade gliomas	LGG
Magnetic Resonance Imaging	MRI
Non-neoplastic lesion	NNL
Phosphorylcholine	ChoP
Positron Emission Tomography	PET
Primary central nervous system lymphoma	PCNSL
Region of interest	ROI
Standardized uptake value	SUV
Time activity curve	TAC
Time to peak	TTP
Tumour to brain (ratio)	TBR (ratio)
Tumour to normal (ratio)	T/N (ratio)
Tumour to striatum	TS

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Tracers:

[11]C-Methyl-L-Methionine	^{11}C-MET
[18]F-Fluorodeoxyglucose	^{18}F-FDG/FDG
[18]F-Fluoroethyl-L-Tyrosine	^{18}F-FET
[18]F-Fluoro-L-Dihydroxy-Phenylalanine	^{18}F-FDOPA
[18]F-fluorothymidine	^{18}F-FLT
[11]C-Choline	^{11}C-CHO
[18]F-Fluorocholine	^{18}F-CHO

Introduction

Gliomas constitute the majority of primary brain tumours with median survival for the most common type (45%), the highly malignant glioblastoma, barely exceeding one year [1]. The clinical behaviour of gliomas varies, with certain subtypes growing slowly over a number of years ('low grade') before exhibiting malignant features. Gliomas can be characterised by cellular morphology (astrocytoma (AS), oligodendroglioma (OD), oligoastrocytoma (OA)) and according to proliferative features. The World Health Organization (WHO) classification of central nervous system tumours divides diffuse gliomas into grade I-II (low grade glioma, LGG), grade III (anaplastic) and grade IV (glioblastoma).

Microscopic examination incompletely captures glioma malignant potential, whereby a proportion of tumours of 'low grade' morphology progress rapidly [2]. Mutations in the isocitrate dehydrogenase (IDH) gene, (most commonly at codon 132 on chromosome 2), are an early event in glioma-genesis [3] and occur characteristically in LGG. Up to 80% of WHO grade II-III oligodendrogliomas, astrocytomas [4] and virtually all secondary glioblastomas carry an IDH mutation [5]. Secondary glioblastomas (10%) are thought to develop through malignant transformation of LGGs [6]. In glioblastoma as well as in LGG, the presence of an IDH mutation is a prognostic marker of a better outcome [7,8]. While IDH mutation is the most frequent genetic mutation in LGGs, oligodendrogliomas are defined by additional loss of 1p and 19q (1p/19q co-deletion). In one genome-wide study, IDH mutated LGGs with 1p/19q co-deletion was associated with longer survival (mean 8 years) compared to IDH mutant astrocytomas with no co-deletion (mean 6.3 years) [9].

The majority (90%) of glioblastomas (WHO grade IV) arise de novo without IDH mutations (IDH wild-type). They affect older patients (>55 years) and have a dismal prognosis (median survival is 12-14 months) [5]. Many IDH wild-type (IDH_{wt}) WHO II-III gliomas follow a clinical

course similar to that of glioblastomas, reflecting their biological overlap. Since 2016, the WHO classification of brain tumours includes molecular assessment for an integrated glioma diagnosis [10]. To permit early aggressive therapy for IDH_{wt}, the distinction of LGG according to IDH status has become an important objective of pre-surgical imaging work up.

Anatomical MRI plays an important role in the initial characterisation of brain masses [11], but it cannot reliably predict glioma grade, malignant potential or molecular status. For example, the presence of MRI contrast enhancement, indicative of blood-brain barrier (BBB) breakdown, is typical of high grade but not specific [12], whereby 40-45% of non-enhancing lesions are malignant gliomas [13], and up to 16% of anaplastic tumours do not enhance. Advanced MRI techniques such as diffusion, perfusion and spectroscopy can support the identification of aggressive gliomas, but there is diagnostic overlap, especially with oligodendroglioma on perfusion imaging [14]. Following adjuvant therapy, the MR imaging assessment of glioma is complicated by treatment-induced lesions, which may mimic tumour. This review discusses the potential role and evidence for the use of PET imaging techniques in the pre- and post-therapeutic assessment of glioma.

Methods

Search strategy and selection

PubMed and Google Scholar were searched to identify relevant studies published from 2007 to January 2018 addressing PET in glioma diagnostics. A combination of search terms was used including glioma, PET, proton-emission tomography, IDH, IDH1/2, isocitrate dehydrogenase, glioblastoma, PET tracers, FDG, amino acid tracers, glioma grading, FDOPA, choline, MET, FET,

FLT. For the post treatment section, the search terms pseudo progression and radiation necrosis were included.

Inclusion and exclusion criteria

The search was restricted to studies describing ^{18}F-FDG, choline, ^{18}F-FDOPA and/or amino acid tracer PET in gliomas, PET findings in correlation with glioma histopathological diagnosis and/or molecular status. Only articles in English were selected, and the search was limited to humans. Publications were excluded if they involved hypoxia tracers, did not include adults, described in vitro and/or animal studies, case reports and spinal cord tumours.

Tracers

[18]F-Fluorodeoxyglucose (^{18}F-FDG)

^{18}F-FDG exploits the upregulation of glycolysis in cancer cells [15]. It is the most used PET imaging agent and accumulates through sodium-independent glucose transporter (typically GLUT-1) cellular uptake. Like native glucose, intracellular ^{18}F-FDG becomes phosphorylated by hexokinase (which is overexpressed in many tumour cells) to form 2-[^{18}F] fluoro-2-deoxy-d-glucose-6-phosphate (^{18}F-FDG-6P) [16]. The fluorine atom in ^{18}F-FDG-6P precludes further progression through the normal glycolytic cycle trapping [18]FDG-6P within tumours cells [17]. Several studies have demonstrated a link between ^{18}F-FDG uptake in gliomas and prognosis [18–24]. However, high physiological uptake of ^{18}F-FDG diminishes contrast, particularly in the cortex, to the extent that tumours and normal brain activity may become indistinguishable. These limitations are reflected in the current UK ^{18}F-FDG PET/CT guidelines, which restrict neuro-oncological applications to 1) grading of glioma with inconclusive findings on anatomical

imaging, 2) lymphoma assessment and 3) differentiation of cerebral tumour from infection in immuno-compromised patients with indeterminate lesions on conventional imaging [25].

Non-FDG PET Tracers

The enhanced amino acid uptake required for growing tumour protein synthesis and cell division is basis for an alternative PET approach using radiolabelled amino acids tracers [26]. Uptake and transport of amino acids in tumour cells occur through system L (Na$^+$ independent) amino acid transporters (LAT), including LAT1 and LAT2 [27]. HGG frequently demonstrate LAT1 overexpression [28].

^{11}C-Methyl-L-Methionine (^{11}C- MET)

^{11}C-MET has been used as a radiolabelled amino acid for brain tumour imaging since the early 1980s [29,30]. ^{11}C-MET is transported across tumour cell membranes via LAT [31], and incorporated into proteins synthesis and metabolised via alternative pathways, meaning its distribution does not reflect protein synthesis alone [32]. A principal advantage of this tracer is high radiochemical yield and low uptake in normal brain [33,34]. Nonetheless with a short half-life (20 minutes), it requires on-site cyclotron facilities with a risk of compromised image quality in delayed acquisitions [35].

^{18}F-Fluoroethyl-L-Tyrosine (^{18}F-FET)

^{18}F-FET is a tyrosine analogue radiolabelled tracer that accumulates within tumours without metabolization or incorporation into proteins. Its transport mechanism is similar to ^{11}C-MET, thus ^{18}F-FET uptake more directly reflects transport rate [36]. Fluoridated labelled radiotracers have longer half-lives (110 minutes) [34], making them more suitable for clinical

use. Increased uptake has been demonstrated in demyelination and ischaemia [35], with normal or reduced uptake in some low grade and anaplastic astrocytomas [13].

18F-fluorothymidine (18F-FLT)

Developed in 1998, ^{18}F-FLT is an injectable nucleoside radiotracer used to measure and visualise DNA synthesis [37,38]. ^{18}F-FLT permeates cell membrane by diffusion, whereby BBB breakdown is an important promoting factor. ^{18}F-FLT is phosphorylated by the upregulated S-phase-specific enzyme thymidine kinase 1 to 3´-flurothymidine monophosphate (FLT-MP) in the proliferating cell, and subsequently trapped intracellularly [39]. ^{18}F-FLT uptake has been demonstrated in a range of tumours, including lung- and colorectal cancer, malignant melanoma and non-Hodgkin's lymphoma [40–43]. Usually, uptake is low in normal brain parenchyma, providing good image contrast [44], but tracer accumulation may also occur in non-neoplastic BBB disruption, bone marrow and dural venous sinuses [45,46]. ^{18}F-FLT accumulation within brain tumours is rapid (5-10minutes), shortening the injection-to-scan time.

18F-Fluorocholine (18F-CHO) and 11C-Choline (11C-CHO)

^{18}F-CHO which was originally used in PET studies in prostate cancer, was first synthesized for brain tumour imaging in 2002 [47]. Choline is a phospholipid precursor partaking in cell membrane synthesis via phosphorylation by choline kinase (CK)[48], and integration into phosphatidylcholine (lecithin), a major phospholipid membrane component. Choline can alternatively be labelled with ^{11}C, which is biochemically identical to natural choline [49]. High physiological uptake is seen in non-tumoural structures [50], including choroid plexus, venous sinuses and the pituitary gland [32]. False positives can occur in abscesses, inflammatory granulomas, tuberculoma and some demyelinating diseases, limiting specificity [51].

18F-Fluoro-L-Dihydroxy-Phenylalanine (18F-DOPA)

18F-FDOPA (amino acid analogue) was originally developed to assess the presynaptic dopaminergic function in patients with neurodegenerative and movement disorders [52–54]. It was approved for the assessment of recurrent brain tumours in Europe in 2009, and has since been increasingly trialled for pre-operative glioma characterisation [54,55]. 18F-FDOPA uptake occurs via LAT1[27], and appears to be independent from BBB breakdown [56]. There is minimal uptake in normal cortex [57], but mild non-pathological uptake is seen in the basal ganglia, potentially impeding lesion assessment in this area.

PET imaging of glioma

Primary diagnosis

The objective of imaging is to confirm the presence of a glioma (versus other brain tumour types and non-neoplastic differentials), and to predict its grade and/or molecular subtype enabling improved prognostication. This will determine the urgency and type treatment needed (i.e. resection, radiotherapy and/or chemotherapy).

Distinction of glioma from other diseases

18F-FDG PET was the first PET tracer in brain tumour imaging [17] and its most relevant use, reflected in some recent retrospective studies [58,59], is in the distinction of CNS lymphoma from HGG and metastasis (Figure 1). In one study 18F-FDG SUV_{max} >12 had sensitivity of 100% for CNS lymphoma (specificity 71.4%) [59]. Distinctively high uptake in lymphomas have also been demonstrated in larger cohorts (n=56), although a significant number of lymphoma

patients (21%) lacked histopathological confirmation of the diagnosis [60]. Semiquantitative ^{18}F-FDG PET results may be affected by the measuring techniques, such as region of interest (ROI) placement where Wang et al [61], demonstrated higher CNS lymphoma SUVs when assessing the maximum signal area versus a non-targeted ROI placement. This study also highlighted measurement limitations in patients with multiple lesions, where T/N ratios may be more difficult to establish in cases of bilateral tumour infiltration. Furthermore, when assessing PCNSL, SUVs may be reduced following steroid administration. Despite these challenges, and no single established SUV cut-off, the current studies still suggest metabolic differences between tumour types and that a high ^{18}F-FDG uptake (reported range >12-19) is effective in distinguishing lymphoma from glioblastoma [49,51,58] (figure 2).

Further important distinctions between metastatic brain tumour and glioma have also been made using ^{18}F-FDG, where significantly higher $SUV_{mean/max}$ were found in HGG (8.57 ±2.69, 11.58 ± 3.7) compared to metastatic tumours (5.72 ± 2.15, 7.87 ± 2.73) (p<0.05) [58]. However, findings are inconsistent; in a more recent larger retrospective cohort involving metastatic brain tumours (n=52), lymphomas (n=6) and HGG (n=18), whilst all parameters including $SUV_{mean/max}$ were higher in CNS lymphomas compared to HGG (p<0.01) and metastatic lesions (p<0.05) replicating previous findings, there was no significant difference between ^{18}F-FDG uptake in HGG and metastatic tumours [62]. Groups were largely unbalanced however, and larger studies with mixed tumour cohorts are needed to validate results with other non-FDG tracers as well.

Of the amino acid tracers, ^{11}C-CMET appears to be the most commonly used in brain tumour diagnostics (figure 3); ^{11}C-CMET has similarly to ^{18}F-FDG demonstrated significantly higher

uptakes in lymphoma patients compared to glioblastomas in one retrospective study [63]. However, potential difficulties in absolute quantification with the observed 10-fold lower SUV cut-off value using ^{11}C-CMET for diffuse large B cell lymphomas (DLBCLs) (>1.17, sensitivity 100%, specificity 100%) compared to ^{18}F-FDG (>12, sensitivity 92%, specificity 86%) in a small sample (n=19), make the evidence for using ^{11}C-CMET in this context appear much less robust. Furthermore, literature evaluating ^{11}C-CMET uptake in brain metastases is scarce; in an early study with post irradiated metastatic brain tumours (n=51) and gliomas (n=26), recurrent metastatic tumours had lower L/N ratios than recurrent gliomas [64], which was further replicated in a later study [65]. However, a more recent report demonstrated no significant differences in ^{11}C-CMET uptake in gliomas and metastatic lesions [66]. Additionally, its utility appears limited as studies have mostly been undertaken in a post-treatment/recurrence context.

Amino acid tracers may be more useful in glioma diagnostics specifically, which was demonstrated in a meta-analysis assessing diagnostic performance of ^{18}F-FET in patients with brain tumours; the best diagnostic performance for glioma diagnosis was a TBR_{mean} >1.7 (sensitivity 71%, specificity 72%) and TBR_{max} >2.1 (sensitivity 65% and specificity 56%) [67]. However, only 5 studies (180 patients) were included, and TBR thresholds inconsistently defined. In a more recent meta-analysis, by the same research group, comparing diagnostic performance of ^{18}F-FET and ^{18}F-FDG PET [68], and in a subsequent study with a lager cohort of neoplastic lesions (of which 143/145 were gliomas) [69], ^{18}F-FET PET uptake appears higher in gliomas compared to non-neoplastic lesions (NNLs) (figure 4). In the meta-analysis, ^{18}F-FET was superior to ^{18}F-FDG, which could not make this distinction. Whilst these studies demonstrate the utility of ^{18}F-FET in glioma diagnostics, a caveat to the results from the meta-

analysis was that 1) limited semiquantitative data was provided (only 2/5 studies reported $TBR_{mean/max}$ values for both tracers) 2) two studies originated from same centre, and 3) few non-glial tumours were included. Observations are further challenged by an even larger glioma cohort (n=236), in which high glioma ^{18}F-FET PET positivity (89%) had limited specificity (68%) due to increased uptake in NNLs, particularly inflammatory lesions (100% were ^{18}F-FET PET positive, n=13) [11]. The reported SUV cut-offs from Rapp et al. are also problematic considering how histological grade captures malignant potential incompletely; a threshold of TBR_{max} >2.5 was reported to differentiate between neoplastic lesions and NNLs (sensitivity 57%, specificity 92%). However, the same cut-off value was also suggested for the differentiation between HGG (n=66) and LGG (n=70) (sensitivity 80%, specificity 65%) [69]. Thus ^{18}F-FET TBR_{max} < 2.5 may only be useful in potentially excluding HGG.

Less well established tracers, like ^{18}F-FDOPA, have in comparative studies with ^{11}C-MET and ^{18}F-FET exhibited almost identical uptake on visual inspection in gliomas [55,70]. Reported sensitivities are between 90%-100% for unresected gliomas and 100% for glioma recurrence [56,70]. The semiquantitative SUVs are higher for ^{18}F-FET PET studies however, which is possibly more beneficial when attempting to distinguish pathological uptake from physiological uptake. The current ^{18}F-FDOPA studies are limited by lacking negative pathology and distinctions of possible variable patterns of tracer uptake in de novo and recurrent gliomas in mixed tumour cohorts (figure 5). Similarly ^{18}F-CHO was also assessed in glioma diagnostics in a comparative study with ^{18}F-FDG and ^{11}C-MET (n=95, grades II-IV); only 13.7% of gliomas demonstrated increased uptake (T/N ratio >2) with ^{18}F-FDG, compared to 71.6% with ^{18}F-CHO and 87.4% with ^{11}C-MET [32], thus further supporting the utility of ^{18}F-CHO and amino acid tracers over ^{18}F-FDG in glioma diagnostics (figure 6). Potential benefits of using ^{18}F-CHO over

[11]C-MET in comparative studies is the low ^{18}F-CHO uptake in normal brain tissue $(SUV_{mean} 0.29 \pm 0.007$ compared to 1.25 ± 0.39 with ^{11}C-MET) [32], which improves contrast, providing significantly higher L/N ratios in tumour tissue [71]. Other prospective ^{18}F-CHO studies have found higher uptake in metastases (compared to HGG), and high LNR> 2 in peri-tumoural areas of HGGs [72,73]. Studies to date have been small however, and validation in larger cohorts are needed to fully evaluate the use of this tracer in diagnostics. Another tracer requiring further validation is ^{18}F-FLT; to date, one small mixed tumour cohort (HG tumours n=12, LG tumour n=6, NNLs n=8) demonstrated ^{18}F-FLT PET positivity on visual inspection in all high-grade tumours (100% sensitivity). However false negatives occurred in all grade II astrocytomas (n=3) [46]. In a comparative study, ^{11}C-MET was more sensitive for tumour detection, with sensitivities ranging from 87.8%-91.3% (^{11}C-MET) compared to 78.3%-83.8% (^{18}F-FLT) [45,74]. However, ^{18}F-FLT appeared sensitive (100%) again for malignant gliomas [44,74,75], and false negative ^{11}C-MET PETs were also false negative ^{18}F-FLT PETs [45,74].

Prediction of glioma cell type

^{18}F-FET may be valuable in histological subtyping where it has been demonstrated that LG oligodendrogliomas have a higher ^{18}F-FET uptake compared to astrocytomas [13] (Figure 7). In one cohort, grade II oligodendrogliomas had significantly higher uptake compared to grade II astrocytomas and grade III astrocytomas [11]. Similar observations have been made using ^{11}C-MET, where higher uptakes was demonstrated in grade II oligodendrogliomas compared to diffuse astrocytomas [32,74]. These observations may be secondary to elevated microvessel count in oligodendrogliomas, higher tumour blood volume allowing for increased amino acid uptake [76], and possibly other metabolic properties (such as increased myelin synthesis, cellular densities and rates of cell turnover) [74]. One study failed to demonstrate a higher

uptake in grade II oligodendroglial tumours (compared to grade III-IV astrocytomas) [77], whilst another study, due to large overlaps between histological subgroups, could only demonstrate a statistically significant differences in grade III tumours [78].

These studies however were based on histological grading, and PET based prediction of cell lineage is now of limited value considering that glioma molecular characteristics are in fact the most important prognostic determinants.

Glioma Grading

Diffuse gliomas fall into the WHO grades II-IV, with grade IV tumours being the most malignant. Current methods for tumour grading involve biopsy or resection, but this is not infallible. Firstly, grading can be afflicted by sampling errors, meaning the tissue obtained does not represent the most malignant portion of the sampled glioma. Secondly, a proportion of malignant (IDH$_{wt}$) gliomas will histopathologically resemble LGG but are thought to represent early glioblastoma.

In the previously discussed meta-analyses by Dunet et al. [67,68], both ^{18}F-FET and ^{18}F-FDG demonstrated significantly higher uptakes in HGG compared with LGG; suggested HGG SUV cut-offs using ^{18}F-FDG was TBR$_{mean}$ >1.4, TBR$_{max}$ >1.8, and ^{18}F-FET TBR$_{mean}$ >2.0, TBR$_{max}$ >3.0 [68]. Evidence for HGG and LGG distinction appears more robust using ^{18}F-FET, as cut-offs yielded higher sensitivity, specificity (although in the meta-analysis, there was no statistically significant difference in using these two tracers in glioma grading). ^{18}F-FET PET appears to have been examined more frequently however, as demonstrated in larger cohorts by Gempt et al. (HGG n=113) with cut-offs for HGG established at T/N$_{median}$ >2.26 (sensitivity 79%, specificity

88%) [79], and Rapp et al. (HGG n=66) TBR_{max} cut-off >2.5 (sensitivity 80%, specificity 65%) [69]. Relatively low PPV of 66% and NPV of 79% in the latter study however, still indicate the need for histological confirmation.

Higher uptakes in HGG have also, but to a lesser extent, been observed using ^{11}C-MET. One study reported highest uptake in glioblastomas (T/N ratio 5.03 ± 1.65), followed by anaplastic astrocytomas (3.03 ± 1.02) and diffuse astrocytomas (2.24 ± 0.90), and differences between groups were significant (p<0.001) [32]. Two larger cohorts have also supported this trend in tracer uptake [78][80]. However, less clear cut off values have been provided; Takano et al. used ^{11}C-MET T/N ratio >2 to discriminate HGG from LGG [81], but the sample was small (n=35) and there were high overlaps in tracer uptakes between grades. With mixed tumour cohorts, results are more difficult to interpret; in one study, there was no significant difference in uptake comparing HGG and metastases and LGG and metastases, but significant differences noted between uptakes in HGG and LGG [82]. There are even fewer studies examining ^{18}F-FDOPA in this context, although discrimination between newly diagnosed HGG and LGG have been proposed using SUV_{max} >2.72 (sensitivity 85%, specificity 89%) [83], and SUV_{mean} >2.5 (sensitivity of 70%, specificity of 90%) [84] (figure 8). Whilst there appear to be more studies reporting on the even less commonly used tracer ^{18}F-FLT in glioma grading, the pattern of uptake appears unclear; studies have reported negative ^{18}F-FLT PET in LGG [44,75], with sensitivity for detecting LGG ranging from 20-60% [74,85]. Also reported is the lack of statistically significant difference in uptakes between grades II and III [74,85] which implies that this tracer may not be useful in distinction between LGG and HGG. However, in a comparison study with ^{18}F-FDG, where 9 gliomas were evaluated, ^{18}F-FLT correlated with tumour grade and cellular proliferation, which in contrast to ^{18}F-FDG, failed to show any such

correlations [46]. Despite this, results for ^{18}F-FLT are more difficult to interpret; In one study for instance [44], only 3 LGGs were included, all of which were astrocytomas grade II, previously shown to have low tracer uptakes.

Most of these grading studies were undertaken prior to the discovery of 'early glioblastoma' (IDH wildtype gliomas) as an entity that falls into the LGGs but represents a highly malignant tumour group. Future studies might address if perhaps low tracer uptake could exclude such aggressive lesions in the lower grade stages. Variable results have been demonstrated for predicting the WHO grade of recurrent tumours using several of the PET techniques, and overall this may be unreliable, possibly due to co-existing treatment effects.

Assessment of Glioma Molecular Status

Molecular biomarkers have recently been recognised as important factors in glioma prognostication and survival, with IDH and 1p19q being key mutations. To date, few studies have assessed PET tracer uptake as potential biomarkers of molecular status in gliomas.

8 publications were identified in the search by April 2018, analysing ^{18}F-FDG and/or amino acids tracers and correlation with IDH status. Metellus et al. was unable to establish any correlation between IDH mutation and ^{18}F-FDG uptake in a small study (n=33), which included glioma grades II-III; median SUV_{max} of IDH-mutated tumours versus IDH$_{wt}$ were 2.24 and 2.15 respectively (p=0.775) [86]. Similarly, no correlations between ^{18}F-FET uptake and IDH mutation was found in a LGG cohort, which included 35 IDH mutated patients [87], or in a subsequent HGG cohort [88]. This is in contrast to a study by Vegner et al. where IDH$_{wt}$ glioblastomas (n=47) demonstrated higher ^{18}F-FET PET uptake than IDH mutated

astrocytomas (grade II-III) (TBR_{mean} >1.95, sensitivity 89%, specificity 67% and TBR_{max} >1.95, sensitivity 91%, specificity 59%) [89]. Trends in dynamic ^{18}F-FET PET have also been explored, where IDH mutated LGG tumours have typical increasing time activity curves (TAC) as opposed to homogenously decreasing TAC, in which only 25% had IDH mutation (p<0.001) [90]. These observations are supported by IDH_{wt} glioblastomas demonstrating faster time to peak (TTP) where TTP<30 had sensitivity 72% and specificity 81% (p<0.01) [89]. The evidence from one ^{11}C-MET study is less convincing as IDH_{wt} gliomas (n=109, grades II-IV) appeared to have significantly higher uptake on initial analysis, but on evaluation of glioblastomas (grade IV) only, IDH_{wt} glioblastomas did not exhibit higher uptakes compared to IDH mutated glioblastomas (SUV_{max} 6.2 versus 3.7, p=0.288 and SUV ratio 3.7 versus 2.6, p=0.176) [91]. In contrast, an ^{18}F-FDOPA study involving 43 patients (IDH mutated n=34 , IDH_{wt} n=9) showed higher tracer uptake in IDH mutated tumours compared to IDH_{wt} (TN SUV_{max} ratios 1.6 versus 1.2, TS SUV_{max} 0.9 versus 0.6, p<0.05) [92]. However, the most recent cross-sectional ^{18}F-FDOPA study could not replicate these findings and suggested that ^{18}F-FDOPA uptake was not significantly different dependent on IDH status [93].

A few of these studies have also assessed 1p/19q co-deleted tumours and correlation with tracer uptake. ^{18}F-FET uptake appears high in 1p/19q-codeleted tumours (TBR >2.0, sensitivity 100%, specificity 6.7%), in keeping with previous findings, suggesting that a low uptake could exclude the possibility of this marker with high probability [87]. On the other hand, no correlation was found between ^{18}F-FDOPA uptake and 1p/19q co-deleted tumours [92]. The small volume of studies and retrospective nature make it difficult to draw any conclusions about the utility of PET in molecular glioma assessment currently, and further multi-centre studies are needed to validate use in clinical practice.

Post treatment imaging of gliomas with PET

Depending on gliomas subtype, standard treatment may involve maximal resection followed by radiotherapy (RT) with or without adjuvant chemotherapy with PCV (procarbazine, lomustine, vincristine) regimen or temozolomide (TMZ) for glioblastoma. RT planning relies on neuroimaging where targets have to be precise to minimise radiation damage to healthy tissues. Prior to treatment, one aim of PET could be to improve delineation of metabolically active lesions not necessarily evident on structural MRI [48]. Post treatment, patients undergo MRI surveillance for tumour recurrence (which has a high incidence due to infiltrative nature)[48]. The occurrence of therapy effects in the form of pseudoprogression (PsP)[94] and radiation necrosis (RN)[95] continues to severely hamper the post-treatment assessment, particularly in glioblastoma. PP is thought to represent a subacute (within 12 weeks) post-treatment reaction; Typically, there is increased enhanced lesion and oedema on MRI, mimicking tumour progression and recurrence. However, it does not require treatment and undergoes spontaneous resolution [96]. RN tends to be a later complication, manifesting within 6 month after standard RT, but can occur within months to years [94]. RN is also associated with oedema, contrast enhancement and mass effect on MRI [97], usually in close vicinity to the original tumour [48]. Conventional imaging does not allow for discrimination between PP, RN and recurrence [96], due to exhibiting similar MRI features. Although advanced MRI techniques provides additional information, no single technique permits a completely reliable distinction or is able to identify the volume of viable tumour [98]. PET may assist in discriminating these entities, which is crucial considering that therapeutic strategies and prognosis are very different. It is controversial which PET tracer is superior in distinguishing recurrence from RN.

The most reported tracers appear to be ^{18}F-FDG and ^{11}C-MET; one meta-analysis including 26 studies and 780 treated patients, suggested that ^{18}F-FDG and ^{11}C-MET had moderately good overall accuracy for diagnosing glioma recurrence. ^{18}F-FDG assessments were mainly visual, whereas for ^{11}C-MET PET there was also semi-quantitative assessment to support this [99], (figure 9). Recurrence appeared visually hypermetabolic with both ^{11}C-MET- and ^{18}F-FDGPET in another small retrospective study, although no semi-quantitative differences between recurrence and RN groups using either tracer was found [100]. This study was limited by its small sample (recurrence n=7, RN n=3), with only 3 histopathological confirmation of recurrence. Further semiquantitative SUVs and cut-offs for recurrence and RN distinction have, however, been suggested in other cohorts also using ^{11}C-MET; In 26 glioma patients, Terakawa et al. found that an L/N_{mean} >1.58 provided the best sensitivity (75%) and specificity (75%) for glioma recurrence [64]. Slightly higher L/N ratios in recurrence were reported in a multi-centre study including 31 glioma patients (L/N_{mean} 1.7 ±0.8 versus RN L/N_{mean} 1.3 ±0.41, p<0.02) [66]. In a larger comparative study with 50 patients post-resection and RT for malignant glioma, ^{11}C-MET PET was superior in differentiating glioma recurrence from RN compared to ^{18}F-CHO and ^{18}F-FDG. They reported ^{11}C-METcut off L/N >2.51 (sensitivity 91%, specificity 87.5%) for detection of recurrence [101]. Again, ^{18}F-FDOPA has been used to evaluate recurrence to a much lesser extent but in a prospective study with 21 recurrent gliomas ^{18}F-FDOPA was superior to ^{18}F-FDG in evaluating recurrence, and ^{18}F-FDOPA T/N ratio of >1.3 had sensitivity 100% and specificity 85.7% [102], (figure 10). This was the only study providing cut-off values, but on visual assessment of 9 recurrent gliomas in another retrospective study, all were found to be ^{18}F-FDOPA positive, in contrast to only 6 being positive on ^{18}F-FDG PET [103].

Evidence for tracers other than ^{18}F-FDG and ^{11}C-MET is sparse. The[18]F-FDOPA studies are limited by the small number of patients included and lack for quantitative data for comparison.

Whilst ^{11}C-MET may be beneficial for semi-quantitative assessment in recurrence and to aid in the distinction from RN, there is a lack of established cut-off values (figure 11); The range of ^{11}C-MET uptake values reported may reflect more complex metabolic events taking place. In RN, tracer uptake may occur through passive diffusion through a disrupted BBB, in contrast to in tumour recurrence, where tracer transport is active across cell membranes of proliferating tumour cells. Furthermore, RN may also have increased biological activity, due to inflammatory reactions and reactive gliosis post treatment. Mixed pathology, with RN and residual/recurrent tumour also complicate making the distinction between recurrence and RN further. Future validation of the current observations is needed in larger prospective multi-centre studies to provide larger quantitative data sets for comparisons and evidence for utility in clinical practice.

Future Developments in Glioma Imaging with Gallium-68 and Novel Tracers

[68]-Ga

Overexpression of PSMA (prostate specific membrane antigen) in neovasculature in solid tumours has been the underlying rationale for using gallium-68 labelled tracers such as ^{68}Ga PSMA-11 in tumour imaging. With limited availability of amino acid tracers, gallium-68 as a radionuclide for PET imaging has been growing in the last decade, but most commonly used in prostate cancer still. The expression of PSMA in glioblastoma has been demonstrated however [104,105], and the limited data to date suggest that PSMA expression vary with glioma grade. Additionally, in mixed tumour cohorts, metastatic brain tumours have less intense PSMA staining compared to gliomas [105], an important observation for future studies evaluating utility of PSMA targeted PET tracers. Furthermore, in a small comparison study with ^{18}F-FDG,

GA PSMA-11 could identify all cases (n=4) of glioma recurrence with the advantage of better contrast images due to absence of physiological uptake [106].

TSPO tracers

The 18-kDa mitochondrial translocator protein (TSPO) has shown to be upregulated in glioma, correlating with cell proliferation. Uptake of novel selective radiotracers for this protein (11C-(R)PK11195) appear significantly higher in HGG compared to LGG [107], with the suggestion that TSPO uptake may be predictive of anaplastic transformation in glioma [108]. In a recent pilot study, including 11 patients with either new IDH$_{wt}$ glioma diagnosis or recurrence (glioblastomas n=10, anaplastic astrocytoma n=1), using third generation tracer 18F-GE-180 (with a longer half-life), there was remarkably high tumour-to-background contrast. Additionally, uptake was seen in areas without contrast enhancement on T1-weighted MRI [109]. This suggests potential for use in further evaluation of tumour extent, but TSPOs exact function in neoplastic cells need to be addressed in future studies.

Hypoxia Imaging

Other novel tracers include hypoxia imaging agents such as ^{18}F-fluoromisodazole (^{18}F-FMISO) , which passively diffuses into cells with reduced tissue oxygen partial pressures and is trapped by nitroreductase enzymes [110], leading to accumulation in hypoxic viable cells but not dead necrotic cells [111]. High uptakes have been found in HGG but not in LGG, and one study demonstrated a significant relationship between uptake and expression of VEGF-R1, a marker of angiogenesis [112]. Although mainly used in the pre-clinical setting, summarised by Bell et al. [113], and in other non-neurooncological settings [111], ^{18}F-FMISO may have potential in

assessment of treatment response in glioblastoma, where higher measures of hypoxia prior to RT have been associated with shorter time to progression and reduced survival [114].

Synthetic Amino Acid Tracers

[18]F-Fluciclovine (FACBC) is a new synthetic amino acid (1-aminocyclobutanecarboxylic) tracer labelled with [18]F. Similar to other amino acid tracers discussed, the accumulation in cells reflect amino acid metabolism, and accumulation is normally high in glioma with low uptake in normal brain tissue. Additionally, there is low uptake in inflammation. Comparable to ^{11}C-MET, FACBC has been more sensitive and effective than T1-weighted MRI in detecting glioma extent and response to treatment [115]. This was replicated in a recent phase IIb multi-centre clinical trial with 40 glioma patients [116,117], suggesting its ability to improve tumour delineation aiding resection with potential survival benefit.

Summary of Current Recommendation for PET in Glioma

The use of ^{18}F-FDG in neuro-oncology has declined due to several limitations outlined previously. Current data favour use of acid tracers over ^{18}F-FDG PET in glioma diagnostics, but Gallium-68 and more novel tracers need further validation in larger cohorts and comparisons studies. Recommendations for PET-CT in the UK reflect the literature findings where ^{18}F-FDG is the primary tracer for lymphoma staging, assessment of remission and to guide treatment response. For glioma imaging, the recommendations appear slightly outdated as ^{18}F-FDG is indicated in grading, identification of suspected relapse and assessment of HGG transformation in LGG. Although, amino acid tracers ^{11}C-MET and ^{18}F-FET are recognised as superior for tumour extent assessment compared to ^{18}F-FDG, indications for use are restricted to grading and tumour extent in some glioma patients for staging or suspected recurrence to target biopsy

and treatment planning [25]. RANO (Response Assessment in Neuro-Oncology) has highlighted the limited specificity of ^{18}F-FDG in glioma diagnostics due to the considerable uptake overlaps seen between tumour types, as well as difficulties in distinction between glioma and NNLs. They recommend amino acid PET for any diagnostic uncertainty as well as in biopsy and surgical planning (to enable better identification of malignant foci and tumour extent), RT planning and assessment of treatment response [118]. Other tracers have limited applications, with ^{18}F-FDOPA indicated in neuroendocrine tumours (NETs), and Choline and gallium tracers being preserved for metastatic prostate cancer only [25]. Clinical applications are further summarised in table 1.

Conclusion

PET in conjunction with structural MR imaging data appears valuable in selected oncological settings to identify metabolically active glioma tissue. Background physiological glucose uptake makes ^{18}F-FDG as the most widely available tracer less reliable. Based on the hypothesis that amino acid transport is upregulated in tumour cells, high tracer uptake has been demonstrated in several glioma studies. As such, amino-acid PET could support the distinction of glioma and non-glial tumours, grading and molecular subtyping where standard tests remain inconclusive. Amongst potential indications, PET may be most helpful for the identification of recurrent glioblastoma, which remains challenging even with advanced MRI techniques. Standardisation of diagnostic tracer use and threshold values will be important to maximise clinical utility in the future.

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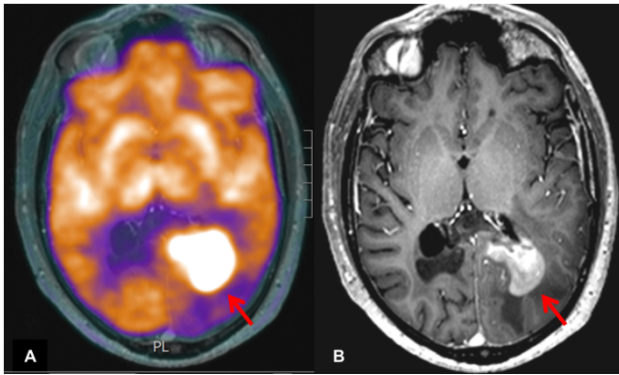
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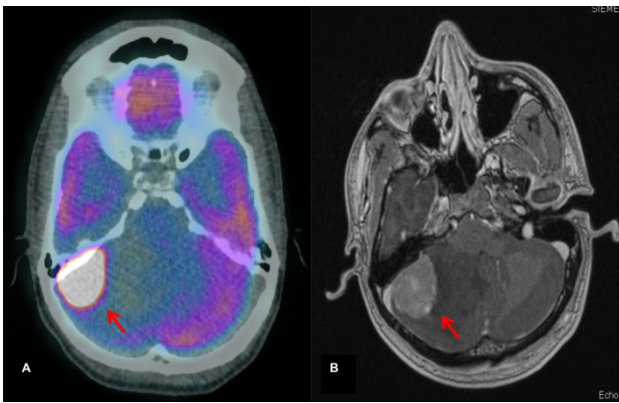
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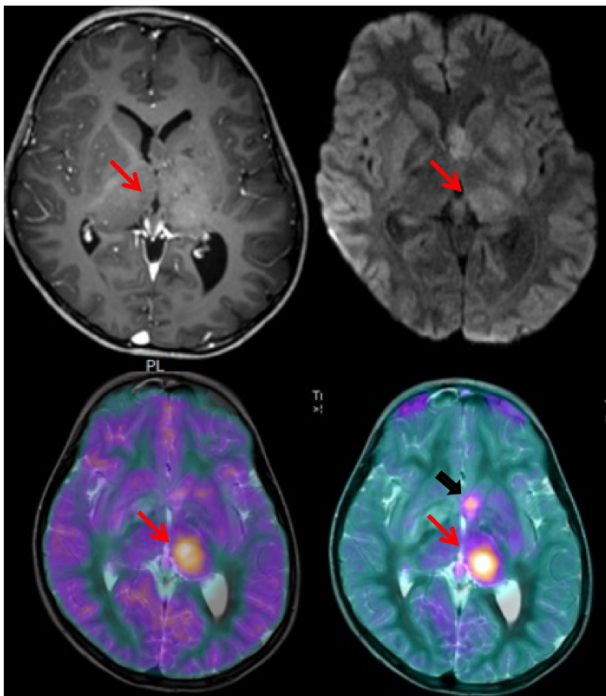
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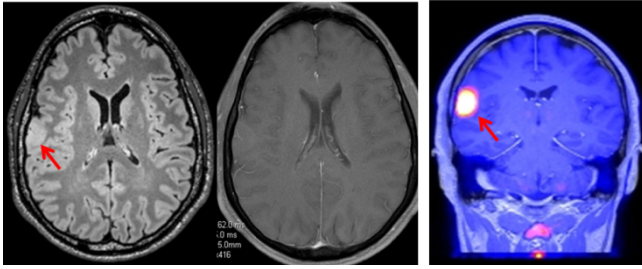
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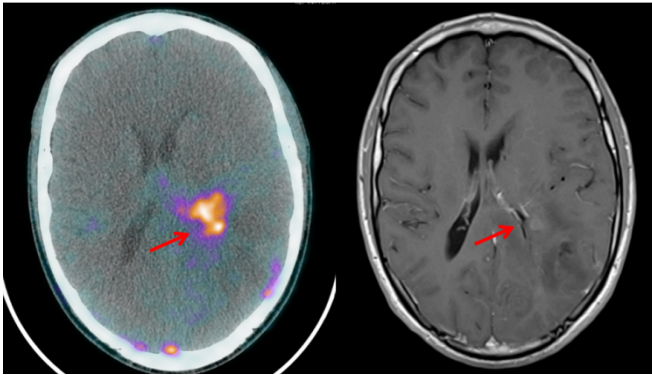
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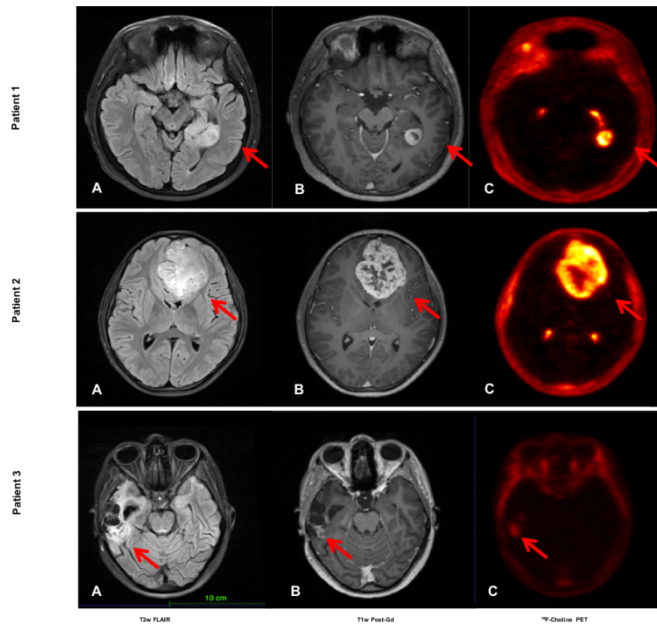
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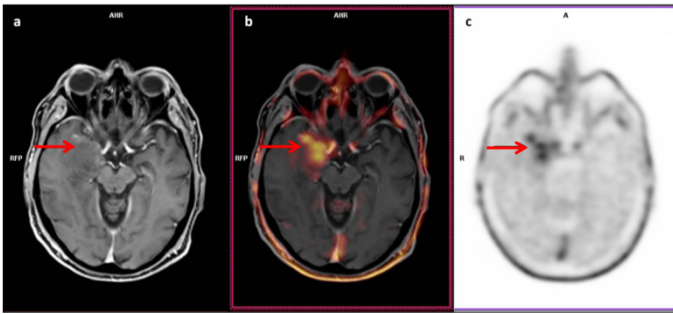
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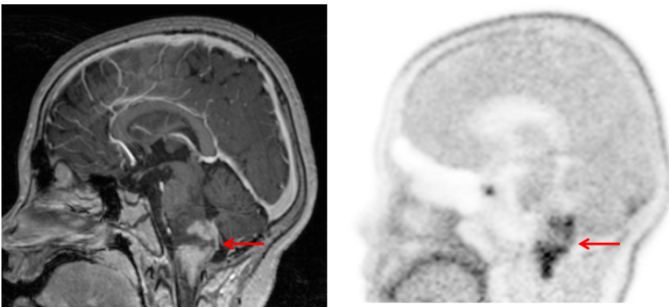
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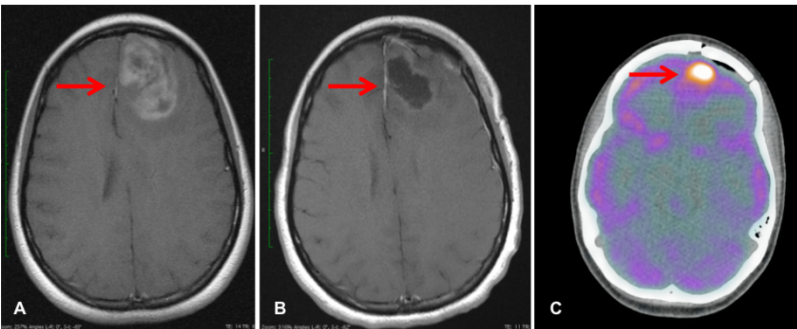
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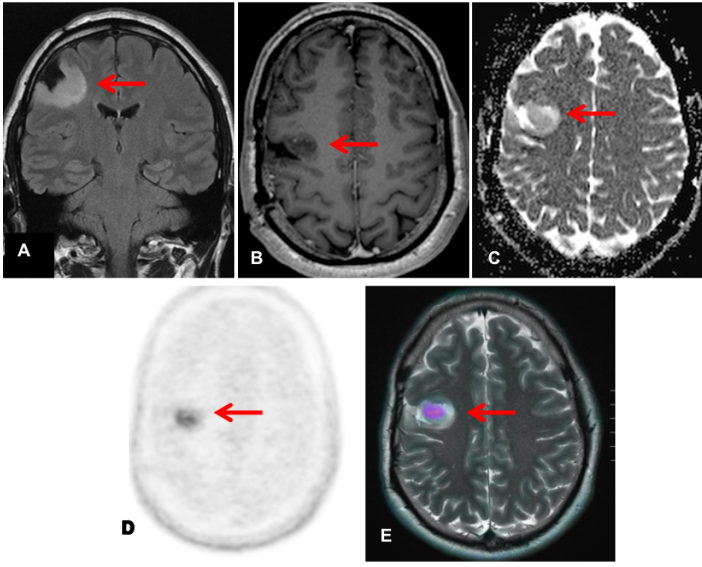
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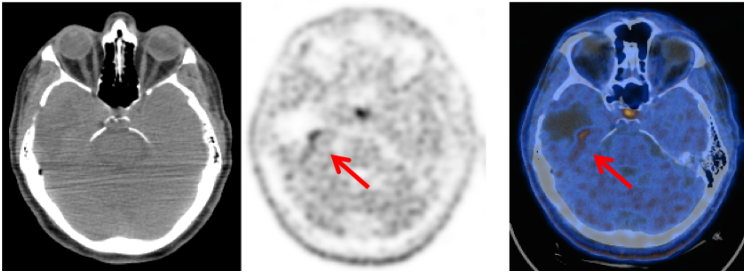
Figure 11.

Figure legends

Figure 1 A, B: Patient with CNS lymphoma where axial fused ^{18}F FDG PET/MR (**A**) and post contrast T1WI (**B**) demonstrate intense increased FDG uptake in the periventricular region of the posterior horn of the left lateral ventricle (**A**, *arrow*) which corresponds to an enhancing lesion on the post contrast MR (**B**).

Figure 2 A, B: Patient with previous lymphoma completed chemotherapy 2 months prior, presented with cerebellar signs and MRI showed a right cerebellar mass. Axial fused ^{18}F FDG PET/CT (**A**) and post contrast T1WI (**B**) show intensely avid –enhancing right cerebellar lesion (arrows) in keeping with relapsed CNS lymphoma.

Figure 3: Patient with a non-enhancing left thalamic HGG (post Gadolinium T1WI, top left) showing mild restricted diffusion (b1000 image top right, ADC map not shown). FDG PET (bottom left) shows intense metabolic activity in the left thalamus but 11C-MET PET (bottom right) clearly demonstrates presence of viable tissue also in the anterior commissure (black arrow).

Figure 4: 50-year-old patient who underwent PET/MRI for tumour diagnosis, delineation and grading. MRI (FLAIR (A) and T1WI post contrast (B)) showed a non-enhancing tumour in the right temporal hemisphere. FET PET demonstrated focus, SUV max 7.6. Following ultrasound guided biopsy, histopathological diagnosis of anaplastic oligoastrocytoma WHO III.

Figure 5: A patient with (A) F-DopaPET/CT showing intense uptake in a minimally enhancing (B, post contrast T1WI) high grade glioma (arrows)

Figure 6: Axial T2W FLAIR **(A)**, axial post contrast T1WI **(B)** and axial ^{18}F-Choline PET **(C)** in Patients 1-3.
Patient 1: 17 year old patient with grade I pilocytic astrocytoma demonstrates increased [18]FCholine uptake in the enhancing component **(C)** of the tumour.
Patient 2: 18 year old patient with grade I Schwannoma demonstrates a high intensity left frontal lobe mass (**A**), with peripheral enhancement and central non-enhancing area (**B**) which corresponds to increased [18]FCholine uptake in the enhancing component (**C**).
*Patient 3***:** 21 year old patient with suspicious recurrence from glioblastoma. T2 FLAIR (**A**)demonstrates high signal in the surgical cavity of right temporal lobe (arrow) with areas of susceptibility artefacts; B shows minimal enhancement at its posterior-lateral component (*arrow*), that corresponds to mildly increased [18]FCholine uptake.

Figure 7: 54-year-old female patient with suspicious right temporal glioma (arrows) on axial post contrast T1WI **(a),** fused ^{18}F-FET PET/MRI **(b)** and ^{18}F-FET PET **(c)**. ^{18}F-FET PET showed an area of increased radiopharmaceutical uptake corresponding to the anterior portion of the cerebral lesion, suggestive of HGG. This was confirmed on ^{18}F-FET PET -guided biopsy.
Courtesy of Dr G. Treglia Oncology Institute of Southern Switzerland, Bellinzona, Switzerland

Figure 8: 24-year-old female patient with suspicious midbrain HGG (arrows) on sagittal post contrast T1WI **(a),** and ^{18}F-DOPA PET **(b)** scan. Both MRI and PET show an area of increased contrast and uptake corresponding to tumour.

Figure 9 A-C: Patient diagnosed with glioblastoma where axial post contrast T1WI (**A, B**) and axial fused FDG PET/CT (**C**) demonstrated an enhancing left frontal lobe mass. Follow up post-operative MR imaging shows post-operative changes in the left frontal lobe with no convincing enhancing residual tumour (**B**). Additional functional imaging with FDG PET/CT shows an avid focus in the left frontal lobe **(C)**, consistent with active residual disease.

Figure 10 A-D: Patient with previously operated right frontal lobe HGG, with subsequent 4 years of stable post op MR appearance. Coronal T2W FLAIR (**A**), axial post contrast T1WI (**B**), axial ADC map (**C**), axial ^{18}F DOPA PET (**D**) and axial fused ^{18}F DOPA PET/MR (**E**) demonstrates a high signal, non-enhancing area in the right frontal lobe (**A, B**) with mildly facilitated diffusion (**C**). Further imaging with ^{18}F DOPA shows increased tracer uptake in the right frontal lobe tumour (**D, E**), consistent with active residual disease. The patient had further treatment 2 weeks, demonstrating active tumour which was completely excised.

Figure 11: Patient with previous astrocytoma grade III, where MET-PET shows the presence of a small focus of faint uptake (SUVmax 2 T/B ratio 1.3) in the right temporal lobe (arrows). The finding is suspicious for local recurrence and requires monitoring. (Case courtesy of Dr. Castellucci, University St. Orsola Malpighi, Bologna, Italy).

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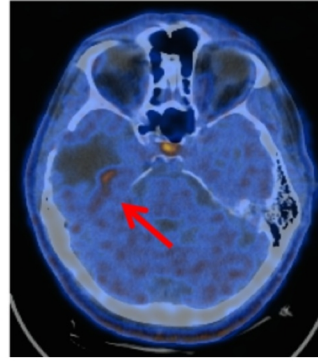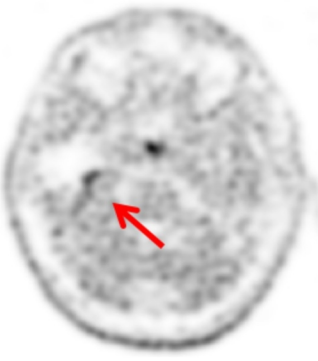
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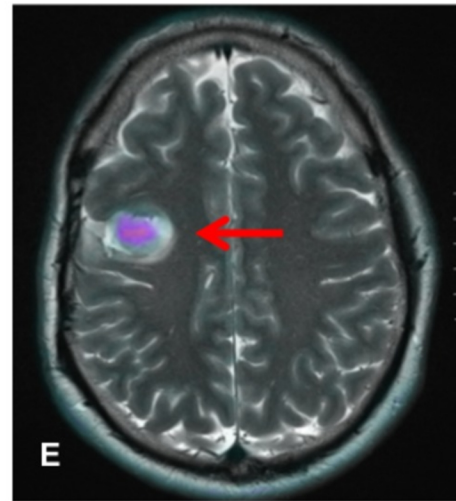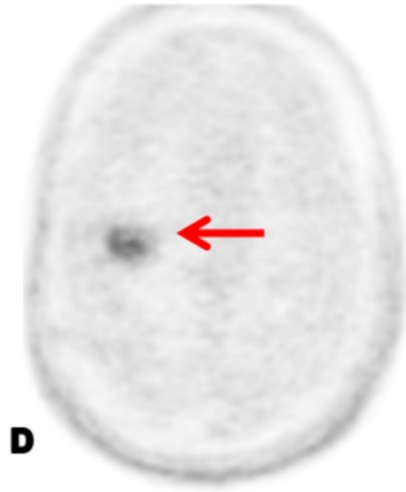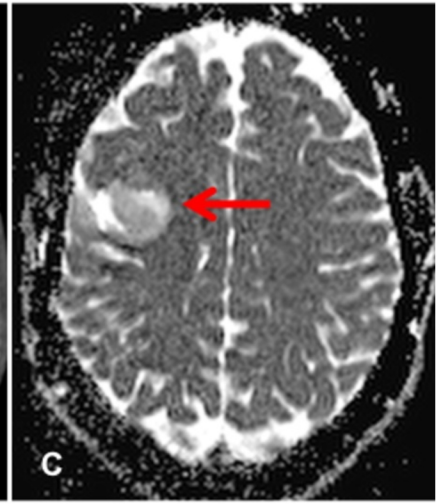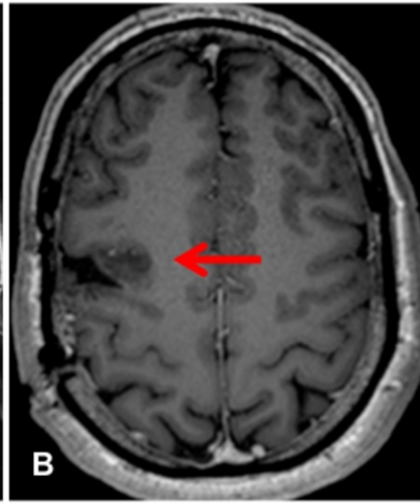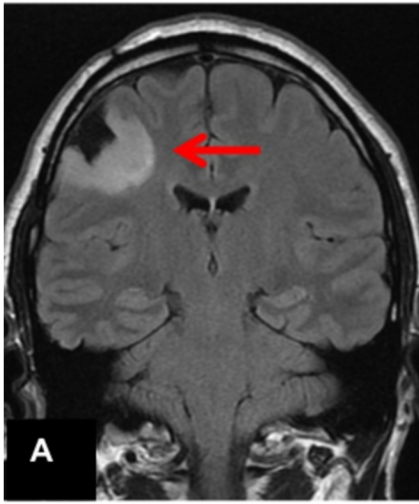
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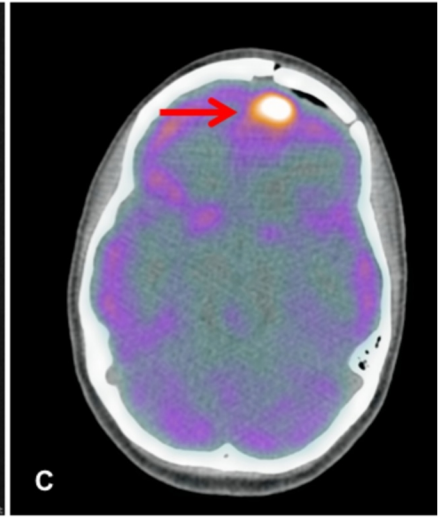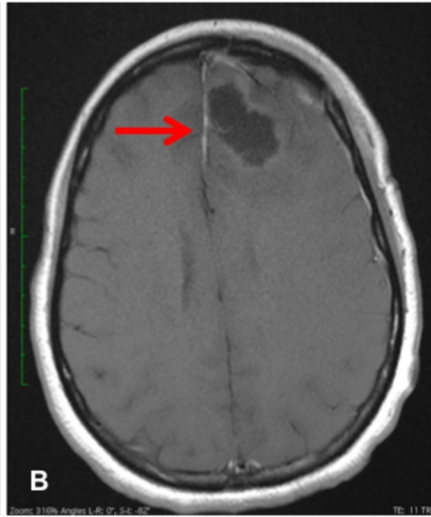
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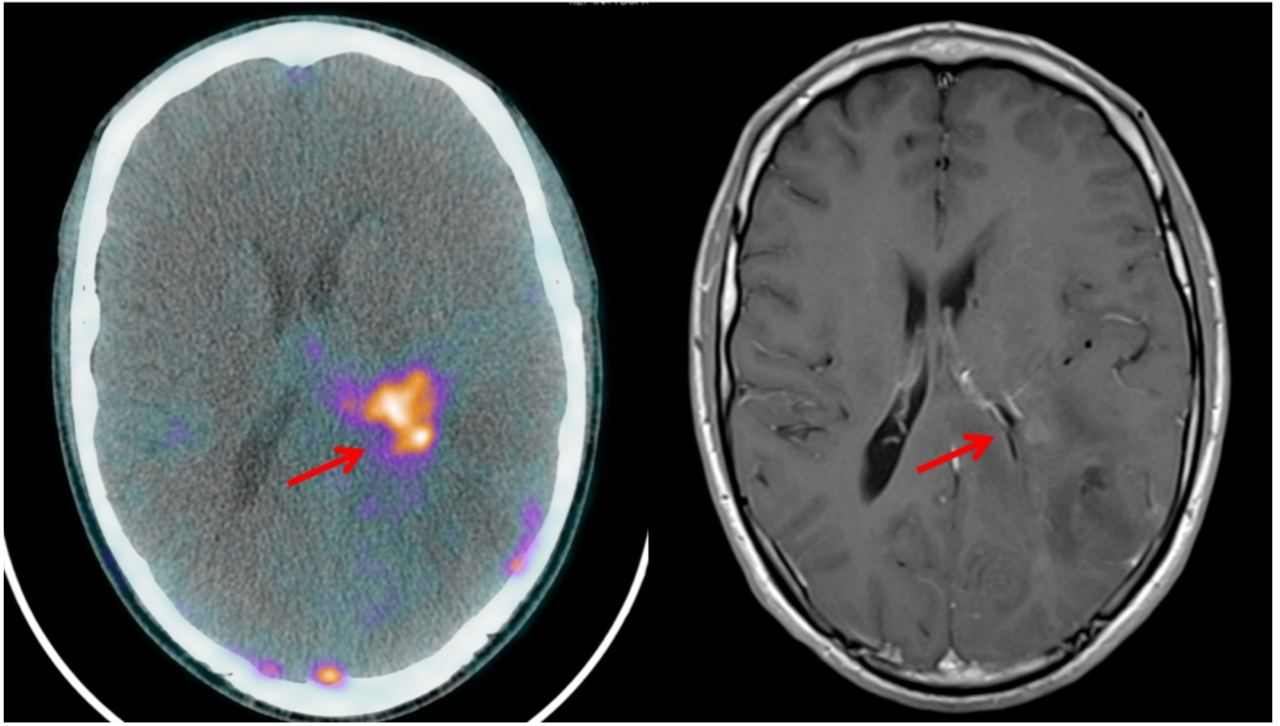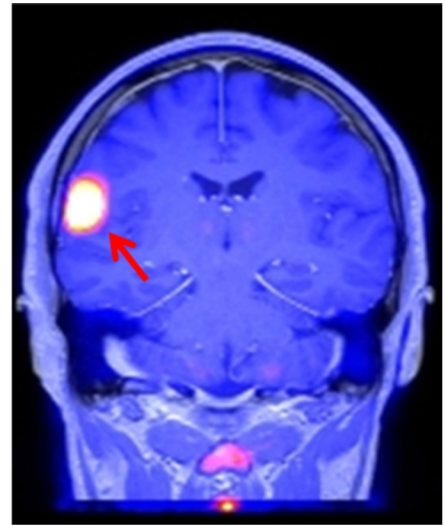File name: Figure8.png
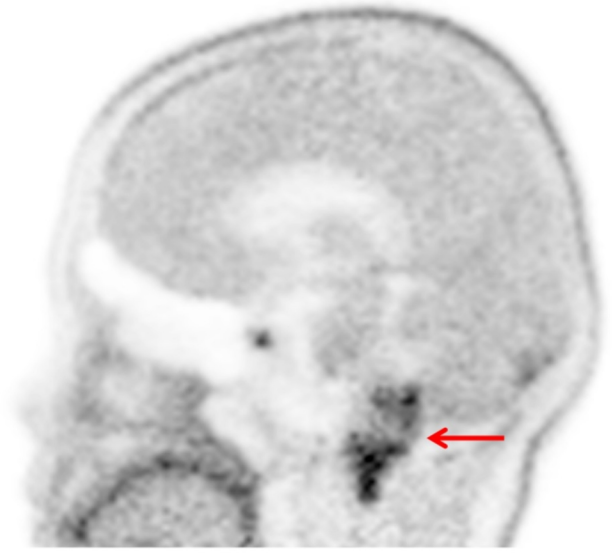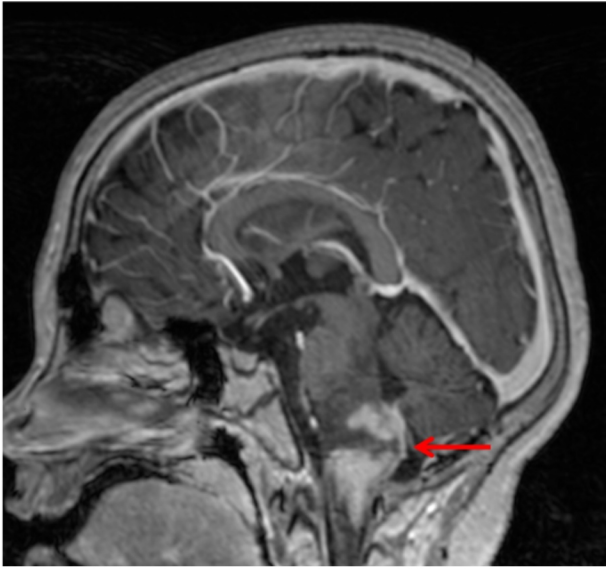
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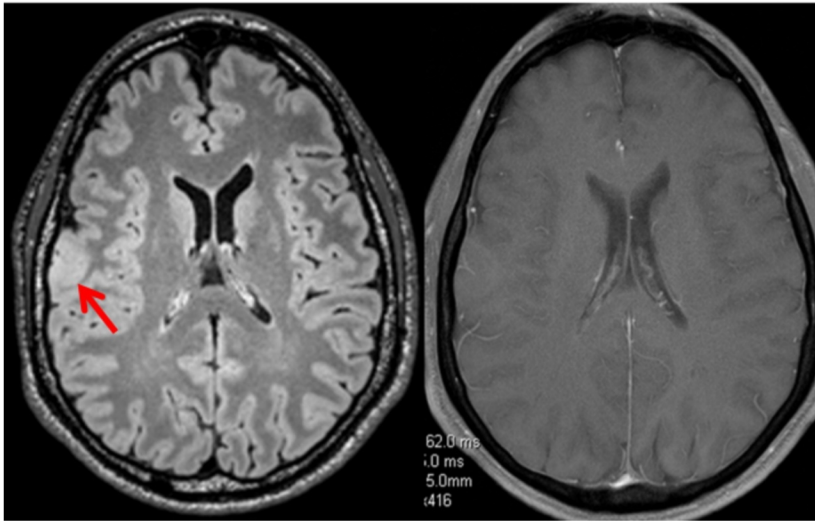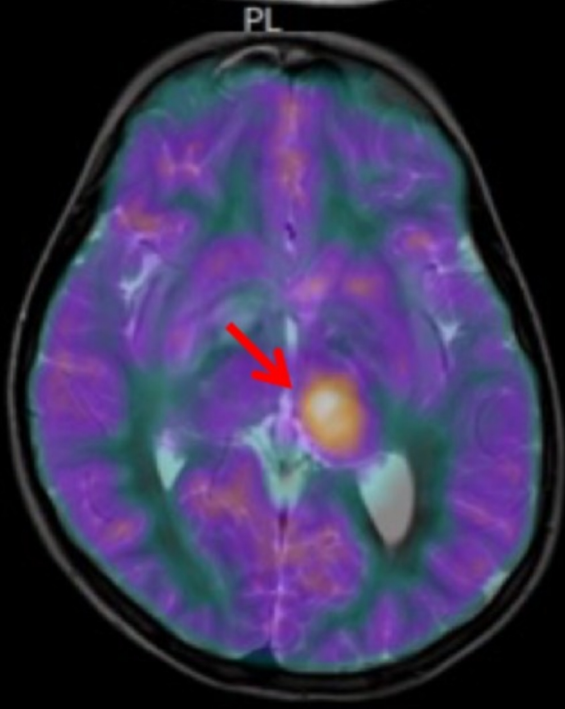File name: Figure7.png
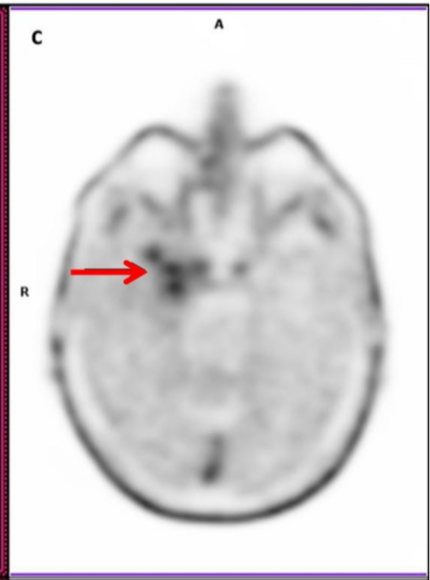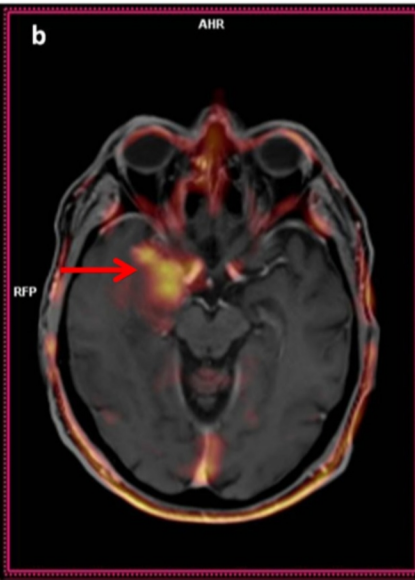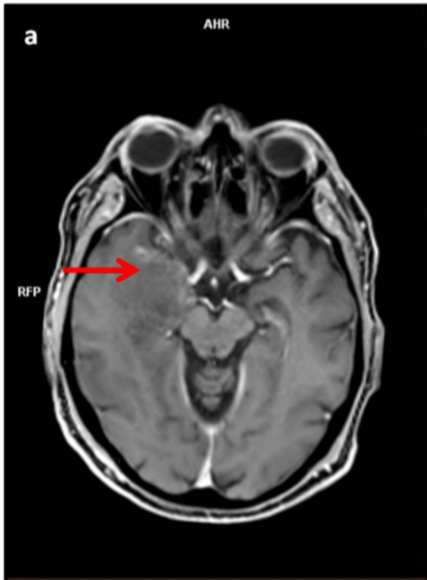
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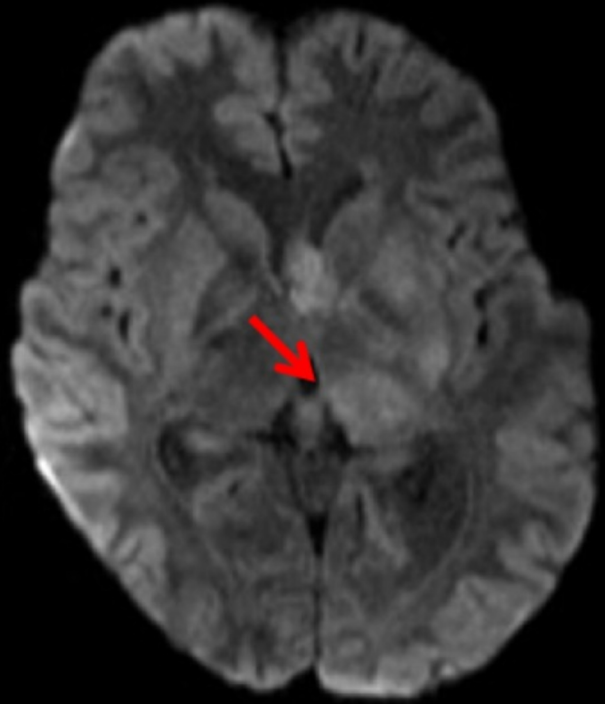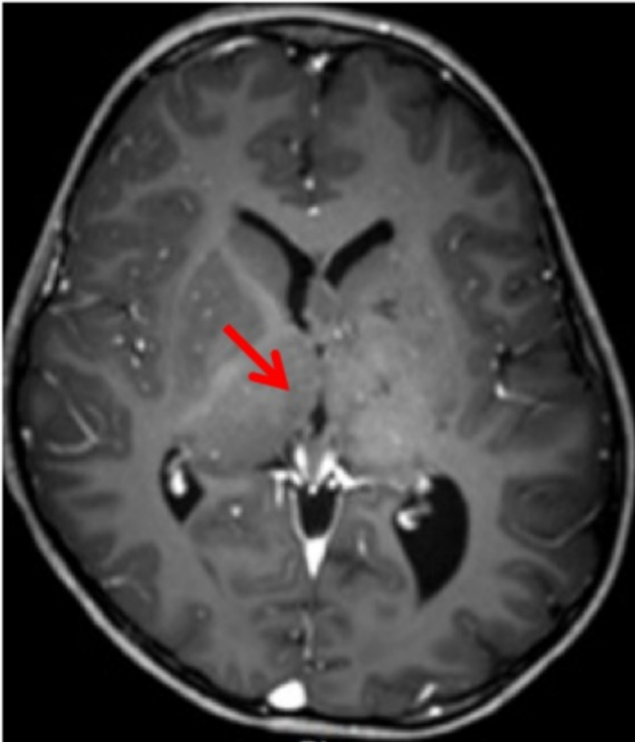File name: Figure5.png
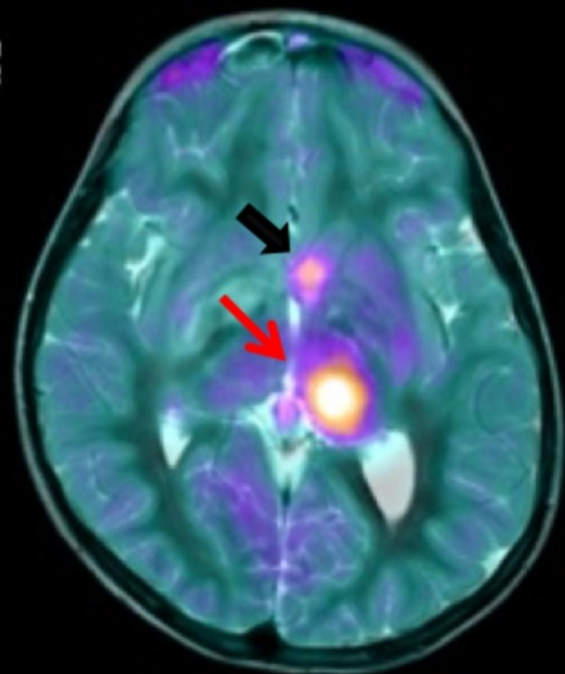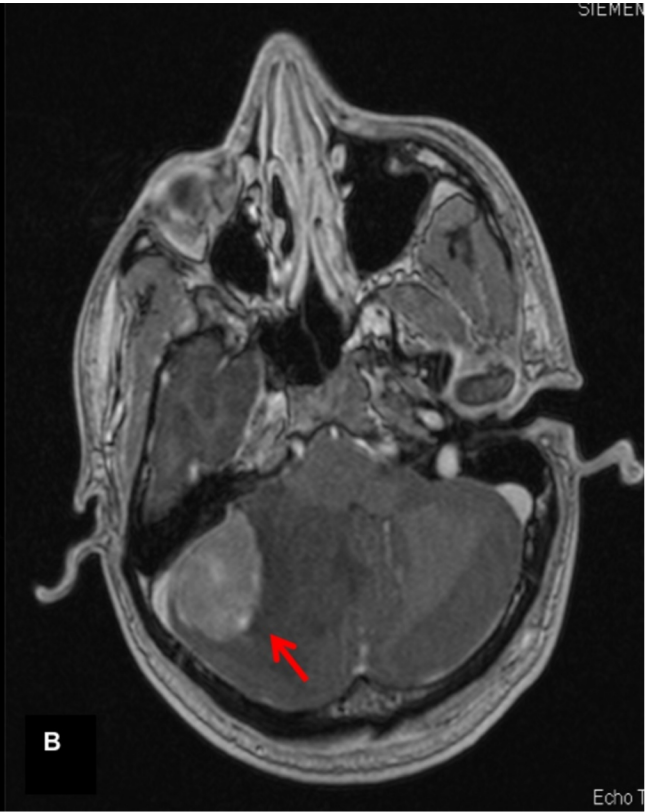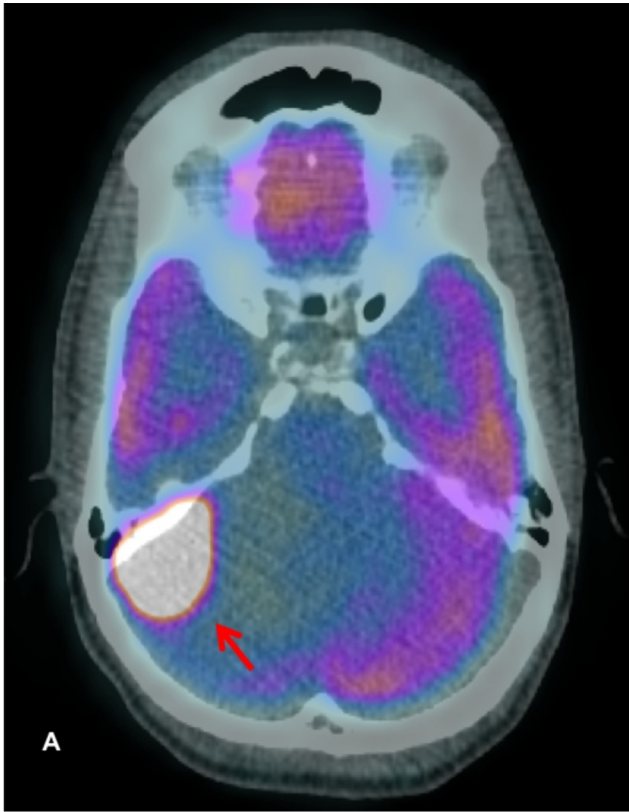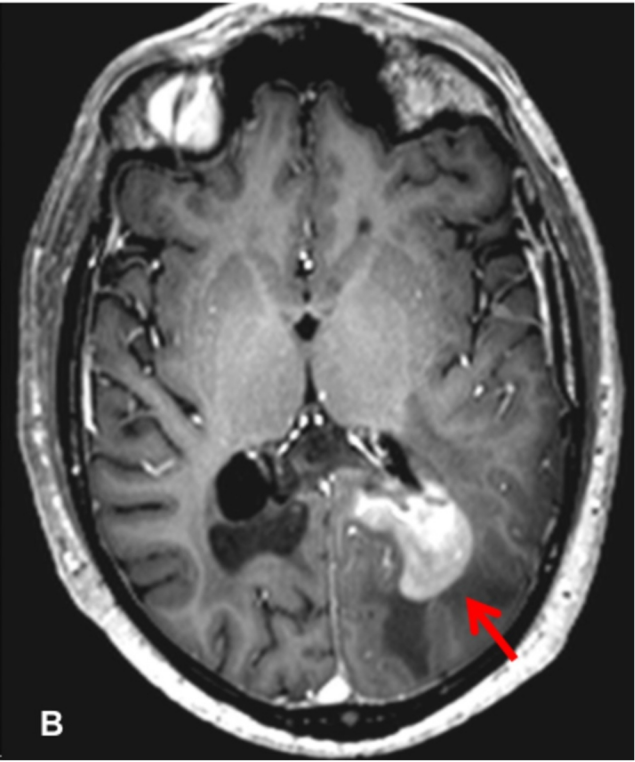
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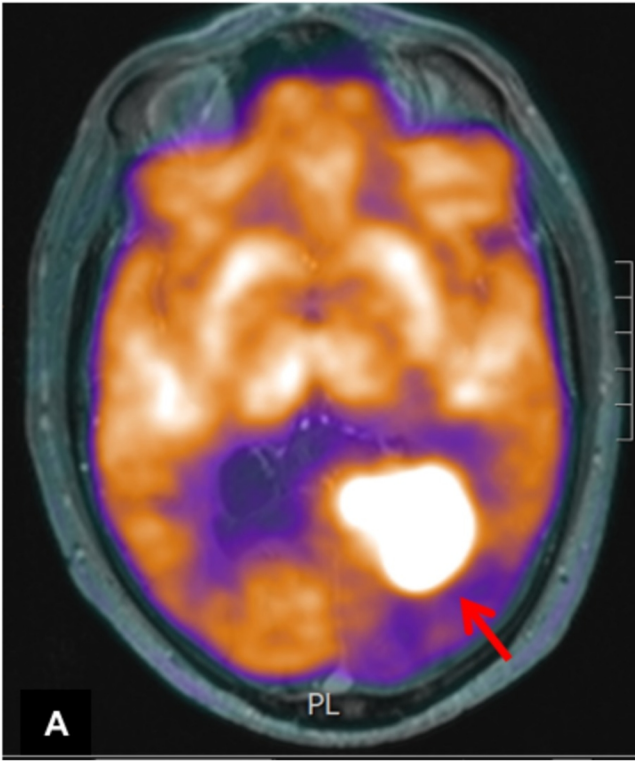File type: Figure
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Table 1: Summary of PET tracers in glioma imaging

| PET tracer	Advantages	Limitations	Clinical Applications in Glioma				
			Brain Tumour Diagnostics	Glioma vs NNLs	Glioma Grading	Recurrence vs Treatment Related Changes	Assessment of Treatment Response
^{18}F-FDG	Long half-life (110mins) Widely available	High physiological uptake in brain tissue High uptake in inflammation (macrophages)	Tracer of choice for diagnosis and treatment monitoring of PCNSL.	Recommended for differentiating tumour from atypical infection in immunocompromised patients with indeterminate lesions on MRI/CT.	Higher uptake in WHO grades III/IV, but limited value due to significant overlap in uptake values.	Used in suspected relapse for surgery/RT planning, but only moderate additional value to MRI for differentiation between malignant recurrence and RN due to low specificity.	Decrease in ^{18}F-FDG uptake correlates with treatment response.
[11]C-MET	Convenient production with high radiochemical yield Low uptake in normal brain tissue	Short half-life (20mins), with no use in dynamic studies Requires on-site cyclotron Several metabolic pathways		Higher diagnostic accuracy than MRI alone. Superior to ^{18}F-FDG in defining tumour extent.	Higher diagnostic accuracy than MRI alone. Assessment of tumour grade and extent in some patients with glioma for staging and recurrence to target biopsy and plan treatment.	Higher diagnostic accuracy than MRI.	Superior to MRI alone. Decrease in uptake, associated with treatment response in gliomas WHO grades III/IV.
^{18}F-FET	Long half-life (110mins) Dynamic PET aquisition Possible measure of amino acid transport rate	Slow renal elimination False positives in astrocytosis, MS and ischaemia False negatives can occur in gliomas			Dynamic ^{18}F-FET uptake improves diagnostic accuracy between WHO grades I and WHO grades III/IV.	Higher diagnostic accuracy than MRI. May facilitate diagnosis of pseudoprogression in glioblastoma within 12 weeks following completion of chemoradiotherapy.	
^{18}F-FLT	Long half-life (110mins) Rapid tracer accumulation (5-10mins) followed by stable retention Low uptake in normal brain tissue	Uptake facilitated by BBB breakdown False negatives in LGG False positives in infarction, MS, radiation necrosis					
^{18}F-CHO	Long half-life (110mins) Rapid clearance from circulation	High uptake in choroid plexus, venous sinuses and pituitary gland False positives in abscesses, inflammatory granulomas, tuberculoma, demyelinating diseases False negatives may occur in small tumours					

18F-FDOPA	Long half-life (110mins) Measure of amino acid transport rate	Rarely used in glioma imaging High uptake in basal ganglia	Higher diagnostic accuracy than MRI alone.	Superior to MRI alone.

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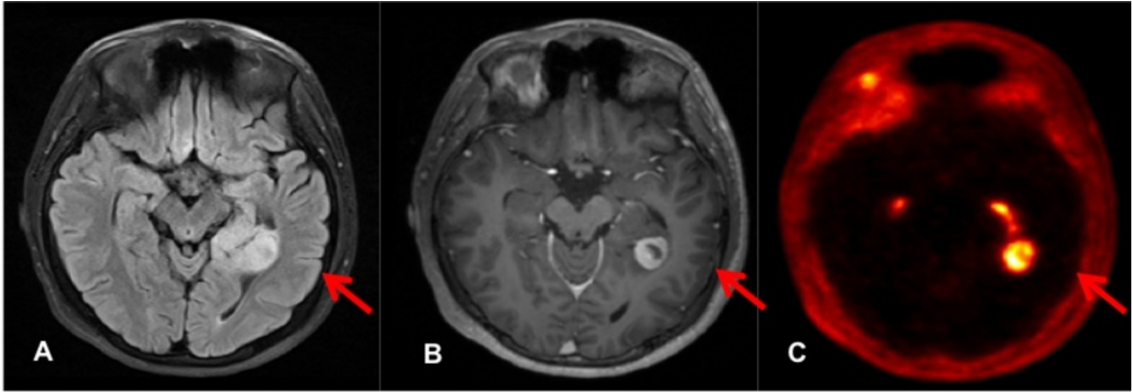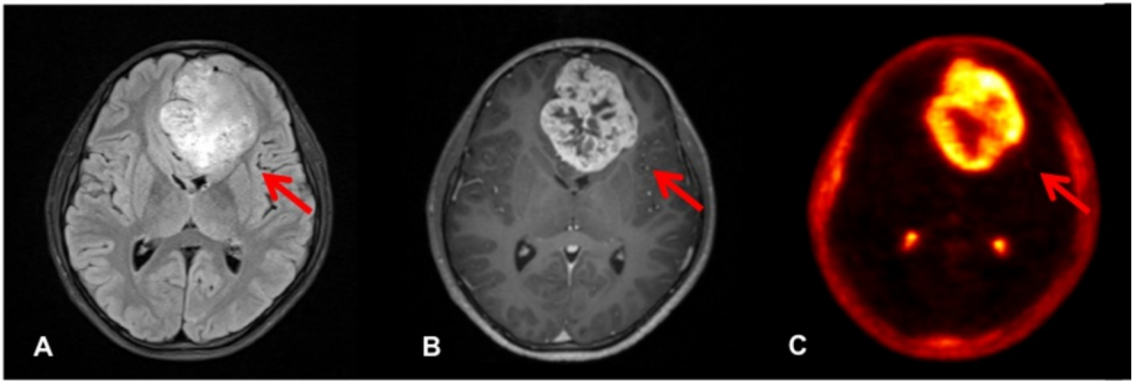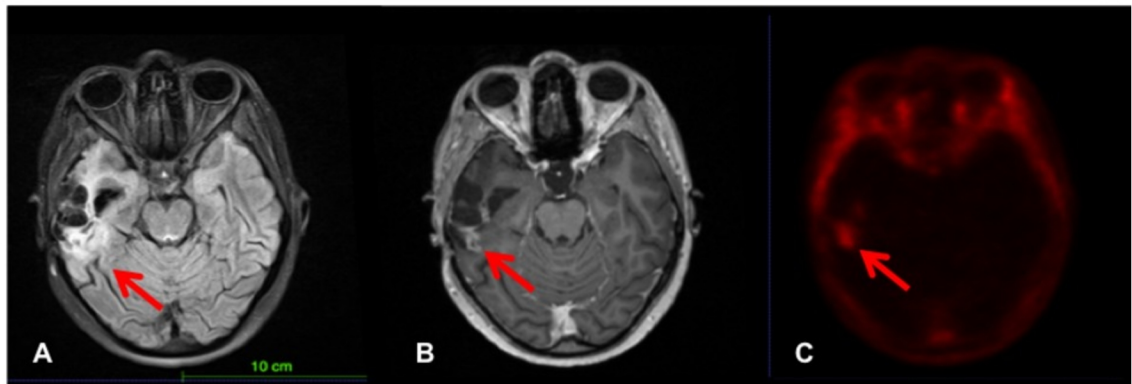
Patient 1		
Patient 2		
Patient 3		
T2w FLAIR	T1w Post-Gd	18F-Choline PET