Combined Positron Emission Tomography / Magnetic Resonance Imaging (Combined PET/MRI) in Brain Glioma Imaging

Abstract

Gliomas are the most common primary brain tumours in children and adults, consisting of a heterogeneous group of neoplastic diseases arise from the supporting cells of the central nervous system (glial cells). Their histopathological and molecular characteristics vary considerably as well as their management and prognosis. Conventional gadolinium-enhanced Magnetic Resonance Imaging MRI is considered the primary imaging modality for primary work up and follow up of patients with gliomas. Still, this modality has few limitations, especially in differentiating high from low grade tumours, as well as in distinguishing disease recurrence from post-therapy changes. Hybrid Positron Emission Tomography - Computed Tomography (PET/MRI) is a relatively novel tool that combines MRI sequences with metabolic information from Positron Emission Tomography (PET), and therefore different PET radiotracers, in a single scan. This article aims to show the main pros and cons of the combined PET/MRI compared to other conventional or more available imaging tools, such as MRI or combined Positron Emission Tomography - Computed Tomography (PET/CT). The main uses of PET/MRI and most commonly used PET radiotracers in providing diagnostic, prognostic and predictive information in patients with glioma are covered.

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1 Introduction

1.1 Primary brain tumours; an overview

Primary brain neoplastic diseases arise from different cells in the central nervous system (CNS) and show a great diversity in histopathological and molecular characteristics. Based on their histological and molecular features, the new 2016 World Health Organization (WHO) classification of CNS tumours includes more than 120 types of primary CNS tumours which have different prognoses (Komori, 2017).

In children, primary nervous system tumours are the most common solid cancers accounting for around 26% of all childhood cancers (American Cancer Society, 2016). Around half of the paediatric brain tumours arise from CNS supportive glial cells (gliomas) with the astrocytoma subtype representing 40% of the cases (Child with cancer UK organization, no date).

In adults, glioma of astrocytoma subtype is the most common type. The WHO classification defines 4 grades; grade I (pilocytic astrocytomas) and II (diffuse astrocytoma) are usually called low grade tumours; while grade III and IV are high grade tumours. Grade IV astrocytoma, also known as glioblastoma multiform (GBM), is the most common and aggressive primary brain malignancy, with 5-year survival of around 4% (Davis, 2016). Grade III astrocytoma (anaplastic astrocytoma) which also carries a poor prognosis (Komori, 2017). Although the diffuse astrocytomas (grade II) are considered as low grade gliomas they usually progress to a higher grade (anaplastic or secondary GBM) (Gerges *et al.*, 2013). Differentiating among these subtypes is very important, as it affects management strategy and prognosis.

1.2 Combined PET/MRI; an overview

Hybrid Positron emission tomography–magnetic resonance imaging (PET/MRI) combines the high contrast and morphological resolution of the MRI with the metabolic and physiological information from the integrated PET scan, by applying different PET radiopharmaceutical tracers. This advanced technology was a product of many years of research and development to overcome many technical difficulties. One major technical problem in combining both modalities in the same device was the interference of the strong magnetic field produced by the MRI with the PET components. This problem was solved by using rings of magnetic-field-insensitive PET detectors inside a 3T MRI gantry (Tudisca, Nasoodi and Fraioli, 2015). First successful combined PET/MRI was developed by Siemens (Biograph mMR System) and approved for clinical use in 2011. It allowed whole body acquisition of the MRI and PET data, lowering the scanning time from 60-90 minute (for 2 sequential acquisitions) to approximately 30 minutes (Koktysh, 2017). Combined PET/MRI is currently used for clinical and

research purposes for diagnosis, treatment planning and following-up various oncological and non-oncological disorders of different body systems.

2 PET radiopharmaceuticals

It is important to have a basic understanding about some of the PET radiotracers that are used for imaging brain tumors, in research or clinical practice. Different PET radiopharmaceuticals target different metabolic processes or receptors and can provide valuable information about tumors physiological activities.

2.1 ^{18}F-Fluodeoxyglucose (^{18}F-FDG)

18F-fluodeoxyglucose ^{18}F-FDG is a well-known and most available PET tracer, which is an indicator of glucose uptake and metabolism. One application of FDG-PET is to assess the tumor grade. High grade gliomas show higher tracer uptake compared to low grade tumors, besides, CNS lymphoma usually shows significantly higher FDG uptake compared to high and low grade gliomas (Fig. 1) (Das *et al.*, 2011). Another important use of FDG is to optimize biopsy site, if it is taken from the most avid part of the tumour, which represents the viable, and usually the more aggressive part, of the tumour (Spence, Mankoff and Muzi, 2007). Still, physiological FDG uptake by normal brain tissue causes poor tumor margins delineation, subsequently, its information is less useful for radiotherapy or surgery planning compared to other PET radiopharmaceuticals (amino acid and choline labeled radiotracers). Another drawback is its non-specific uptake (increases with inflammation) which might affect its ability to differentiate tumor recurrence from post-therapy inflammation (Fig. 2), though, it was used for this purpose with relatively moderate sensitivity and specificity (around 77%) (Nihashi, Dahabreh and Terasawa, 2013).

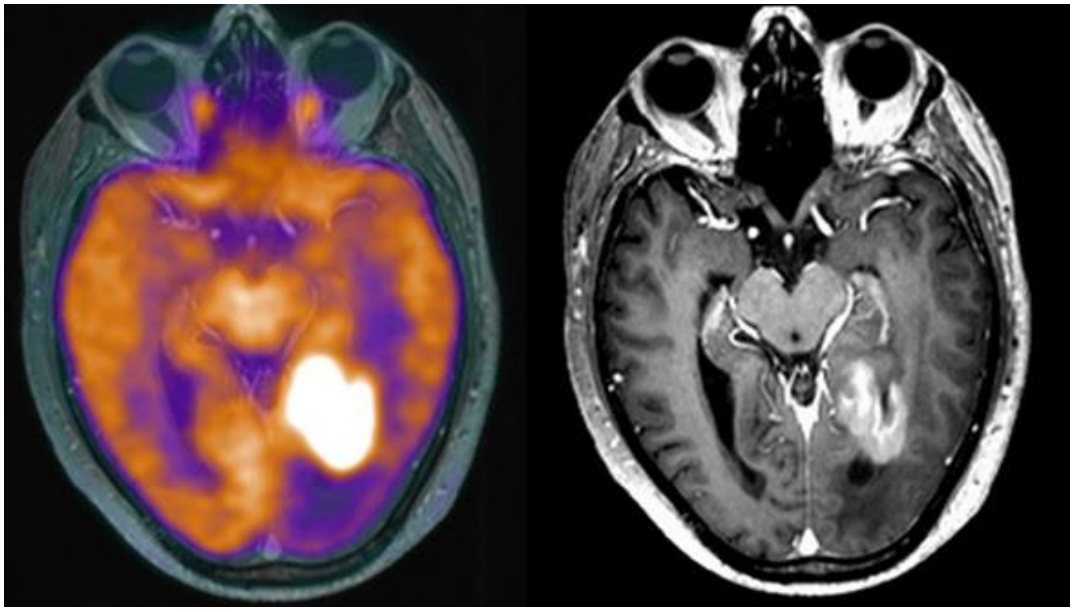

Figure 1. Primary CNS lymphoma. Left to right: fused 18F-Fluodeoxyglucose PET/MRI and gadolinium-enhanced T1 MRI images. There is intense FDG uptake in the enhanced left parieto-occipital lesion. Notice the high physiological FDG uptake by normal brain tissue.

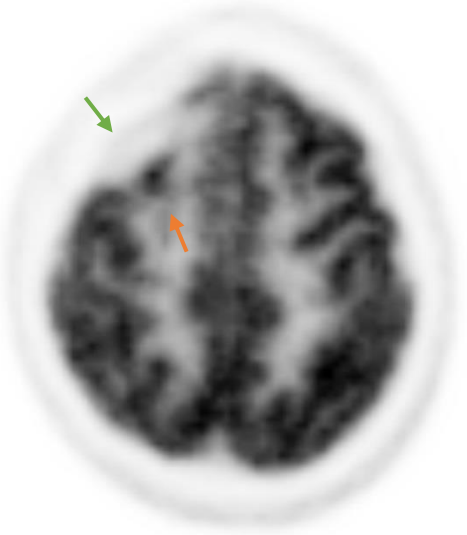

Figure 2. Axial FDG-PET scan in a patient with resected high-grade glioma in the right frontal lobe. The 18F-Fluodeoxyglucose uptake (orange arrow) in the area adjacent to the resected tumour (photopenic area, green arrow) could represent a physiological cerebral uptake, an inflammatory uptake, or a residual tumour.

2.2 Radiolabelled amino acids PET tracers

Amino acids (AA) transport and consumption are increased in malignant cells. Radiolabeled AA, such as ^{18}F-deoxyphenylalanine, *^{18}F-fluoro-ethyl-tyrosine (*^{18}*F-FET)*, ^{11}C-methionine (*^{11}*C*-MET), and ^{18}F-Fluoro-L-3,4-dihydroxyphenylalanine (^{18}F-FDOPA), can be used as markers of AA uptake and protein synthesis by tumor cells. Generally AA-radiotracer uptake is low by the normal brain tissue, allowing better tumor delineation compared to FDG, making them more reliable for surgery and radiotherapy

planning (Ciarmiello and Mansi, 2016) (Fig. 3). Still, they have limited ability to differentiate low from high grade gliomas in pre-treatment assessment (Ciarmiello and Mansi, 2016). Still, some other studies showed that ^{11}C-MET-PET (Kato *et al.*, 2008) and ^{18}FET-PET (Kunz *et al.*, 2011) are able to differentiate low from high grade gliomas with high sensitivity and specificity. Kunz et al (2011) studied 55 patients with suspected grade II gliomas (based on MRI findings) to assess the correlation between the hot spots on dynamic ^{18}FET-PET and the higher-grade tumour parts, and whether this PET tracer is able to change tumour grading. Histopathologically, 44% of the originally grade II gliomas harboured high grade components (grade III or IV). Examination of 373 biopsy samples indicated a strong correlation with the analyses of the ^{18}FET-PET uptake kinetics ($p < 0.0001$), and anaplastic foci can be accurately identified by using ^{18}FET-PET mapping. (Kunz *et al.*, 2011).

Another important advantage of these tracers is they are less influenced by inflammation; still, they are not absolutely tumour specific. AA-PET tracers are more reliable than FDG in differentiating tumour recurrence from inflammation and necrosis in post-therapy assessment (Ciarmiello and Mansi, 2016).

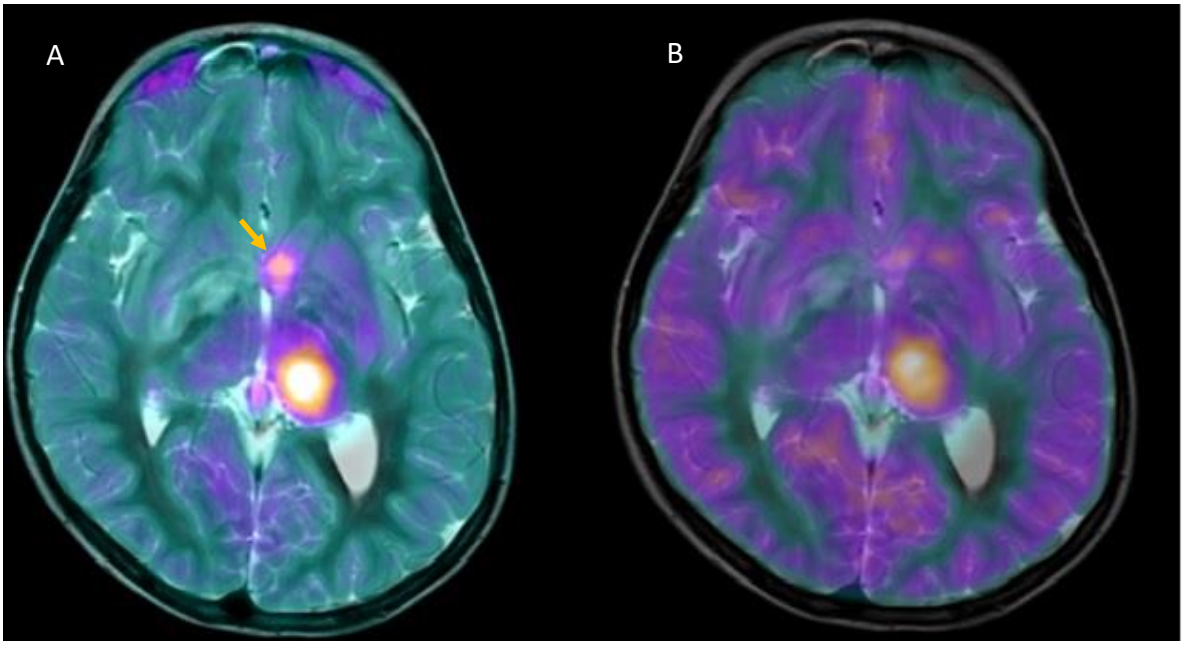

Figure 3. Comparison between ^{11}C-Methionine PET/MRI (A) and 18F-Fluodeoxyglucose PET/MRI (B) in a patient with high-grade glioma. Notice the low normal brain tissue uptake of ^{11}C-Methionine compared to ^{18}F-FDG, which allowed identifing a further spot of focal uptake in the right anterior commissure (arrow).

2.3 Choline labelled PET tracers

^{18}F-fluorocholine and ^{11}C-choline are markers of cell membrane turnover (lipid metabolism) which also increases in malignant tumors. One advantage of using labeled choline tracers is the significantly low

uptake by the normal brain tissue compared to other tracers, allowing superior tumour delineation (Fig. 4).

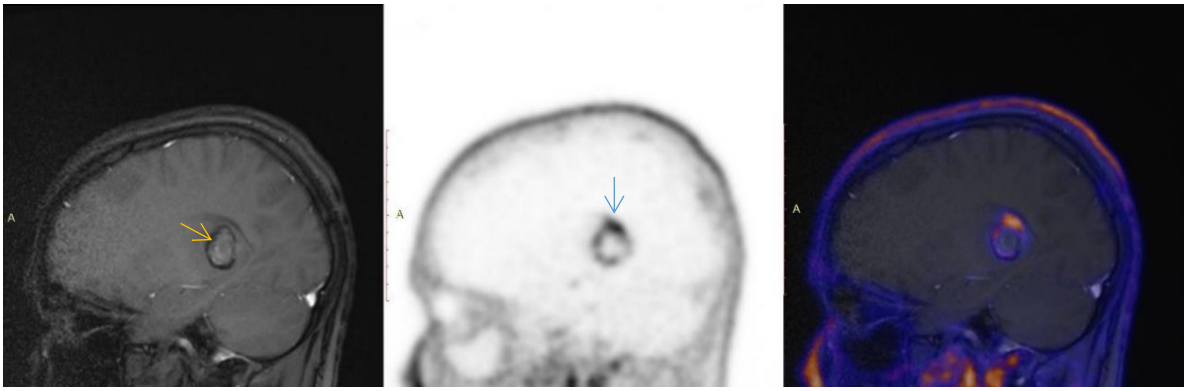

Figure 4. Left to right, sagittal T1 MRI with a post-biopsy haemorrhagic core (yellow arrow), F-Choline PET, and fused PET/MRI images in a patient with high grade glioma. Notice the high F-Choline uptake especially in the superior part of the tumour (blue arrow) with the negligible uptake by the normal brain tissue.

A comparison between F-DOPA and F-choline in a patient with WHO grade III anaplastic astrocytoma is illustrated in Fig. 5.

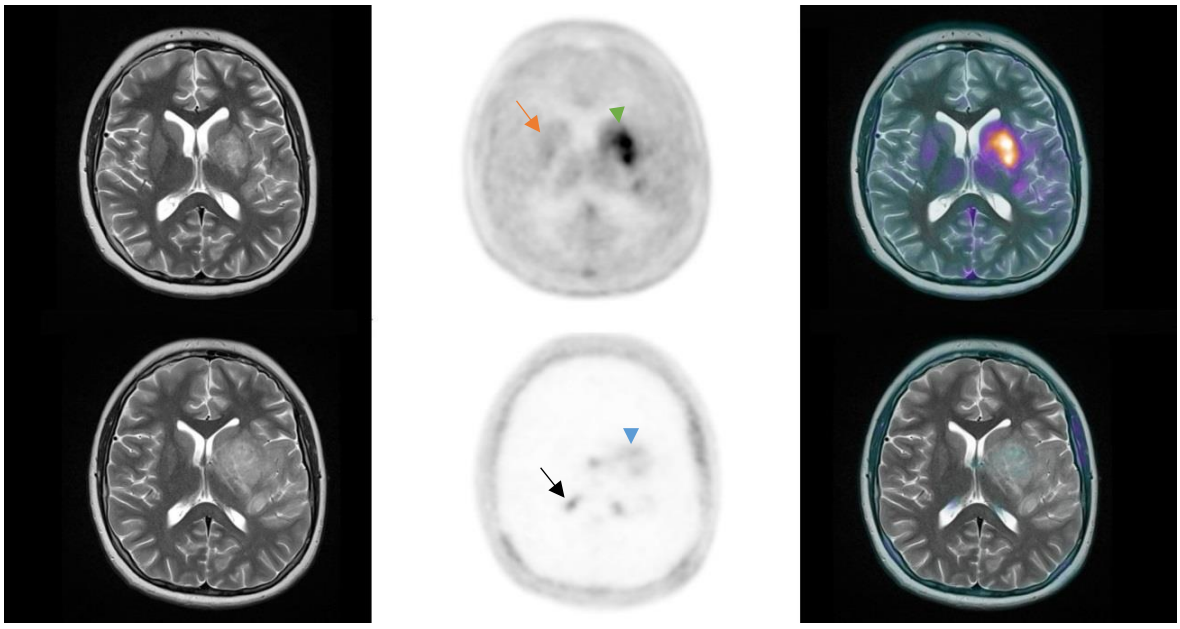

Figure 5. 18F-dihydroxyphenylalanine (F-DOPA) (top row) and F-choline (bottom row) in a patient with World Health Organization (WHO) grade III anaplastic astrocytoma. The uptake in the lesion is more consistent with F-DOPA (green arrow head) than with F-choline tracer (blue arrow head). Notice the physiological uptake of F-DOPA in the basal ganglia (orange arrow) and F-choline in the choroid plexus (black arrow).

The advantages, disadvantages and the potential uses of some PET radiotracers in brain glioma imaging are summarized in Table 1.

PET radiopharmaceutical	Mechanism of uptake/ indicator of:	Advantages	Disadvantages
^{18}F-FDG.	Glucose uptake and metabolism.	• Readily available. • Relatively less expensive. • Can differentiate low from high grade gliomas and helps in guiding biopsy (Spence, Mankoff and Muzi, 2007). • longer half-life of ^{18}F (110 min)	• High physiological tracer uptake by normal brain tissue. • Low specificity (uptake by inflammation or infection) • Less reliable in post-therapy assessment compared to AA and choline -PET radiotracers.
^{11}C-Choline. **^{18}F-fluorocholine (F-choline).**	Lipid metabolism (plasma membrane synthesis).	• Better tumor delineation (very low normal brain tissue uptake) • Differentiating low from high grade gliomas and guiding biopsy (Hara *et al.*, 2003). • Better than FDG and conventional MRI in differentiating tumor recurrence from post-therapy changes (Tan *et al.*, 2011).	• Logistic problems regarding the short half-life of ^{11}C (20 min) which requires on-site cyclotron. However, this was overcome with ^{18}F labeled choline. • Physiological uptake in choroid plexus, venous sinuses and pituitary gland could affect its accuracy. • Uptake in some CNS inflammatory, granulomas and demyelinating diseases.
11C-MET.	Amino acid uptake and protein synthesis.	• More specific and sensitive than FDG in differentiating recurrent from necrosis in post-therapy scenarios. • Less affected by inflammation. • Low normal brain tissue uptake, allowing better tumor delineation. • Carbon is a building block of all organic compounds, so can be substituted with radioisotope ^{11}C without disturbing their basic physiological functions.	• Shorter half-life of ^{11}C (20 min). • Might be less reliable in differentiating high from low grade gliomas.
^{18}F-FET. **^{18}F-FDOPA .**	Amino acid uptake (transport)	• Extra advantage of the longer half-life of ^{18}F compared to ^{11}C.	• Physiological uptake of 18F-FDOPA in the basal ganglia, potentially affect its accuracy in assessing lesions close to these areas.

Table 1. Mechanism of uptake, advantages, disadvantages and uses of some PET radiotracers in brain gliomas imaging. ^{18}F-FDG, ^{18}F-Fluodeoxyglucose; ^{11}C-MET, ^{11}C-Methionine; ^{18}F-FET, ^{18}F-Fluoroethyltyrosine; ^{18}F-FDOPA, ^{18}F-Fluoro-L-3,4-dihydroxyphenylalanine; AA, amino acid; PET, Positron Emission Tomography; MRI, Magnetic Resonance Imaging.

3 Combined PET/MRI in pre-treatment brain glioma imaging

In the pre-treatment assessment, what particularly important is to evaluate the extent of the tumour, the probable grade of tumour and the possibility of malignant transformation of low grade glioma.

The other important point is to assess the best site to biopsy. PET tracers can provide valuable information on these fronts.

Current guidelines do not support using PET/MRI (or Positron Emission Tomography - Computed Tomography, PET/CT) for primary diagnostic work-up of suspected primary brain tumour. However, they suggest using PET imaging in pre-treatment work-up as they may correlate with tumour grade or provide the optimal area for biopsy (National Comprehensive Cancer Network, 2018). Gadolinium-enhanced MRI (GdE-MRI) scan is the imaging modality of choice. However, MRI still has its limitation in differentiating low from high grade gliomas. On GdE-MRI, around 10% of GBM and 30% of anaplastic astrocytomas show no enhancement; on the other hand, low grade gliomas sometimes show enhancement (Knopp *et al.*, 1999) (Scott *et al.*, 2002).

Some studies showed discrepancy between MRI and PET findings; so, combining both modalities provides a better approach to reach more accurate diagnosis. In one study, ^{11}C-Met PET-MRI identified the most aggressive part of the tumor which was not always related to the areas of high cell membrane proliferation seen with magnetic resonance spectroscopy (MRS) (Bisdas *et al.*, 2013). In another study, Filss et al. compared the information obtained from ^{18}F-FET PET with the perfusion-weighted MR imaging (PWI) regional cerebral blood volume (rCBV) in patients with gliomas (n=56). The concluded that the 2 modalities displayed different information, and ^{18}F-FET PET showed larger tumours volumes than rCBV maps, with poor spatial congruence between them i.e. the locations of the local hot spots vary considerably (Filss *et al.*, 2014) .Therefore, PET data adds metabolic and physiological information to the MRI and increases its diagnostic power. Some of the possible applications of PET imaging in pre-treatment brain gliomas assessment are summarized in Table 2.

Pre-therapy application	Used PET radiotracers	Notes
Better delineation of the tumor; helps in surgical and radiotherapy planning.	Amino acid (Ciarmiello and Mansi, 2016) and Choline (DeGrado *et al.*, 2001).	fluorodeoxyglucose-positron emission tomography (FDG-PET) might be applied in high-grade gliomas with marked intratumoral heterogeneity, where the hot spots could be targets with a higher radiation dose (Ciarmiello and Mansi, 2016).
Tumor grading.	18f-fluorodeoxyglucose (FDG) (Delbeke *et al.*, 1995) and Choline (Kato *et al.*, 2008).	There is controversy over whether amino acid tracers are suitable for grading tumors(Kato *et al.*, 2008; Kunz *et al.*, 2011) or not (Chen *et al.*, 2006).
Guiding biopsy.	FGD (Spence, Mankoff and Muzi, 2007) , Choline (Hara *et al.*, 2003), and amino acids (Kunz *et al.*, 2011).	Directing the stereotactic biopsy to the most avid part increases the yield of the biopsy.
Prognosis.	FDG and amino acid (Kim *et al.*, 2005).	Increase uptake correlated with worse prognosis.

		Kim et al. found that ^{11}C-MET is better than FDG for this purpose (Kim *et al.*, 2005).

Table 2. Possible applications of some PET radiotracers in per-therapy assessment of brain gliomas.

4 Combined PET/MRI in post-therapy glioma evaluation

PET/MRI is used to assess brain tumours during the post-therapy follow-up to differentiate possible tumour residual, recurrence or progression from tumour necrosis/scarring (Fig. 6 and 7)

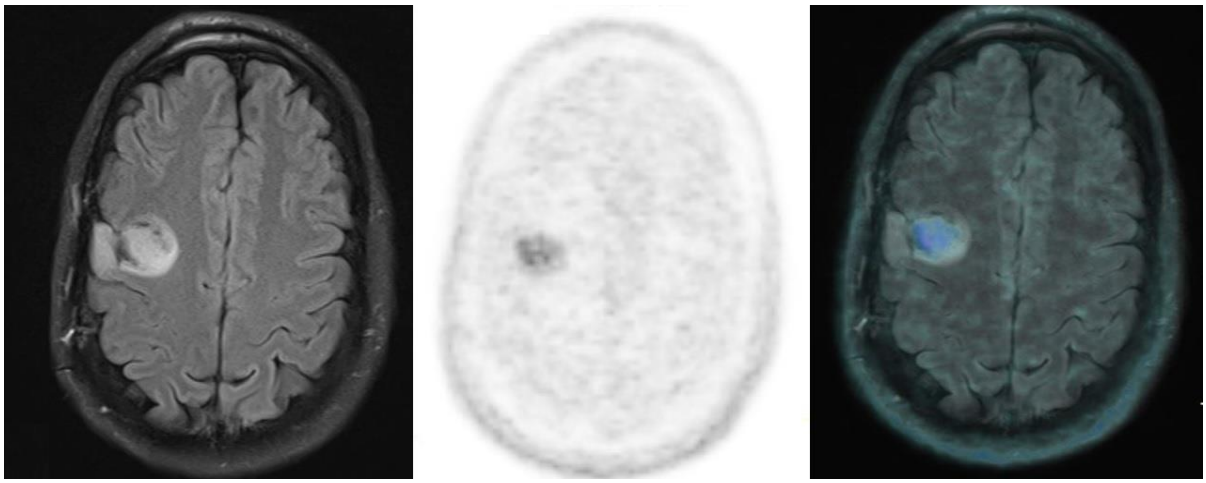

Figure 6. Left to right: axial flair MRI, 18F-dihydroxyphenylalanine (F-DOPA) PET, and fused PET/MRI in a patient with previously de-bulked glioma in the right frontal lobe showing focal F-DOPA uptake indicating recurrent tumour.

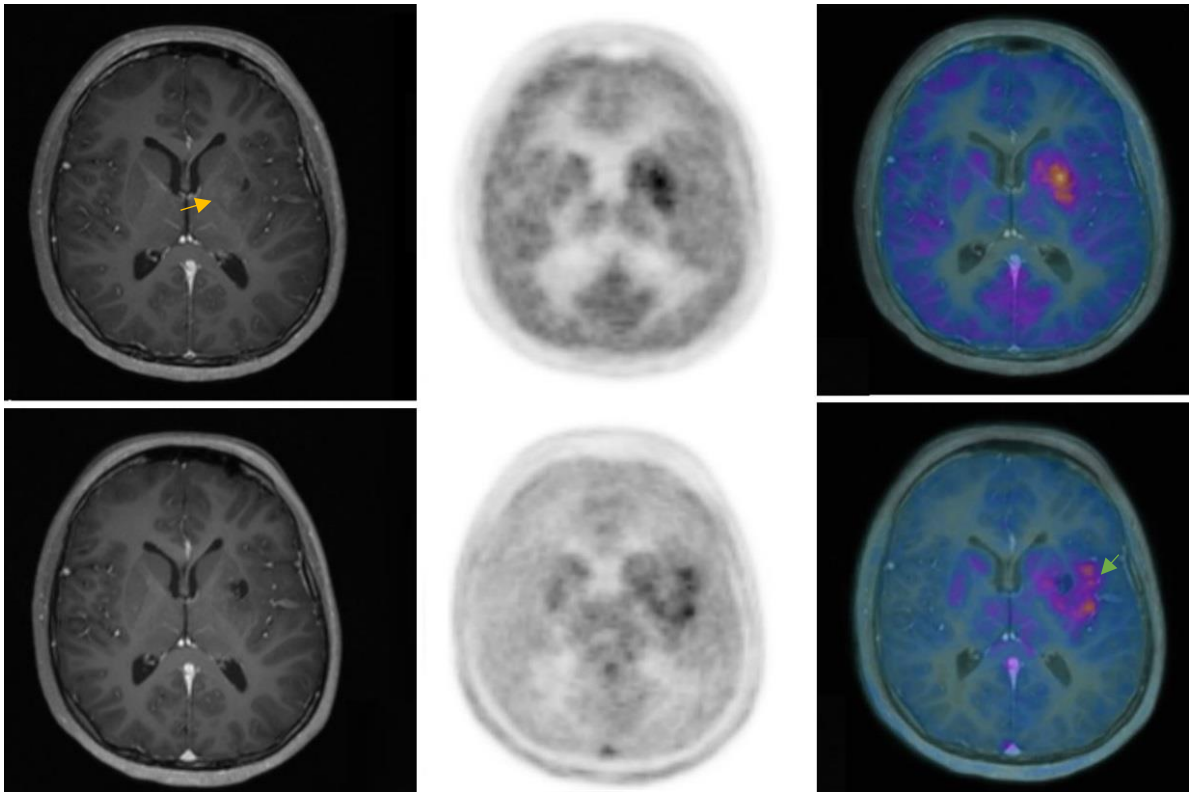

Figure 7. Two 18F-dihydroxyphenylalanine (F-DOPA) PET/MRI studies for a patient with anaplastic astrocytoma treated with chemoradiation. First study (top row) showed avid tumour in and around the left basal ganglia, with minimal gadolinium enhancement (yellow arrow). The second scan (bottom row) was taken 6 months later and showed lateral disease extension to the left insula (green arrow) indicating disease progression, with no significant radiological changes on MRI.

Radiolabelled AA PET tracers showed better accuracy than contrast enhanced MRI in differentiating between pseudoprogression and progression in patients with GBM after radiochemotherapy treatment. For this purpose, Galldiks et al. (2015) conducted a study on 22 patients who had recently completed radiochemotherapy for glioblastoma. All lesions showed > 25% enhancement on GdE-MRI. They found that pseudoprogression has significantly less ^{18}F-FET uptake than the early progression (^{18}F-FET tumour/brain ratio max (TBR max) was 1.9 ± 0.4 vs. 2.8 ± 0.5, respectively, $P < 0.001$) (Galldiks *et al.*, 2015).

Regarding the diagnostic accuracy of ^{11}C- MET, ^{11}C-choline and ^{18}F-FDG in distinguishing glioma recurrence from radiation necrosis, Takenaka et al. (2014) compared the results from patients with suggestive glioma recurrent on MRI scans (n=50). They found that ^{11}C- MET had superior diagnostic accuracy compared to ^{11}C-choline and ^{18}F-FDG in distinguishing recurrence from radiation necrosis, and when ^{11}C-MET lesion/normal brain uptake ratio > 2.51 is considered, it showed the best sensitivity and specificity for diagnosing glioma recurrence (around 91% and 87%, respectively) (Takenaka *et al.*, 2014).

Once more, combining PET and the MRI data increases the accuracy of the test, especially when advanced MRI sequences are included. To distinguish recurrence from radiation necrosis, Jena et al.

(2016) conducted a study on previously treated glioma patients (n=26) using simultaneous ^{18}F-FET-PET/MRI with measuring choline/creatine (Cho/Cr) ratio (magnetic resonance spectroscopy, MRS) and normalised mean relative cerebral blood volume (rCBVmean). The combined results from these different modalities yielded higher diagnostic accuracy. Combined ^{18}F-FET TBRmax (or TBRmean) and Cho/Cr ratio accuracy was 97%, and combined ^{18}F-FET TBRmean, rCBV and Cho/Cr ratio produced the maximum area under the curve (AUC) (Jena *et al.*, 2016). In more recent study by Hojjati et al (2018) to differentiate GBM recurrent from post-radiation necrosis, they found that combining the data from FDG-PET/MRI with the perfusion MRI resulted in an area under the curve of 1.0, indicating highest sensitivity and specificity (Hojjati *et al.*, 2018).

5 Advantages of combined PET/MRI, key points

5.1 Combined PET/MRI vs. combined PET/CT

- One of the main advantages of PET/MRI over PET/CT is the elimination of the ionising radiation of the CT component. Given the fact that brain tumour is the most common solid malignancy in children and the need for multiple follow-up scans, this advantage is more significant in these scenarios.
- MRI has a superior soft tissue resolution which allows more detailed imaging compared to the CT scan (Fig. 8). It excels in imaging brain pathologies, and allows better diagnostic images of the tumour structures.

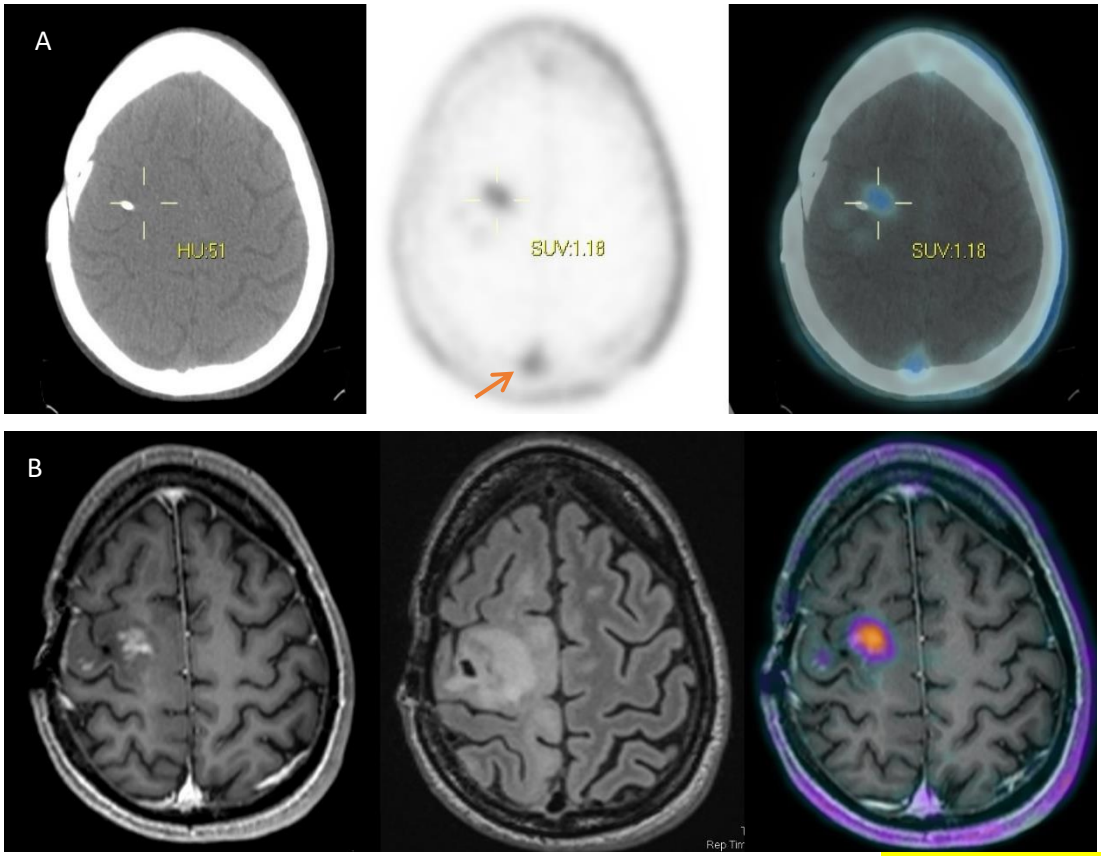

Figure 8. Comparison between ^{18}F-choline PET/CT and PET/MRI in a patient with recurrent glioblastoma multiforme (GBM). Axial F-choline PET/CT (A) and axial F-choline PET/MRI (B) (Please correct the letter in the sent file) show disease recurrence at the site of previously resected GBM. Notice the superior details of the tumour extension on the MRI images compared to the CT scan. There is physiological uptake of F-choline in the sagittal sinus (orange arrow).

5.2 Combined PET/MRI vs. MRI scan alone

- Additional metabolic information from different PET tracers will be added to the morphological and molecular information from the MRI, which allows more accurate diagnosis.
- Targeting most avid part of the tumour increases the yield of the stereotactic biopsy.
- Post-therapy changes can be differentiated from tumour residual or recurrence with more confidence when PET information is added to the MRI images.
- More accurate detection of malignant transformation of low grade gliomas.

5.3 Combined PET/MRI vs. sequential PET and MRI acquisitions

- The simultaneous acquisition of PET and MRI data allows shorter scanning time which alleviates the patient's stress and the staff's workload and improves workflow.
- It eliminates the need for two administrations of general anaesthesia in young children and claustrophobic patients.
- Combined PET/MRI allows acquisition of data simultaneously in space and time, minimising the chance of images misregistration, and eliminates the interval changes that could happen in between the two scans.

6 Disadvantages of combined PET/MRI

The high price of the hybrid PET/MRI system along with the cost of the device maintenance reflected negatively on its availability. The price of the PET/MRI system is 3-4 times higher than that of a PET/CT system. The cost of the combined PET/MRI machine ranges from $4-5 million, with additional 10% for the annual maintenance and operation (Koktysh, 2017).

Another factor that affects the spread of the combined PET/MRI scan is the presence of the PET/CT scan, which has already established its place as a valuable imaging modality with lower cost and faster performance, besides, it is supported by enormous evidence-based data and guidelines. Combined PET/MRI, on the other hand, is a relatively newer technology with limited spread, and this imposes a problem regarding conducting large and multi-centre studies that can support establishing standardized protocols among specialists and centres.

Another issue with the combined PET/MR is related to the attenuation correction (AC). In the combined PET/CT, the CT component is used for AC and anatomical localization. However, in PET/MRI, the MR signal is not directly correlated to the tissue density, for example, cortical bone and air have poor/no signal, but they cause the highest and lowest attenuation in PET, respectively; therefore MRI cannot be directly utilised for AC (Wagenknecht *et al.*, 2013). Methods for MR-based AC, such as Dixon, ultra-short echo (UTE) or zero echo time (ZTE) are fast techniques, still, they are subjective to image noise and artefacts (Chen and An, 2017).

Other limitations are related to the absolute and relative contraindications of the MRI itself, such as patients with cochlear implant, sensitive heart pacemaker, metallic foreign body in the eye and others.

7 Conclusion

Combined PET/MRI is a valuable tool for imaging brain gliomas and can provide morphological and physiological information about the tumour after a single scan. It is superior to the conventional MRI in differentiating low form high grade gliomas and detecting malignant transformation of the low grade ones. It also can support radiotherapy and surgery planning, provide prognostic information, and differentiate tumour recurrence from benign post therapy changes more accurately than the MRI scan alone. Nevertheless, the higher cost of the combined PET/MRI and the presence of other alternatives, such as PET/CT, act adversely on its availability.

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Key points

Hybrid positron emission tomography- magnetic resonance imaging (PET/MRI) is a relatively new technology that combines the high contrast and morphological resolution of the MRI with the physiological information from the integrated PET scan.

The complexity of brain structure and the subtility of the neuropathologies makes hybrid PET/MRI an ideal tool for imaging primary brain tumours.

Hybrid PET/MRI eliminates the ionising radiation of the CT component, and allows shorter scanning time which alleviates the patient's stress and the staff's workload and improves workflow.

Nonetheless, the wide-spread and lower cost of the positron emission tomography–computed tomography (PET-CT) along with its well-established guidelines and consensuses, negatively impact the spread of the PET/MRI.

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References

American Cancer Society (2016) *Cancers that Develop in Children*. Available at: https://www.cancer.org/cancer/cancer-in-children/types-of-childhood-cancers.html (Accessed: 25 October 2018).

Bisdas, S. *et al.* (2013) 'Metabolic Mapping of Gliomas Using Hybrid MR-PET Imaging', *Investigative Radiology*, 48(5), pp. 295–301. doi: 10.1097/RLI.0b013e31827188d6.

Chen, W. *et al.* (2006) '18F-FDOPA PET imaging of brain tumors: comparison study with 18F-FDG PET and evaluation of diagnostic accuracy.', *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*. Society of Nuclear Medicine, 47(6), pp. 904–11. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16741298 (Accessed: 29 October 2018).

Chen, Y. and An, H. (2017) 'Attenuation Correction of PET/MR Imaging.', *Magnetic resonance imaging clinics of North America*. NIH Public Access, 25(2), pp. 245–255. doi: 10.1016/j.mric.2016.12.001.

Child with cancer UK organization (no date) *Brain Tumours & Spinal Cord Tumours | Children with Cancer UK*. Available at: https://www.childrenwithcancer.org.uk/childhood-cancer-info/cancer-types/brain-spinal-tumours/ (Accessed: 25 October 2018).

Ciarmiello, A. and Mansi, L. (2016) *PET-CT and PET-MRI in neurology: SWOT analysis applied to hybrid imaging*, *Springer Nature*. Switzerland.

Das, K. *et al.* (2011) 'Role of (18)F-fluorodeoxyglucose Positron Emission Tomography scan in differentiating enhancing brain tumors.', *Indian journal of nuclear medicine : IJNM : the official journal of the Society of Nuclear Medicine, India*. Wolters Kluwer -- Medknow Publications, 26(4), pp. 171–6. doi: 10.4103/0972-3919.106698.

Davis, M. E. (2016) 'Glioblastoma: Overview of Disease and Treatment.', *Clinical journal of oncology nursing*. NIH Public Access, 20(5 Suppl), pp. S2-8. doi: 10.1188/16.CJON.S1.2-8.

DeGrado, T. R. *et al.* (2001) 'Synthesis and evaluation of (18)F-labeled choline analogs as oncologic PET tracers.', *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*, 42(12), pp. 1805–14. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11752077 (Accessed: 29 October 2018).

Delbeke, D. *et al.* (1995) 'Optimal cutoff levels of F-18 fluorodeoxyglucose uptake in the

differentiation of low-grade from high-grade brain tumors with PET.', *Radiology*, 195(1), pp. 47–52. doi: 10.1148/radiology.195.1.7892494.

Filss, C. P. *et al.* (2014) 'Comparison of 18F-FET PET and Perfusion-Weighted MR Imaging: A PET/MR Imaging Hybrid Study in Patients with Brain Tumors', *Journal of Nuclear Medicine*, 55(4), pp. 540–545. doi: 10.2967/jnumed.113.129007.

Galldiks, N. *et al.* (2015) 'Diagnosis of pseudoprogression in patients with glioblastoma using O-(2-[18F]fluoroethyl)-l-tyrosine PET', *European Journal of Nuclear Medicine and Molecular Imaging*, 42(5), pp. 685–695. doi: 10.1007/s00259-014-2959-4.

Gerges, N. *et al.* (2013) 'Pediatric high-grade astrocytomas: a distinct neuro-oncological paradigm.', *Genome medicine*. BioMed Central, 5(7), p. 66. doi: 10.1186/gm470.

Hara, Toshihiko *et al.* (2003) 'Use of ^{18} F-choline and ^{11} C-choline as contrast agents in positron emission tomography imaging—guided stereotactic biopsy sampling of gliomas', *Journal of Neurosurgery*, 99(3), pp. 474–479. doi: 10.3171/jns.2003.99.3.0474.

Hojjati, M. *et al.* (2018) 'Role of FDG-PET/MRI, FDG-PET/CT, and Dynamic Susceptibility Contrast Perfusion MRI in Differentiating Radiation Necrosis from Tumor Recurrence in Glioblastomas.', *Journal of neuroimaging : official journal of the American Society of Neuroimaging*. Wiley-Blackwell, 28(1), pp. 118–125. doi: 10.1111/jon.12460.

Jena, A. *et al.* (2016) 'Glioma Recurrence Versus Radiation Necrosis', *Clinical Nuclear Medicine*, 41(5), pp. e228–e236. doi: 10.1097/RLU.0000000000001152.

Kato, T. *et al.* (2008) 'Metabolic Assessment of Gliomas Using ^{11} C-Methionine, [^{18} F] Fluorodeoxyglucose, and ^{11} C-Choline Positron-Emission Tomography', *American Journal of Neuroradiology*, 29(6), pp. 1176–1182. doi: 10.3174/ajnr.A1008.

Kim, S. *et al.* (2005) '11C-methionine PET as a prognostic marker in patients with glioma: comparison with 18F-FDG PET', *European Journal of Nuclear Medicine and Molecular Imaging*, 32(1), pp. 52–59. doi: 10.1007/s00259-004-1598-6.

Knopp, E. A. *et al.* (1999) 'Glial Neoplasms: Dynamic Contrast-enhanced T2*-weighted MR Imaging', *Radiology*, 211(3), pp. 791–798. doi: 10.1148/radiology.211.3.r99jn46791.

Koktysh, L. (2017) *The Past, Present and Future of PET/MRI Scanners | Imaging Technology News*. Available at: https://www.itnonline.com/article/past-present-and-future-petmri-scanners (Accessed:

20 October 2018).

Komori, T. (2017) 'The 2016 WHO Classification of Tumours of the Central Nervous System: The Major Points of Revision.', *Neurologia medico-chirurgica*. Scientific Journal Publishing Dept., Medical Tribune, Inc., 57(7), pp. 301–311. doi: 10.2176/nmc.ra.2017-0010.

Kunz, M. *et al.* (2011) 'Hot spots in dynamic (18)FET-PET delineate malignant tumor parts within suspected WHO grade II gliomas.', *Neuro-oncology*. Oxford University Press, 13(3), pp. 307–16. doi: 10.1093/neuonc/noq196.

National Comprehensive Cancer Network (2018) *Central Nervous System Cancers (Version 1.2017)*. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf (Accessed: 2 February 2019).

Nihashi, T., Dahabreh, I. J. and Terasawa, T. (2013) 'Diagnostic accuracy of PET for recurrent glioma diagnosis: A meta-analysis', *American Journal of Neuroradiology*. doi: 10.3174/ajnr.A3324.

Scott, J. N. *et al.* (2002) 'How often are nonenhancing supratentorial gliomas malignant? A population study.', *Neurology*, 59(6), pp. 947–9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12297589 (Accessed: 14 May 2018).

Spence, A. M., Mankoff, D. A. and Muzi, M. (2007) *The role of PET in the management of brain tumors*, *Applied Radiology*. Available at: https://appliedradiology.com/articles/the-role-of-pet-in-the-management-of-brain-tumors (Accessed: 1 March 2019).

Takenaka, S. *et al.* (2014) 'Comparison of (11)C-methionine, (11)C-choline, and (18)F-fluorodeoxyglucose-PET for distinguishing glioma recurrence from radiation necrosis.', *Neurologia medico-chirurgica*, 54(4), pp. 280–9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24305028 (Accessed: 23 November 2018).

Tan, H. *et al.* (2011) 'Comparison of MRI, F-18 FDG, and 11C-Choline PET/CT for Their Potentials in Differentiating Brain Tumor Recurrence From Brain Tumor Necrosis Following Radiotherapy', *Clinical Nuclear Medicine*, 36(11), pp. 978–981. doi: 10.1097/RLU.0b013e31822f68a6.

Tudisca, C., Nasoodi, A. and Fraioli, F. (2015) 'PET-MRI: clinical application of the new hybrid technology', *Nuclear Medicine Communications*, 36(7), pp. 666–678. doi: 10.1097/MNM.0000000000000312.

Wagenknecht, G. *et al.* (2013) 'MRI for attenuation correction in PET: methods and challenges.',

Magma (New York, N.Y.). Springer, 26(1), pp. 99–113. doi: 10.1007/s10334-012-0353-4.