Chapter 8

Molecular Imaging of Brain Tumours

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Additional information is available at the end of the chapter

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Abstract

This chapter is a review of the most common radiotracers currently used in clinical brain tumour imaging, and an update of future potentially useful radiotracers for imaging brain tumours with positron emission tomography (PET). It will focus mainly on glioma —the most common type of primary brain tumour—and intracranial metastases, as the cause of the majority of morbidity and mortality in neurooncology. Emerging data support the use of somatostatin analogue PET in the treatment planning and surveillance of meningiomas. There is currently a limited role of PET in other non-glial brain neoplasms including neuronal tumours, pineal and pituitary tumours, germ cell tumours and embryonal tumours (PNET, neuroblastoma). Finally, the newest hybrid imaging modality of PET/MRI and the promise it holds for obtaining state-of-the-art structural and functional imaging data simultaneously, are concisely reviewed.

Keywords: PET, molecular imaging, brain tumour, neurooncology, radiotracer

1. Introduction

Structural imaging using contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) is crucial for the initial detection and diagnosis of brain tumours. However, it has limitations in post-treatment surveillance where tumour- and therapy-related changes can appear similarly. Molecular imaging with positron emission tomography (PET) provides additional information that can better delineate tumour extent and burden, for example fluorodeoxyglucose (FDG) depicts the metabolic activity and fluroethyltyrosine (FET) and fluorodihydroxyphenylalanine (FDOPA) depict the amino acid turnover of otherwise nonspecific soft tissue changes on CT and MRI. This could ultimately improve clinical decision-making and anatomical targeting of tumour for biopsy, radiotherapy or surgery.

2. Brain tumour types

Brain tumours affect approximately 5–10 persons per 100,000 populations. In adults, about half of all brain neoplasms are primary tumours and the other half are metastatic. In childhood, brain neoplasms account for up to 20% of all cancers. Seventy percentage of childhood brain tumours arise from the posterior cranial fossa, whereas in adults, a similar proportion arises above the tentorium [1].

Intracranial tumours may spread directly to adjacent structures, along white matter tracts, or through the cerebrospinal fluid (CSF) spaces. It is rare for brain malignancy to metastasise to other parts of the body.

The most widely accepted system for classifying brain tumours is the World Health Organisation (WHO) classification of tumours of the central nervous system (CNS), which is based on the histological characteristics of the tumour. The latest revision was published in 2007 [2].

2.1. Gliomas

Gliomas are tumours of glial cells and include astrocytomas, oligodendrogliomas and ependymomas. Unlike most neurons, glial cells retain the ability to undergo cell division in the adult CNS. Since carcinogenesis is related to the sequential accumulation of genetic aberrations through cell division, it is not surprising that gliomas are the most common primary brain malignancy and account for about half of all adult brain tumours. The WHO classification of CNS tumours additionally classifies gliomas into Grade I to IV depending on the degree of tumour histological differentiation (**Table 1**).

	I	II	III	IV		I	II	III	IV
Astrocytic tumours									
Subependymal giant cell astrocytoma	•				Central neurocytoma		•		
Pilocytic astrocytoma	•				Extraventricular neurocytoma		•		
Pilomyxoid astrocytoma		•			Cerebellar liponeurocytoma		•		
Diffuse astrocytoma		•			Paraganglioma of the spinal cord	•			
Pleomorphic xanthoastrocytoma		•			Papillary glioneuronal tumour	•			
Anaplastic astrocytoma			•		Rosette-forming glioneuronal tumour of the fourth ventricle	•			
Glioblastoma				•					
Giant cell glioblastoma				•					
Gliosarcoma				•	**Pineal tumours**				
					Pineocytoma	•			
Oligodendroglial tumours					Pineal parenchymal tumour of intermediate differentiation		•	•	
Oligodendroglioma		•			Pineoblastoma				•
Anaplastic oligodendroglioma			•		Papillary tumour of the pineal region		•	•	
Oligoastrocytic tumours									
Oligoastrocytoma		•			**Embryonal tumours**				
Anaplastic oligoastrocytoma			•		Medulloblastoma				•
					CNS primitive neuroectodermal tumour (PNET)				•
Ependymal tumours					Atypical teratoid / rhabdoid tumour				•
Subependymoma	•								
Myxopapillary ependymoma	•				**Tumours of the cranial and paraspinal nerves**				
Ependymoma		•			Schwannoma	•			

	I	II	III	IV		I	II	III	IV
Anaplastic ependymoma			•		Neurofibroma	•			
					Perineurioma	•	•	•	
Choroid plexus tumours					Malignant peripheral nerve sheath tumour (MPNST)		•	•	•
Choroid plexus papilloma	•								
Atypical choroid plexus papilloma		•			**Meningeal tumours**				
Choroid plexus carcinoma			•		Meningioma	•			
					Atypical meningioma		•		
Other neuroepithelial tumours					Anaplastic/malignant meningioma			•	
Angiocentric glioma	•				Haemangiopericytoma		•		
Chordoid glioma of the third ventricle		•			Anaplastic haemangiopericytoma			•	
					Haemangioblastoma	•			
Neuronal and mixed neuronal-glial tumours									
Gangliocytoma	•				**Tumours of the sellar region**				
Ganglioglioma	•				Craniopharyngioma	•			
Anaplastic ganglioglioma			•		Granular cell tumour of the neurohypophysis	•			
Desmoplastic infantile astrocytoma and ganglioglioma	•				Pituicytoma	•			
Dysembryoplastic neuroepithelial tumour	•				Spindle cell oncocytoma of the adenohypophysis	•			

Table 1. WHO grading of tumours of the CNS.

2.2. Brain metastases

The most common primary malignancies that metastasise to the brain are carcinomas of the lung, breast and melanoma [3]. The meninges are also a frequent site of metastatic disease involvement.

The following sections on molecular imaging with PET radiotracers will focus on gliomas and intracranial metastases as the cause of the majority of morbidity and mortality in neurooncology.

3. Fluorodeoxyglucose

3.1. Tumour detection

F-18 FDG is an analogue of glucose (**Figure 1**). Its active transport into the cell is mediated by a group of structurally related glucose transport proteins (GLUT) and once intracellular, FDG

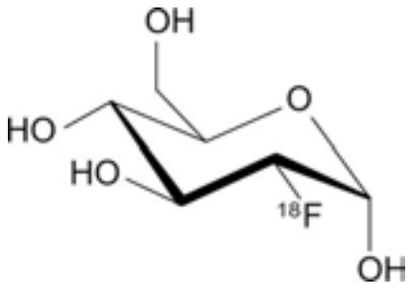

Figure 1. Chemical structure of F-18 fluorodeoxyglucose.

is phosphorylated by the enzyme hexokinase as the first step towards glycolysis. However, unlike glucose, once phosphorylated FDG-6-phosphate cannot continue along the glycolytic pathway and effectively becomes trapped intracellularly. FDG uptake in PET is thus an indication of the metabolic activity of the structure in which it is being taken up. Most malignant cells are metabolically active and demonstrate an increased expression of glucose transport proteins, particularly GLUT-1 and GLUT-3, as well as higher levels of hexokinase.

FDG is the single most important, widely used and explored radiotracer in PET; however, its current role in brain tumour imaging is limited due to the presence of intense physiological FDG uptake in the normal brain resulting in poor tumour-to-background contrast. Thus, an underlying brain tumour, even if FDG-avid, can escape detection on FDG PET (**Figure 2**). In some studies, increased FDG uptake in gliomas was only reported in 21–47% of high-grade tumours and as few as 3–6% of low-grade tumours [4, 5]. Delayed imaging (e.g. 6 h) following FDG administration instead of the usual imaging performed 60–90 min post-radiotracer can improve discrimination between tumour and physiological background uptake as FDG is retained in tumour longer than in normal brain parenchyma [6].

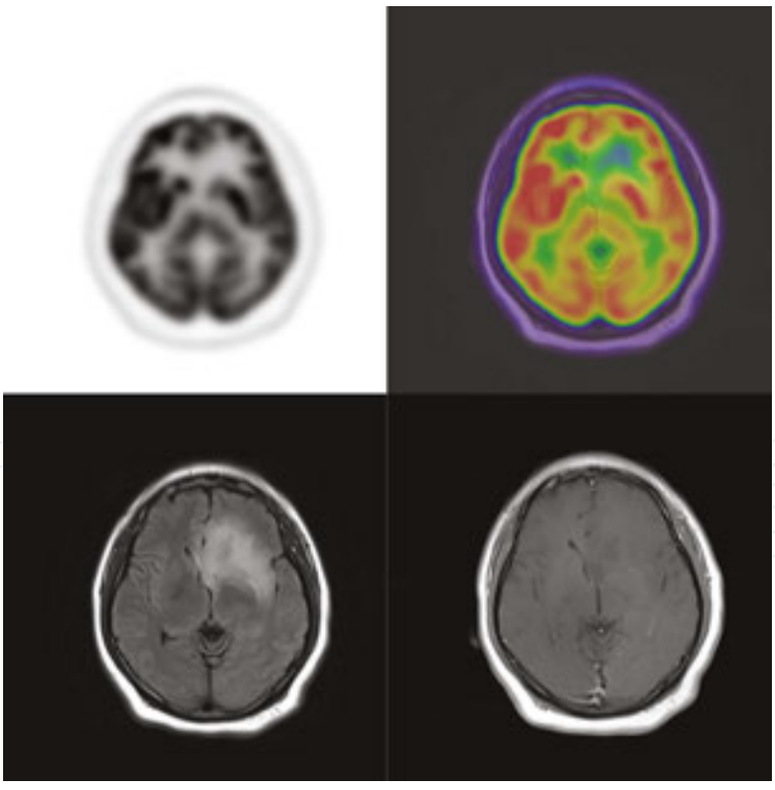

Figure 2. FDG uptake in a left frontal cerebral glioma on PET/CT. *Top row:* The tumour is not readily discernible from intense physiological FDG activity in the adjacent cerebral parenchyma. *Bottom row:* The tumour is much better depicted on MRI FLAIR imaging (*bottom left panel*) and shows no contrast enhancement due to its low grade (*bottom right panel*).

3.2. Tumour grading and prognosis

The uptake of FDG in a neoplasm is a consequence of the increased expression and activity of glucose transporter proteins and of hexokinase, a glucose phosphorylating enzyme. FDG uptake generally correlates with tumour grade [7–9], with low-grade tumours showing similar FDG uptake as white matter, and high-grade tumours similar uptake as grey matter. Tumours can be heterogeneous and contain areas of low- and high-grade dedifferentiation.

FDG uptake in gliomas has also been shown to correlate with survival [10, 11]. Median survival for intracranial metastases is typically less than 1 year, with these metastases generally showing a high-grade pattern of FDG uptake.

3.3. Localisation for biopsy

FDG PET can be useful in selection of a biopsy site where uptake is highest in the tumour, thereby ensuring sampling of the most malignant tissue [12–16].

3.4. Radiotherapy planning

MRI is the current technique of choice for radiotherapy planning. Due to its relatively low tumour-to-background contrast, FDG PET has limited utility for conventional treatment planning. More recently, the addition of PET imaging of some radiotracers—in particular the amino acid analogues—in radiotherapy planning has been shown to be promising in the identification of microscopic residual tumour post-surgery and differentiation of tumour from brain tissue, thereby improving local control and reducing radiation to healthy brain parenchyma (see Section 4).

3.5. Assessment of treatment response

The differentiation of tumour recurrence from radiation necrosis following treatment is one of the most common and important clinical indications for MRI and PET. Both viable tumour and post-radiotherapy necrosis demonstrate contrast enhancement on MRI. Similarly, increased FDG uptake cannot reliably differentiate residual/recurrent tumour from radiation necrosis. Furthermore, false-negative MRI and FDG PET can result from decreased enhancement (due to antiangiogenic therapy) and poor tumour-to-background contrast, respectively.

Whilst the criteria for Response Assessment in Neuro-Oncology have been updated to mitigate these potentially confounding factors in MRI [17–19], advancements in response assessment in PET have focused on other (non-metabolic) radiotracers.

4. Amino acid radiotracers

Amino acids are the building blocks of proteins and critical to nearly every biological process in the human body. They serve as components in metabolic cycles which are upregulated in cancer cells with increased proliferative activity. Because the brain uses glucose almost

exclusively for fuel (except during prolonged starvation), PET imaging of brain tumours with amino acid and amino acid analogue radiotracers has a significant advantage of high tumour-to-background contrast (**Figure 3**).

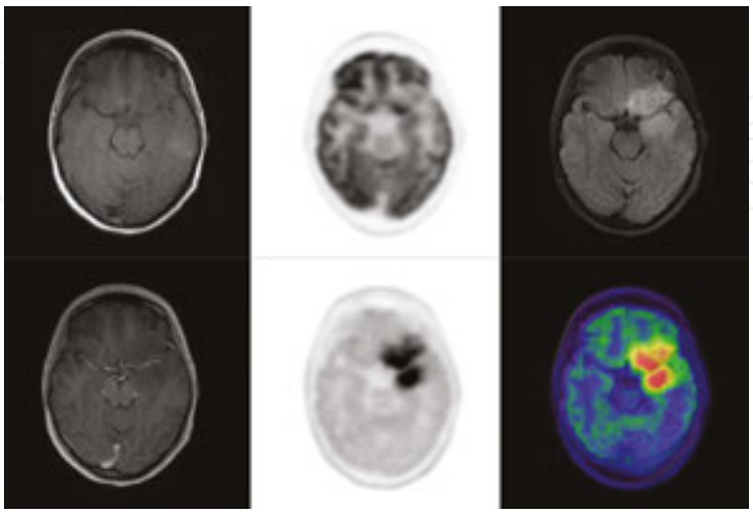

Figure 3. F-18 FDG PET/CT (*top row*) and F-18 FDOPA PET/CT (*bottom row*) of a left frontotemporal low-grade non-enhancing cerebral glioma showing the high tumour-to-background contrast of amino acid imaging compared with metabolic imaging.

4.1. Methionine

Methionine (MET) is a sulphur-containing naturally occurring amino acid (**Figure 4**) whose transport into malignant glioma cells and the supporting vasculature of these tumours is strongly upregulated [20–22].

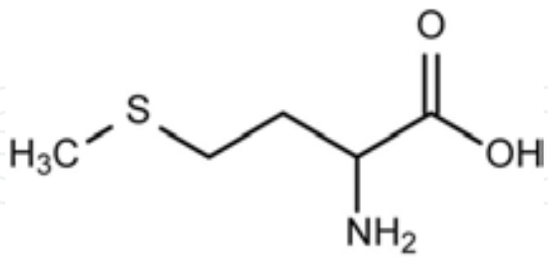

Figure 4. Chemical structure of methionine.

C-11 MET is one of the most widely used amino acid radiotracers for PET imaging in neuro-oncology, mainly due to its relative ease of production that can be performed rapidly with high yield and without the need for complicated purification steps.

The overall sensitivity of MET PET for malignant gliomas ranges from 76 to 95%, with higher rates of detection for higher grade tumours [23]. Increased uptake of MET is also seen in low-

grade gliomas—with reported sensitivities of 65–85% [23, 24]—in which there is typically little or absent contrast enhancement on MRI and low uptake on FDG PET [24, 25].

MET is also generally regarded as the reference in prognostication of disease, image-guided biopsy and radiotherapy planning, and the detection of tumour recurrence [26–34], making it the most important radiotracer in the amino acid category.

The main limitation of C-11 MET is its short half-life (20 min), confining its use to centres with a cyclotron on-site or very nearby. It has also been shown to accumulate in brain abscesses and inflammation (cerebritis) [35], important false positives to exclude in the diagnosis of brain tumour.

F-18 has a much longer half-life (110 min) than C-11 and opens up the possibility of radiotracer transport to another centre for diagnostic imaging. F-18 labelled amino acids include F-18-labelled fluoroethyltyrosine (FET) and dihydroxyfluorophenylalanine (FDOPA).

4.2. Fluoroethyltyrosine

FET is an artificial amino acid (**Figure 5**) taken up by upregulated tumour cells but not incorporated into proteins (unlike naturally occurring amino acids such as methionine). As such, its use in the characterisation of brain lesions and the grading of gliomas requires dynamic analysis of activity over time [36]. Its overall accuracy in the diagnosis of gliomas is comparable to MET [37, 38]. It is an excellent tool for differentiating tumour from non-tumour causes in the initial evaluation of newly diagnosed brain lesions [39] (**Figure 6**). FET PET can also distinguish active tumour from radiation necrosis following treatment [40, 41].

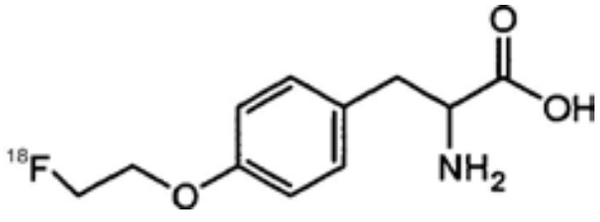

Figure 5. Chemical structure of F-18 fluoroethyltyrosine.

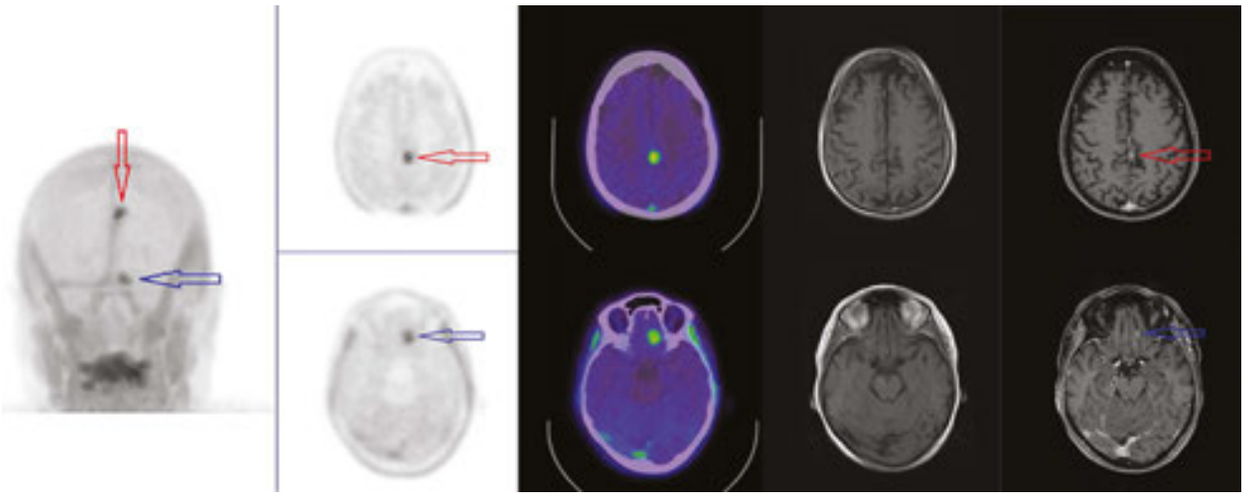

Figure 6. FET PET/CT (*left-sided panels*) and pre/post intravenous gadolinium MRI (*right-sided panels*) in a patient with two small cerebral melanoma metastases (*red and blue arrows*).

4.3. Fluorodihydroxyphenylalanine

FDOPA was originally developed for imaging the DOPA-decarboxylase pathway in Parkinson's disease and other neurodegenerative diseases. It is a fluorinated form of L-DOPA (**Figure 7**) which is used to increased dopamine concentrations in the treatment of Parkinson's disease. FDOPA has since been shown to be a marker of amino acid transport in brain tumours and metastases.

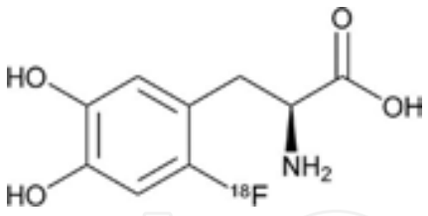

Figure 7. Chemical structure of F-18 fluorodihydroxyphenylalanine.

FDOPA uptake has been shown to correlate with tumour proliferation and grade [42], and more accurate than FDG for evaluating low-grade tumours and distinguishing tumour recurrence from radiation necrosis [43].

It also accumulates in neuroendocrine tumours (NETs) such as phaeochromocytomas and paragangliomas.

5. Fluorothymidine

Thymidine (T) is the pyrimidine deoxynucleoside in DNA that pairs with deoxyadenosine (A). F-18 fluorothymidine (FLT) is a thymidine analogue (**Figure 8**) and a substrate for thymi-

dine kinase 1 (responsible for synchronising cells in G1/early S phase), but unlike thymidine, FLT is a poor substrate for mitochondrial thymidine kinase 2 and its uptake is therefore specific to the cell cycle and a marker of cellular proliferation.

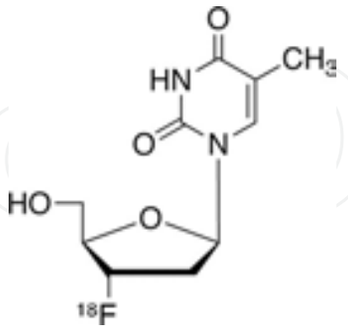

Figure 8. Chemical structure of F-18 fluorothymidine.

FLT uptake in normal brain cells is limited by the blood–brain barrier, thus FLT PET provides higher tumour-to-background contrast than FDG PET. FLT is more sensitive than FDG PET for the detection of recurrent high-grade glioma and also correlates better with tumour progression and survival [44].

However, its use as a quantitative marker of the activity of DNA synthesis in gliomas remains a subject of debate, particularly whether FLT can discriminate moderately proliferative tumours driven by thymidine salvage pathway utilisation from highly proliferative tumours primarily driven by de novo synthesis of thymidine. Quantitative FLT PET with kinetic modelling may also be useful for distinguishing glioma recurrence from radiation necrosis [45].

6. Choline

Choline is a water-soluble B-complex vitamin (**Figure 9**), normally found in blood, which is phosphorylated and subsequently integrated into lecithin, a component of cell membrane phospholipids. Malignant tumour cells demonstrate increased proliferation which results in increased cell membrane turnover and a greater demand for cell membrane components such as choline.

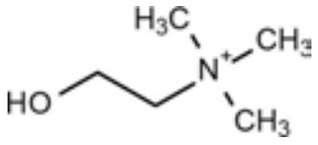

Figure 9. Chemical structure of choline.

Like the amino acid radiotracers, PET imaging with choline offers excellent delineation of tumour from brain with a 10:1 contrast ratio achievable within 5 min of radiotracer injection

[46]. Higher choline uptake generally corresponds with more malignant tumours, and choline PET also appears promising for radiotherapy planning because of more precise delineation of biological target volume [47]. It also has higher accuracy than FDG PET and MRI for the differentiating radiation necrosis and tumour recurrence [47].

Choline can be radiolabelled with C-11 or F-18, permitting its use in centres without an on-site cyclotron.

It has also been investigated extensively for imaging in prostate cancer, with some studies also suggesting a potential role in oesophageal and lung cancer [46, 48–50].

7. Hypoxia radiotracers

Hypoxia is an important factor in the malignant progression of tumour and its resistance to therapy. The majority of hypoxia PET radiotracers belong to a group of compounds known as nitroimidazoles that freely cross the blood–brain barrier, enter cells by diffusion and are subsequently reduced by nitroreductases at a rate inversely proportional to oxygen tension. Thus, in an oxygen-rich environment, they are able to diffuse back out of the cell again, whereas under hypoxic conditions, they are reduced and become irreversibly trapped in the cell. Another favourable property of the nitroimidazoles is their rapid equilibration within the brain parenchyma independently of perfusion.

7.1. Fluoromisonidazole

F-18 fluoromisonidazole (FMISO) was the first of the nitroimidazole radiotracers (**Figure 10**) to be developed for imaging with PET and has been widely used in preclinical and clinical studies.

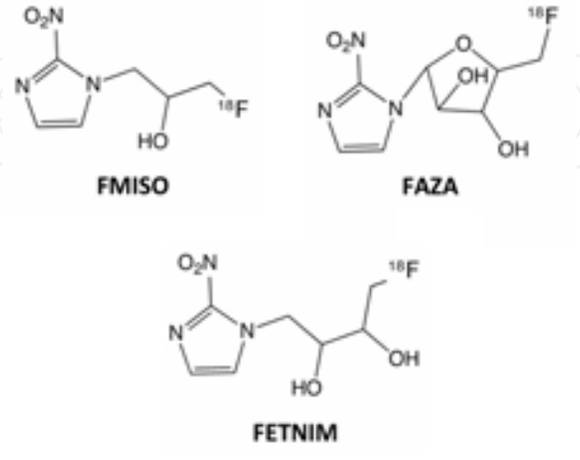

Figure 10. Nitroimidazoles are the most commonly used hypoxia PET radiotracers. FMISO: fluoromisonidazole; FAZA: fluoroazomycin; FETNIM: fluoroerythronitroimidazole.

Hypoxia can be quantified by analysing FMISO PET images using a simple tissue-to-blood ratio of radiotracer activity, with a ratio of 1.2 or greater useful for discriminating and quantifying hypoxic tissue. Hypoxic tumour volume and maximal tumour-to-blood ratio calculated in this way has been shown to predict worse prognosis independent of other factors [51]. FMISO can also differentiate lower from higher grade gliomas better than FDG [52].

More recently, an image-derived region to assess blood activity on FMISO PET has been shown to be an accurate surrogate for serial blood sampling in the quantification of hypoxia [53] and this may obviate the need for routine venous sampling in patients undergoing FMISO PET in the future.

7.2. Fluoroazomycin

F-18 fluoroazomycin (FAZA) is a second-generation nitroimidazole derivative (Figure 10) with more favourable pharmacokinetics than FMISO. FAZA demonstrates faster clearance of unbound radiotracer from non-hypoxic areas (thereby resulting in shorter waiting time for imaging) and improved biodistribution (does not cross the intact blood–brain barrier due to its increased hydrophilicity). Consequently, there is improved hypoxia-to-normoxia contrast, and FAZA shows considerable promise and is expected to overcome the disadvantages of FMISO for imaging hypoxia in brain tumours.

8. Meningiomas

Meningiomas are predominantly benign tumours in adults arising from the meningothelium of the arachnoid mater. Consequently, they occur at the brain surface—over the cerebral convexity, parafalcine region or along the skull base. Rarely, they can occur in intraventricular or intraosseous locations. Meningiomas account for 20–25% of all intracranial neoplasms, with women affected more commonly than men. They are commonly associated with loss of heterozygosity of the long arm of chromosome 22.

On CT and MRI, meningiomas typically appear as rounded or ovoid avidly enhancing masses with dural tails at the tumour margins, variable compressive effect on adjacent brain parenchyma (mainly depending on tumour size) and occasional hyperostosis of the adjacent skull.

Molecular imaging of meningiomas can be accurately performed using somatostatin analogue radiotracers [54] (**Figure 11**).

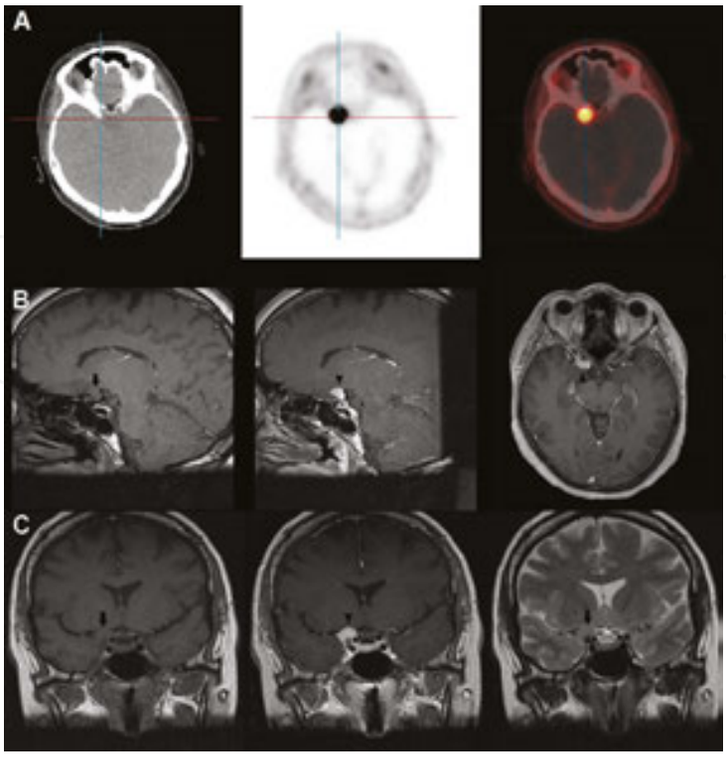

Figure 11. *Row A*: Fusion PET/CT shows a Ga-68 DOTATATE-avid focus directly adjacent to the right anterior clinoid process of the sphenoid bone. *Rows B and C*: Multiplanar MRI sequences show characteristic features of an intracranial meningioma on non-enhanced (*arrows*) and gadolinium-enhanced (*arrowheads*) imaging.

8.1. Somatostatin analogue radiotracers

Currently, the primary indication for using gallium-68 (Ga-68)-labelled somatostatin analogue radiotracers is for PET imaging of carcinoid and other NETs which usually express a high density of somatostatin receptors to which these peptides bind with high affinity [55]. Some non-NETs are also known to express somatostatin receptors, including meningiomas [56–58] which express all of the five somatostatin receptor (SSTR) subtypes but predominantly SSTR1 and SSTR2.

Traditional scintigraphic imaging of meningiomas utilised indium-111-labelled octreotide and single-photon emission computed tomography (SPECT). However, PET imaging with Ga-68-labelled somatostatin analogue radiotracers such as 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-Tyr^3-octreotate (TATE), DOTA-1-Nal^3-octreotide (NOC) and DOTA-Phe^1-Tyr^3-octreotide (TOC) offers superior count statistics and spatial resolution compared with SPECT. It also provides much higher target-to-background ratio of radiotracer uptake and more detailed tumour characterisation and has largely replaced octreotide SPECT imaging. This detailed spatial characterisation of meningiomas, when coupled with anatomical imaging by CT and MRI (in particular), allows for more accurate radiotherapy planning in patients with large, non-resectable tumours.

The demonstration of DOTATATE avidity in an intracranial lesion with only some features of meningioma on CT or MRI could permit differentiation of a meningioma from other tumours such as metastasis or craniopharyngioma, which can have a significant impact on clinical management.

There are also emerging data that DOTATATE uptake on PET improves diagnostic accuracy by delineating meningioma from tumour-free tissue [58] that can potentially enhance on CT and MRI especially in the setting of previous therapy.

FET PET in the late phase may be useful for the non-invasive grading of meningiomas [59].

9. Lymphoma

Almost all patients with primary CNS lymphoma have brain parenchymal lesions which have a predilection for the periventricular and superficial regions. Contrast-enhanced MRI remains the technique of choice when CNS lymphoma is suspected, although it is usually not possible to conclusively differentiate CNS lymphoma from other malignant brain lesions on MRI.

FDG remains the most widely explored radiotracer for PET imaging in CNS lymphoma, though its utility is limited compared with FDG PET in extracranial lymphoma, due to the poor tumour-to-background contrast in the brain. FDG uptake is typically intense in lymphoma—metabolic imaging with PET may help to differentiate lymphoma in the brain from low-grade gliomas and meningiomas [60–62] and may also be suitable for early evaluation of post-treatment response [60]. Infectious pathologies in the brain of immunocompromised subjects can be discerned from lymphoma by their usually hypometabolic nature on FDG PET [63], and high uptake ratio on thallium-201 (Tl-201) imaging [64]. Steroid treatment can cause false-negative results by reducing FDG uptake in CNS lymphoma [62].

MET PET typically shows intense uptake in CNS lymphomas which often involves a larger area than the corresponding enhancing abnormality on CT and MRI and may more accurately delineate the actual tumour margins [65]. It may also be more accurate for the detection of residual or recurrent lymphoma after treatment [65].

10. Other non-glial neoplasms

There is currently a limited role of PET in other non-glial brain neoplasms including neuronal tumours, pineal and pituitary tumours, germ cell tumours and embryonal tumours (PNET, neuroblastoma), although anecdotal evidence, case reports and series exist for some of these tumours.

PET imaging with MET, for example, detected all but one CNS germinoma in a case series of 10 patients [66], and choline uptake correlated with residual intracranial non-seminomatous germ cell tumour in a series of four patients [67].

Pituitary adenomas can appear as hypermetabolic lesions on FDG PET [68, 69], with higher uptake seen in macroadenomas than in microadenomas [69]. Increased DOTATATE uptake has been reported in intracranial metastases of pituitary carcinoma and may be useful in the decision to treat with peptide receptor radionuclide therapy [70, 71]. MET successfully detected all cases of craniopharyngioma in 10 patients [72].

11. PET/MRI

PET/MRI is a relatively novel hybrid diagnostic imaging device that can simultaneously acquire PET and MR images of the brain and other body regions. PET images show the distribution of an intravenously injected radiotracer, whilst MRI depicts the local responses of atomic nuclei to high-frequency radio waves when placed in a strong magnetic field. PET/MRI represents an advance on hybrid PET/CT imaging systems that are currently used in routine clinical practice for the assessment of patients with cancer and other diseases.

The integration of PET with MRI rather than CT has several advantages:

a. ***Reduced radiation exposure for patients.*** The use of MRI to correct PET images for the attenuation of emitted radiation by overlying tissue avoids the ionising radiation of CT. Because the acquisition time for MRI often exceeds that for PET, there are also opportunities to reduce the amount of radiotracer administered, by increasing PET acquisition time.

b. ***More accurate anatomical localisation of areas of radiotracer uptake.*** The simultaneous acquisition of MR and PET images reduces the likelihood of patient movement causing misregistration of the two image sets.

c. ***Compensation for some limitations of PET.*** The ability of PET to identify tumour sites is constrained by background physiological tracer uptake in some organs. For the most commonly used clinical PET radiotracer, FDG, these organs include the brain (as well as the liver and bone marrow) which are frequent sites of tumour recurrence after initial treatment. PET interpretation is also complicated by processes other than tumour infiltration that can cause radiotracer uptake, the most notably inflammation which can be particularly problematic when assessing cancer status after treatment, especially surgery or radiotherapy.

Many of these advantages are particularly relevant to brain tumour imaging, and indeed, the first exploration of feasibility of hybrid PET/MRI in clinical oncology was in brain tumours [73].

PET/MRI could theoretically harness the advantages of PET imaging with various radiotracers to accurately distinguish tumours from surrounding normal brain tissues—and the ability of advanced MRI techniques such as fMRI and diffusion tensor imaging to map the spatial relationship between tumours and adjacent functional brain tissues and white matter tracts—at the same time.

To date, studies in PET/MRI have shown that it can diagnose, grade and evaluate treatment response in glioma patients [74, 75]. Other studies have also shown that PET/MRI can identify areas of greater cellular proliferation and vascularity in brain tumours using a combination of advanced MRI techniques and PET radiotracers for treatment targeting [76–78]. FMISO PET/MRI can quantify hypoxia in recurrent glioma for risk stratification prior to commencement of angiogenesis inhibitor therapy (such as bevacizumab) and assess response to treatment [79, 80].

PET/MRI may gradually replace PET/CT in paediatric oncology due to the radiation dose saving achieved with performing MRI in place of CT, and more specifically in the field of neurooncology, the superior characterisation of brain tumours afforded by MRI over CT. In this arena, PET/MRI with choline and FDOPA have shown promise in the imaging of paediatric astrocytomas [81, 82].

The major disadvantages of PET/MRI currently relate to its high cost and consequent lack of access in many centres, need for optimisation of workflow and image acquisition parameters, and a greater body of evidence to evaluate its perceived superiority over existing techniques in neurooncology such as PET/CT, MRI or indeed PET/CT and MRI with software fusion of PET and MRI data. This would presumably require the results of large randomised controlled trials that should be a focus of future research efforts.

12. Conclusion

Whilst MRI remains the gold standard for imaging of brain tumours, future applications integrating PET—with its enlarging gamut of radiotracers—and MRI are likely forthcoming. This chapter briefly summarised the current status of the most commonly used radiotracers for the molecular imaging of brain tumours (**Table 2**). It will hopefully also serve as a useful guide that the reader can refer back to and build upon with future reading.

Radiotracer	Mechanism	Advantages	Disadvantages
FDG	Glucose analogue, active transport into cell mediated by GLUT transport proteins; phosphorylated by hexokinase and trapped intracellularly	Most widely used and explored radiotracer in PET	Poor tumour-to-background contrast due to intense physiological uptake in normal brain
MET	Essential amino acid transported into malignant glioma cells by LAT1 transporter and incorporated into proteins	Generally regarded as reference in glioma diagnosis, grading, prognosis, imaged-guided biopsy and	Short half-life (20 min) due to C-11 radiolabelling limits use to centres with cyclotron on-site or very nearby

Radiotracer	Mechanism	Advantages	Disadvantages
		radiotherapy planning, and detection of tumour recurrence in PET	
FET	Artificial amino acid transported into upregulated glioma cells but not incorporated into proteins	Overall accuracy for diagnosis of glioma comparable to MET; can distinguish active tumour from radiation necrosis; late phase FET PET may be useful for grading meningiomas	Use in grading of gliomas requires dynamic analysis of activity over time since not incorporated into proteins
FDOPA	Fluorinated form of L-DOPA, the precursor of dopamine that is transported physiologically into brain and abnormally (increased) into glioma	Uptake correlates with tumour proliferation and grade; more accurate than FDG for evaluating low-grade tumours and distinguishing tumour recurrence from radiation necrosis	Limited data outside of use for initial diagnosis of glioma
FLT	Thymidine analogue and substrate for cellular thymidine kinase 1 but poor substrate for mitochondrial thymidine kinase 2	More sensitive than FDG for detection of recurrent high-grade glioma; correlates better with tumour progression and survival	May accumulate in benign brain lesions with disrupted blood–brain barrier
Choline	Water-soluble B-complex vitamin phosphorylated and subsequently integrated into lecithin, a component of cell membrane phospholipids	Can be radiolabelled with C-11 and F-18; higher uptake generally corresponds with higher grade; more accurate than FDG for distinguishing tumour recurrence from radiation necrosis	May accumulate in benign inflammatory lesions
FMISO	First-generation nitroimidazole; enters cells by diffusion and subsequently reduced at a rate inversely proportional to oxygen tension	Permits quantification of hypoxia which has been shown to predict worse prognosis; can differentiate low from high grade gliomas	Requires venous blood sampling for quantification of hypoxia
FAZA	Second-generation nitroimidazole	Better hypoxia-to-normoxia contrast than FMISO	Requires venous blood sampling for quantification of hypoxia
Somatostatin analogues	Bind with high affinity to somatostatin receptors expressed richly by neuroendocrine tumours and some non-neuroendocrine tumours including meningiomas	Excellent tumour-to-background contrast for neuroendocrine tumours; appears promising for tumour delineation in radiotherapy planning	Limited data for use in radiotherapy planning

Table 2. Summary of radiotracers most commonly used in PET imaging of brain tumours.

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