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Molecular Imaging of Brain Metastases with PET

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Abstract: Molecular imaging of brain metastases with positron emission tomography with computed tomography (PET/CT) or with magnetic resonance imaging (PET/MRI) can be performed with a growing number of molecular imaging agents. The most commonly used molecular imaging agent for primary malignancies outside of the brain is a glucose analog radio-labelled with fluorine-18, 18F-fluorodeoxyglucose (18F- FDG), which can be used to identify brain metastases. Likewise, additional molecular imaging agents such as prostate specific membrane antigen (PSMA) ligands (i.e., 68Ga-PSMA-11), alkylphosphocholine analogs (i.e., CLR124/CLR1404), and amino acids (i.e., 11C-MET, 18F-FET, 18F-DOPA, 18F-FACBC) can identify brain metastases. Advantages of PET in brain tumor imaging include co-registration with other imaging technologies, quantitative measurements, and significant potential for improvement in diagnostic accuracy. PET can be used to detect brain metastases while imaging for other sites of metastatic disease, discriminate treatment-related changes from tumor recurrence, and identify patients for targeted radiotherapy from theranostic molecular imaging and targeted radiotherapy agents.

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INTRODUCTION

Metastases to the brain from non-central nervous system (CNS) malignancies comprise the largest percentage of intracranial neoplasms and may be present in up to one-fifth of adult cancer patients (1). According to Stark et al., the most common oncologic etiologies of brain metastases include lung cancer (50%), breast cancer (15%), and melanoma (7%) (2). Most brain metastases occur at the junction of the gray matter and white matter, likely due to the hematogenous spread of tumor emboli that become trapped in the small branches of the terminal arteries (3). Even though recently developed treatment regimens for primary and metastatic brain tumors have improved outcomes in patients, many of these patients still have a high rate of morbidity and mortality. Providing an earlier and/or more accurate diagnosis in brain metastases may help improve the overall clinical outcome in patients.

Magnetic resonance imaging (MRI) is considered the standard for imaging primary and metastatic brain tumors and has a very high sensitivity for tumor detection. However, there are some limitations of MRI imaging of brain tumors and metastases. First, some patients may not be able to obtain an MRI for various reasons such as the presence of certain medical devices or implants, reduced renal function, presence of shrapnel, etc. and thus other imaging modalities must be utilized to diagnose brain metastases. Second, many patients with non-CNS malignancies who are not displaying neurological symptoms do not routinely have an MRI of the brain and thus asymptomatic brain metastases may not be diagnosed. Finally, in the post-treatment setting, particularly with the use of radiation therapy, the specificity for differentiating treatment-related changes from true tumor recurrence may be reduced with MRI.

Molecular imaging using positron emission tomography (PET) with either computed tomography (PET/CT) or magnetic resonance imaging (PET/MRI) can be used to diagnose brain metastases. In contrast to the structural or anatomic evaluation of brain metastases provided by imaging modalities such as MRI and CT, PET with molecular imaging agents can assess the functional status of tumors and thus provide additional complementary information to anatomic imaging. There are numerous molecular imaging agents in clinical use or used in the research setting with potential to detect the presence of brain metastases. As shown in Table 1, commonly used clinical agents or research agents with potential for clinical use include a glucose analog radiolabeled with fluorine-18, 18F-fluorodeoxyglucose (18F-FDG), prostate specific membrane antigen (PSMA) ligands (i.e. 68Ga-PSMA-11), alkylphosphocholine analogs (i.e. CLR124/CLR1404), and amino acids [i.e. 11C-methionine (11C-MET), 18F-fluoroethyltyrosine (18F-FET), 18F-fluorodihydroxyphenylalanine (18F-DOPA), 18F-fluorocyclobutanecarboxylic acid, also known as 18F-fluciclovine and Axumin (18F-FACBC)].

TABLE 1 **Common classes of PET molecular imaging agents which can be used or show promise in the evaluation of brain metastases**

Class	Primary example(s)	Primary diagnostic radiolabel(s), half-life	Mechanism of uptake	Example of potential radiotherapy targeting agent in same class	Primary therapeutic radiolabel(s), half-life
Glucose analogs	FDG	18F, 110 min	Transported through cell membrane by GLUT, trapped after phosphorylation	Not applicable	Not applicable
Prostate Specific Membrane Antigen Ligands	68Ga-PSMA-11	68Ga, 68 min 18F, 110 min 64Cu, 12.7 hours	Binds to PSMA on cell surface leading to internalization	177Lu-PSMA-617	177Lu, 6.6 days 225Ac, 9.9 days
Alkylphosphocholine Analogs	CLR124	124I, 4.2 days	Targets lipid rafts to enter cell	CLR131	131I, 8.0 days 125I, 59.5 days
Amino Acids	11C-MET 18F-FET 18F-FDOPA 18F-FACBC	11C, 20 min 18F, 110 min	Transported into the cell via LAT1, LAT2, and /or ASCT2	Not applicable	Not applicable

MOLECULAR IMAGING AGENTS

Given the large number of molecular imaging agents that have identified or potentially could identify brain metastases in humans, it is not possible to list in detail all potential molecular imaging agents in this chapter. Thus, only agents that have been used clinically or are in clinical trials with a reasonable potential of being used clinically will be included in this review.

Glucose analogs

The tumor microenvironment is important for cancer cell survival and tumor progression (4) and cellular energy metabolism is an important factor in the tumor microenvironment (5). Glucose uptake in both malignant and non-malignant cells is facilitated by 14 sub-types of glucose transporters (GLUT1 – GLUT14). Certain GLUT transporters are predominant in certain tissue types; for instance, GLUT1 is expressed in many tissue types, GLUT2 is highly expressed in the liver, and GLUT3 is highly expressed in the brain. Overexpression of glucose transporters facilitating increased uptake and metabolism of glucose is a hallmark of tumorigenesis. While multiple GLUT transporters have been shown to be overexpressed in various cancers and their metastases, GLUT3 has been shown to have an especially high affinity for glucose and is overexpressed in multiple tumor types including breast cancer, colorectal cancer, and primary brain cancer and brain metastases (6, 7).

Fluorodeoxyglucose (FDG) is a glucose analogue that can be radiolabeled with fluorine-18 (18F) to create the most commonly used PET molecular imaging agent, 18F-FDG. Both FDG and 18F-FDG are similarly transported through the cell membrane into the cytosol by facilitative glucose transporters (GLUT) in both malignant and non-malignant cells. Once FDG and 18F-FDG are transported into the cytosol, they are phosphorylated by hexokinase into FDG-6-phosphate and 18F-FDG-6-phosphate, respectively (8). Once phosphorylated, 18F-FDG-6-phosphate is metabolically trapped unless it is dephosphorylated by glucose-6-phosphatase. There is high uptake of 18F-FDG in the brain, particularly in the metabolically active grey matter and basal ganglia, and along with lack of significant glucose-6-phosphatase activity in the brain to dephosphorylate the 18F-FDG-6-phosphate, there is essentially irreversible binding in the brain. In addition to the physiological uptake of FDG in the brain, primary brain tumors and brain metastases demonstrate increased FDG uptake due to the overexpression of glucose transporters, especially GLUT3. Molecular imaging with PET can take advantage of this upregulated pathway of FDG transport and intracellular trapping through imaging the positron emissions from trapped 18F-FDG-6-phosphate within brain tumors and metastases.

18F-FDG PET has significant clinical impact in oncologic molecular imaging of a wide variety of cancer types and their metastases. It is used for initial diagnosis and staging of disease, identifying appropriate biopsy targets and for surgical planning, radiation therapy planning, evaluation of metabolic treatment response, and other indications. In the brain, there have been multiple studies evaluating the oncologic uses of 18F-FDG in primary and metastatic brain tumors. Examples of clinical uses in brain metastases include: (i) identifying clinically unsuspected

brain metastases in patients undergoing PET imaging for non-CNS primary tumors; (ii) aid in surgical and/or radiotherapy planning for treatment of brain metastases; (iii) differentiating treatment related changes, such as pseudoprogression after radiation therapy, from true tumor recurrence or progression; (iv) assessing metabolic response to systemic therapy or radiation therapy; (v) predicting overall survival; and (vi) providing an imaging alternative for a subset of patients who are not able to obtain an MRI.

An advantage of 18F-FDG imaging in brain metastases includes the ability to identify metastases from a wide variety of primary tumor types due to high FDG avidity in many cancers and their brain metastases. A disadvantage of 18F-FDG imaging is the high background physiological uptake of FDG in the normal brain parenchyma, particularly the grey matter, which can obscure pathological FDG uptake of brain metastases that most commonly occur at the grey matter white matter junction. This results in a low tumor-to-background ratio that can reduce the sensitivity for detection of brain metastases. Furthermore, brain metastases tend to start as small lesions and PET has a relatively limited spatial resolution for lesions smaller than 1 cm and thus the sensitivity for detecting smaller lesions may be further reduced. Of note, however, lesions smaller than 1 cm can still be readily detected in some patients as demonstrated in Figure 1. Hence, in multiple studies with small and/or heterogeneous patient populations, the sensitivity and specificity of 18F-FDG PET for detecting brain metastases or differentiating tumor recurrence from treatment-related change can vary significantly. Galldiks et al. reviewed multiple studies and identified a sensitivity range of 40–95% and a specificity range of 50–100% (9). These findings may lead one to question the utility of FDG imaging for brain metastases, however in properly selected patients FDG PET imaging still has tremendous clinical value. Nonetheless, other PET molecular imaging agents may have advantages over FDG, and clinically relevant examples are included for review in this chapter.

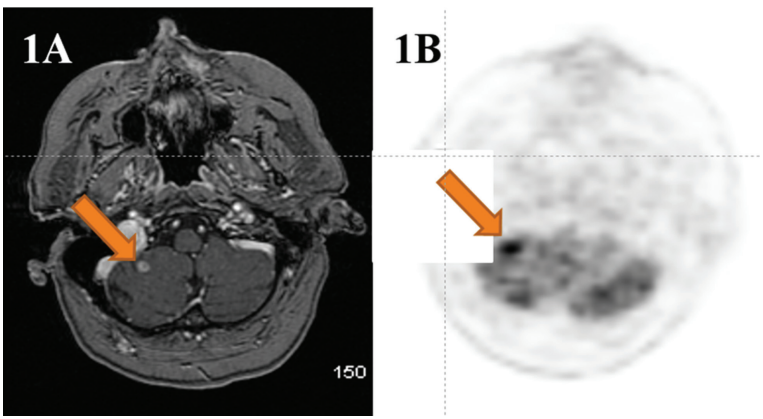


Figure 1. MRI and 18F-FDG PET. Axial T1 contrast enhanced MRI (1A) and axial 18F-FDG PET (1B) of a patient with a small 6 mm right cerebellar brain metastasis from non-small cell lung carcinoma demarcated by solid arrows. Although there is relatively high background physiological uptake of 18F-FDG in the cerebellum, there is higher uptake in the brain metastasis above this background uptake.

Prostate specific membrane antigen ligands

Prostate specific membrane antigen (PSMA) is a transmembrane protein that is most known for its presence in benign as well as malignant prostate tissue. However, despite its name, PSMA is not prostate specific as receptors are found within salivary glands, kidneys, small intestine, liver and spleen. It is also expressed in tumor associated angiogenesis, and is present in other tumors such as glioblastoma, thyroid cancer, gastric, breast, renal and colorectal cancers and their metastases (10). PSMA has an enzymatic role in the cleavage of α-linked glutamate from N-acetylaspartyl glutamate and γ-linked glutamates from polyglutamated folates (11). Additional functions have been attributed to PSMA including in cell migration, cellular nutrition, transport, and signal transduction (12).

Multiple molecular imaging and targeted radiotherapy agents targeting PSMA have been developed for prostate cancer. Given the presence of PSMA in various tumor types, these agents may also be used for other primary tumors and their metastases, including brain metastases. Commonly used molecular imaging agents can be radiolabeled with the positron emitters gallium-68 (68Ga), fluorine-18 (18F), and copper-64 (64Cu). Examples include: 68Ga/18F-PSMA-11 (68Ga/18F-PSMA-HBED-CC); 68Ga/64Cu-PSMA-617; 68Ga-PSMA-I&T; 18F-DCFBC; 18F-DCFPyL; and 18F-PSMA 1007. These PSMA ligands bind to PSMA on the cell surface leading to internalization (13). Commonly used targeted radiotherapy agents can be radiolabeled with the beta-emitter lutetium-177 (177Lu) and alpha-emitter actinium-225 (225Ac). Examples include: 177Lu/225Ac-PSMA-617; 177Lu- PSMA-I&T; 225Ac/177Lu-J591; and 177Lu-Rosopatamab.

Normal brain parenchyma does not have avid uptake on PET with PSMA based molecular imaging agents. However, primary brain tumors and brain metastases from a variety of primary tumor types have shown avid uptake of PSMA based PET molecular imaging agents. This avid tumor uptake in contrast to the low normal background activity results in a high tumor to background ratio that makes identification of brain metastases relatively straight forward. Kasoha et al. demonstrated PSMA expression in primary breast cancer and its metastases, and notably, a higher brain tumor-associated neovasculature expression of PSMA compared to bone tumor-associated neovasculature expression of PSMA (14). Parihar et al. demonstrated avid brain metastasis uptake with 68Ga-PSMA-HBED-CC PET/CT in a patient with prostate cancer (15). There are additional reports of avid uptake of PET PSMA molecular imaging agents in renal cell carcinoma (16), thyroid cancer (17), adenoid cystic carcinoma of the parotid gland (18), and melanoma (19).

Alkylphosphocholine analogs

Lipid rafts are specialized plasma membrane microdomains (20) that spatially organize signaling pathways and regulate cell proliferation and survival (21). Lipid rafts are more abundant in cancer cells relative to normal cells (22) and are overexpressed in many solid tumors and their metastases. 18-(p-[^{127}I] iodophenyl) octadecyl phosphocholine is an alkylphosphocholine (APC) analog that targets lipid rafts to enter cancer cells (23). In addition, there is prolonged retention of this agent within cancer cells which is facilitated by deficient phospholipid catabolizing enzymes commonly encountered in cancer cells (24). This APC

analog can be radiolabeled with iodine-124 (CLR124, aka 124I-CLR1404) for molecular imaging with PET or iodine-131 (CLR131, aka 131I-CLR1404) for molecular imaging with single photon emission tomography (SPECT) as well as targeted radiotherapy.

In human imaging studies, there is avid uptake of CLR124 in a variety of primary and metastatic brain tumors along with negligible uptake in normal brain tissue, resulting in a high image contrast (high tumor to background ratio) and thus clear identification of viable tumor cells and tumor volumes on PET, as seen in Figure 2 (25). Hall et al. demonstrated avid CLR124 uptake with high sensitivity in 12/13 patients with recurrent high-grade gliomas and brain metastases after prior treatments and only 5/12 patients with benign treatment related changes that all demonstrated T1 contrast enhancement and increased T2 signal with MRI. Furthermore, when tumor volumes were compared with PET uptake versus with T1 gadolinium contrast enhancement and T2 signal on MRI, there was concordance in less than 40% of cases with T1 enhancing tumor volumes and no concordance with T2 tumor volumes. Although the clinical significance of this discordance is yet to be fully discerned, the additional molecular information regarding the brain metastases and their surrounding tissue provided with PET imaging is complimentary to MRI and could potentially improve clinical decision making (23).

In addition to the molecular imaging use of CLR124 (i.e., PET) and CLR131 (i.e., SPECT), there is also a potential therapeutic use of this APC analog utilizing a molecular targeted radiotherapy approach. Radioactive pharmaceuticals that have a potential for both diagnostic (i.e., molecular imaging) and therapeutic uses (i.e., targeted radiotherapy) are known as theranostic agents (aka *theragnostic*, aka *diapeutic*). These theranostic agents are able to use a molecular imaging agent as its own biomarker to predict therapeutic response *a priori* with the same or similar therapeutic agent. Using the non-radioactive CLR compound

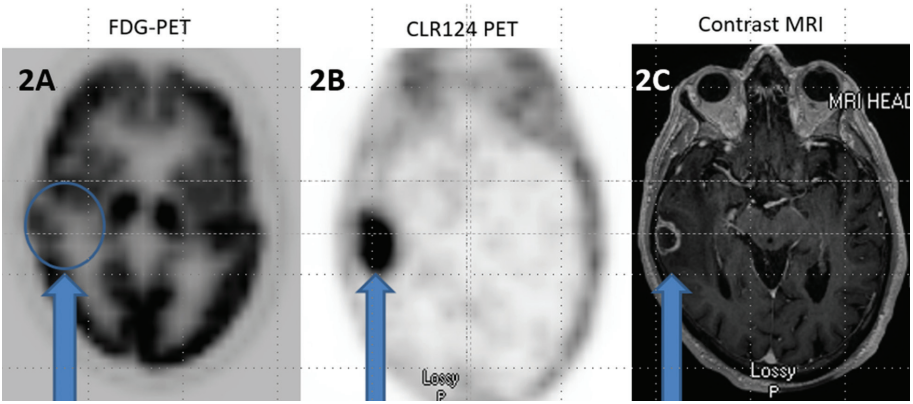


Figure 2. Axial 18F-FDG PET (2A), axial CLR124 PET (2B), and axial T1 contrast enhanced MRI (2C) in the same patient with a right temporal brain metastasis from non-small cell lung carcinoma. Note the high background cerebral uptake of FDG limits identification of the metastasis on 18F-FDG PET whereas the high tumor uptake compared to low background cerebral uptake of CLR124 facilitates easy identification of the metastatic lesion. The lesion is demarcated by arrows on all images and demonstrates enhancement on MRI.

(i.e., 18-(p-[^{127}I] iodophenyl) octadecyl phosphocholine)), the non-radioactive 127I in CLR can be substituted with other radioactive isotopes of iodine for imaging (124I and 131I for CLR124 and CLR131, respectively) and targeted radiotherapy (131I and 125I for CLR131 and CLR125, respectively). Currently there are ongoing clinical trials utilizing this theranostic approach to molecular imaging and targeted radiotherapy in a variety of tumor types.

Amino acids

Clinical use of amino acid PET tracers for evaluation of metastatic disease in the brain has recently been recommended by an international working group, known as the Response Assessment in Neuro-Oncology (RANO) working group. They contend that amino acid PET imaging should be used in addition to MRI, primarily because MRI alone has limitations when evaluating therapy response, especially after radiation (26–29). The most thoroughly researched indication for using amino acid PET imaging for brain metastases has been to discriminate between radiation injury and recurrent disease. Although the studies conducted so far are primarily retrospective in nature at single centers, the data have consistently shown high diagnostic accuracy (29). Amino acid PET may also have higher diagnostic utility than advanced MRI methods [e.g., perfusion-weighted imaging (PWI), MR spectroscopy (MRS), diffusion-weighted imaging (DWI)], but the data are currently very limited in terms of head-to-head comparison (30). The amino acid PET tracers that will be discussed in this chapter are depicted in Figure 3 (31–34).

There are several advantages to amino acid PET. The amino acid PET tracers in general have good tumor-to-brain contrast due a combination of low uptake in

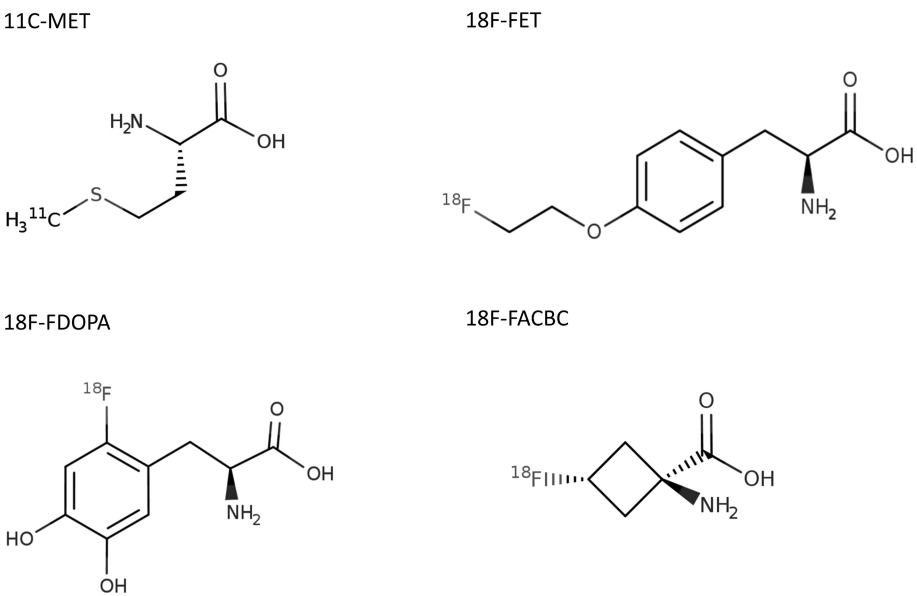


Figure 3. Chemical structure of common amino acid PET tracers (31–34).

normal brain tissue and increased uptake in neoplastic tissue; this favorable contrast ratio lends itself to easier readability (28, 35). Similar results have been observed at multiple institutions involving these tracers, in large part due to practices aimed at standardizing image acquisition and analysis (35). In Europe, utilizing amino acid PET has specifically been shown to be cost effective in distinguishing recurrent metastatic tumor from post radiation changes in the brain. 18F-FET in particular has the most evidence supporting its use for this indication (27). A disadvantage to amino acid PET is that studies are scarce with regards to uptake in untreated metastatic disease in the brain (26). Moreover, uptake may be variable depending on tumor type. For example, a multicenter study showed that metastatic lung cancer to the brain very often had high 18F-FET uptake whereas metastatic melanoma had variable uptake (26, 36).

The mechanism of action for these amino acid PET tracers is that uptake is mainly via the L-type amino acid transporters, LAT1 and/or LAT2, which transport large neutral amino acids. There is high expression of these transporters in tumor cells due to a need to rev up protein synthesis (27–29). Of note, 18F-FACBC also utilizes the alanine, serine, and cysteine transporter 2 (ASCT2), which is also overexpressed in many malignancies. An interesting and favorable characteristic of the amino acid PET tracers is that, unlike MR contrast agents, they can cross the intact blood-brain barrier which may be more important for the detection of primary brain tumors as opposed to brain metastases given that primary brain tumors may retain some of the blood-brain barrier structure (30, 37, 38).

The clinical indication of distinguishing post radiation changes from recurrent metastatic disease in the brain is an important one because it is such a common problem. The risk of radiation necrosis is often around 25% but can reach as high as 50% depending on delivered dose and size of treatment area. The RANO working group contends that the evidence suggests that amino acid PET is likely superior to FDG PET for this indication (29), whereas a meta-analysis by Li et al. found that there was little if any overall difference between the two classes of tracers (38). Their data found that the three amino acid tracers 11C-MET, 18F-FET, 18F-FDOPA had pooled sensitivities of 0.86, 0.83, and 0.86 and pooled specificities of 0.79, 0.89, and 0.88, respectively, with 18F-FDG showing a pooled sensitivity of 0.85 and specificity of 0.90; however, this data was only based on 2 studies each for 11C-MET and 18F-FDOPA and 5 and 6 studies, respectively, for 18F-FET and 18F-FDG.

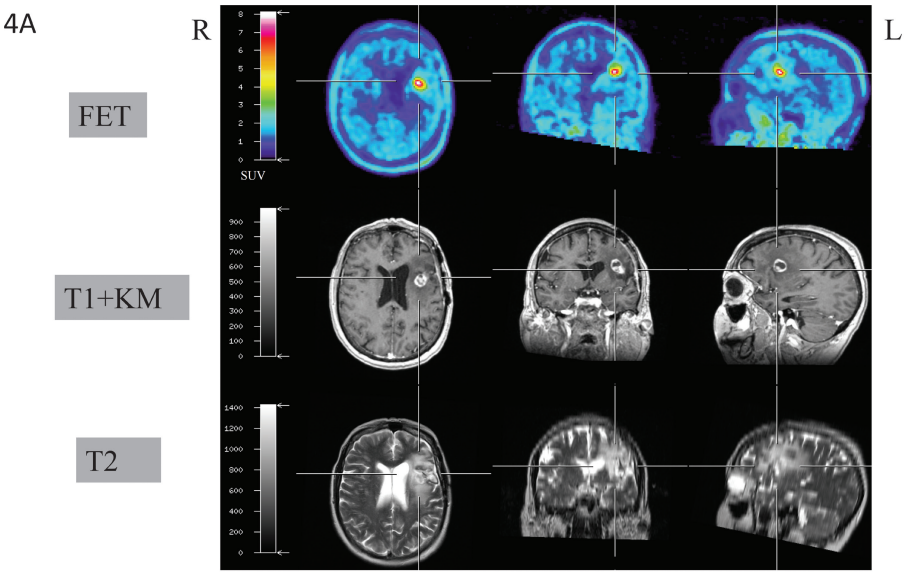
Nevertheless, this metanalysis by Li et al. concluded that amino acid PET and FDG PET had good diagnostic accuracy and are still better than other currently utilized techniques to differentiate radionecrosis from recurrent metastatic tumor in the brain (38). The evidence for utilizing amino acid PET for other clinical indications in the setting of brain metastases is not as strong. For example, currently only limited data is available to suggest that amino acid PET may be helpful in distinguishing immunotherapy pseudoprogression secondary to inflammation from true recurrent disease when MRI findings are indeterminate (28, 29). Immunotherapy drugs that have been associated with pseudoprogression in treatment of brain metastases include the immune checkpoint inhibitors of PD-1 (e.g., pembrolizumab or nivolumab) and of CTLA-4 (e.g., ipilimumab) (35). With regards to the clinical indication of assessing treatment response, there is only preliminary data to suggest that amino acid PET might offer additional value beyond that provided by conventional MRI; for example, decreased degree of

18F-FET activity associated with brain metastases has been seen in melanoma and non-small cell lung cancer patients treated with targeted therapies with stable conventional MRI findings (29, 30, 35, 39). As discussed earlier, given that amino acid PET tracers can cross the intact blood-brain barrier, amino acid PET and contrast-enhanced MRI data together may be able to better identify the margins of brain metastases, i.e., delineation of tumor extent (37).

Contrast-enhanced MRI remains the preferred modality for the clinical indication of detection of newly diagnosed/untreated brain metastases, given that subcentimeter metastases may be too small to be identified with PET. It has not been well studied if amino acid PET might contribute important information regarding prognosis in the setting of brain metastases. Finally, given the variability in number of LAT transporters and degree of uptake on PET, even in different metastases in the same patient, amino acid PET cannot be used to identify the site of origin of the primary tumor based on degree of uptake (29).

11C-MET has been the most commonly used amino acid radiotracer in neuro-oncology over decades. It is an essential amino acid labeled with carbon-11 for use in PET scanners (29). The downside of carbon-11 is its short half-life which is only 20 minutes in comparison to fluorine 18 which has a half-life that is 5.5 times longer at 110 minutes; consequently, 11C-MET imaging is only practical at institutions with an on-site cyclotron (27, 29). Utilizing tumor-brain ratios for analysis, 11C-MET has been shown to have a sensitivity and specificity of approximately 70–80% to distinguish post radiation change from recurrence of metastatic disease in the brain (29, 35). The slightly lower diagnostic accuracy of 11C-MET in comparison to the other amino acid PET tracers 18F-FET and 18F-FDOPA has been thought to be secondary to higher uptake of 11C-MET in inflammation (28). A head-to-head comparison study conducted by Tomura et al. found that 11C-MET PET was better than FDG PET in distinguishing radiation necrosis from recurrent metastatic disease in the brain (38, 40). Another recent study by Tran et al. found that 11C-MET was a reliable marker for detecting recurrent disease in the post radiation setting; for example, 11C-MET was able to correctly identify pathologically confirmed recurrent disease in 7 lesions in 5 patients (41, 42).

18F-FET appears to be in some ways the new and improved version of 11C-MET. Having been safely used in humans since 1999 and first approved as a medical drug in 2014 in Switzerland, this amino acid PET radiotracer has largely taken the place of short-lived radiotracers such as 11-C MET in western Europe due to its proven efficacy in multiple studies and longer half-life owing to its fluorine-18 labeling. Importantly and interestingly, 18F-FET, a synthetic amino acid, has favorable metabolic stability (27, 29). For example, whereas 11C-MET and 18F-FDOPA are utilized in various intracellular processes such as protein assembly and metabolic degradation, 18F-FET is not metabolized after it enters the cell via the transporter LAT and does not appear to be shuttled back out of the cell via an efflux transporter. Consequently, 18F-FET demonstrates a higher retention time in neoplastic tissue than the other natural amino acid radiotracers (27, 29). Utilizing static and dynamic data, 18F-FET PET has been shown to have high sensitivity and specificity in the 80 to 90% range for differentiating post radiation changes from recurrent metastatic disease in the brain (28, 29, 35); image examples are provided in Figure 4. Static parameters include measurements such as tumor-to-brain ratio (TBR) max and mean, and dynamic parameters, which



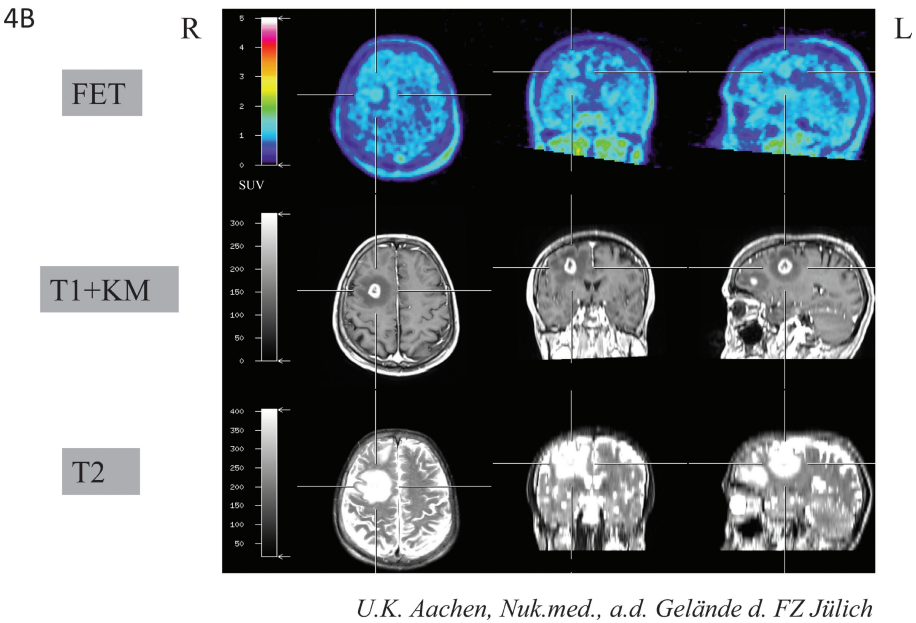


Figure 4. Tumor monitoring. 18F-FET PET correctly indicates the presence of tumor recurrence verified by histology, (4A) and the absence of tumor recurrence, verified by clinical follow up, (4B) whereas MRI is equivocal for tumor recurrence versus radionecrosis after treatment with radiotherapy or radiosurgery for metastatic lung cancer in the brain. (Courtesy of Karl-Josef Langen, Department of Nuclear Medicine, RWTH University Clinic and Research Center Jülich, Germany).

appear to further boost diagnostic accuracy in the case of 18F-FET, include those obtained from a time activity curve such as time-to-peak, slope, and configuration (28, 29). For example, in a study of 62 patients, Ceccon et al. showed that the PPV could be increased from a range of 83-86% using static parameters to up to 91% if dynamic data were incorporated into the analysis when using 18F-FET to differentiate post radiation injury from recurrent metastatic disease in the brain (26). Although the clinical indication of distinguishing between recurrent metastatic tumor and post radiation change in the brain with 18F-FET has the strongest evidence, there is also a small amount of initial evidence to suggest that 18F-FET may also be able to play a role in differentiating pseudoprogression after immunotherapy from true disease progression. A small pilot study involving 5 patients by Kebir et al. showed that 18F-FET uptake was barely visible or absent in patients who had MRI findings suggestive of progression; these patients with melanoma brain metastases who were being treated with the immune checkpoint inhibitor ipilimumab were shown to have a favorable outcome after 6 months (29, 30, 43). Thus, the 18F-FET data seemed to correctly identify the presence of pseudoprogression as opposed to true progressive disease in the setting of immunotherapy.

18F-FDOPA was designed to serve as a way to gauge dopamine synthesis in the basal ganglia and is indeed approved in both the United States and Europe for evaluation of patients with suspected Parkinsonian syndromes (29). Like 18F-FET, 18F-FDOPA benefits from the use of fluorine-18 as its label. It was recognized that 18F-FDOPA could also play a role in the imaging of brain tumors, but there remains considerably more data on the efficacy of 18F-FET for brain tumor imaging as compared to 18F-FDOPA (27). 18F-FDOPA appears to be able to differentiate post radiation change from recurrent metastatic disease in the brain with a high diagnostic accuracy in the 80 to 90% range, similar to 18F-FET. For example, a study of 32 patients by Lizarraga et al. found the sensitivity and specificity to be 81% and 84%, respectively (44), and a study of 42 patients by Cicone et al. found the diagnostic accuracy to be around 91% (45). Of note, one difference between 18F-FDOPA and the other amino acid PET tracers is that 18F-FDOPA demonstrates prominent physiologic uptake within the brain, specifically the striatum, which could potentially interfere with the evaluation of tumor extent depending on the location of the brain metastasis (27, 29).

18F-FACBC, also known under the generic name fluciclovine and brand name Axumin, is a synthetic amino acid PET radiotracer approved in the United States and Europe to identify the location of recurrent prostate cancer in patients with biochemical recurrence. There are only a few studies in the literature about its use in the setting of brain metastasis imaging, however given the success of other amino acids and the increasingly widespread clinical use, this agent may have a good clinical potential in brain metastasis imaging. For example, a study involving 8 patients with a total of 15 lesions was conducted by Parent et al. in which they encouragingly found that 18F-FACBC could be used to differentiate recurrent metastatic disease in the brain from radionecrosis with 100% accuracy up to 30 minutes after injection and 87% accuracy at 55 minutes after injection using a SUVmax threshold of ≥1.3 (46); the metastases in this study were from various primary malignancies, specifically lung, renal, breast, and colon. A case report from Johannessen et al. showed high tumor to background ratios in brain metastases using 18F-FACBC (37). Because 18F-FACBC utilizes both the ASCT2 and LAT1 transporters as opposed to the other amino acid PET radiotracers which

mainly use LAT (28), it is suggested that the uptake characteristics of this amino acid PET tracer as compared to the others may differ in the evaluation of metastatic disease to the brain. For example, it has been shown that the transport of 18F-FACBC across the intact blood brain barrier is lower as compared to 11C-MET (47). One potential explanation for this is that ASCT2 is not expressed on the luminal side of the vasculature, and 18F-FACBC utilizes ASCT2 more than LAT1 (37). The authors of the case report hypothesize that it is possible that 18F-FACBC might be better for detecting early tumor recurrence, and 11C-MET and 18F-FET might be better for evaluating more advanced disease given that there is some data suggesting that ASCT2 is more active in early disease stages and LAT1 is more predominant in later stages, but obviously much more investigative work will have to be done to better evaluate 18F-FACBC's potential role in the evaluation of metastatic disease in the brain.

CONCLUSION

Brain metastases are becoming a more frequent occurrence in the clinical setting. This is probably due to a combination of advancements in imaging technology and improved survival due to better treatment regimens (26, 37, 38). Some of the most common primary tumor locations that can give rise to metastatic disease in the brain include breast, melanoma, lung, colon, and renal malignancies (26, 38). Metastases in the brain are encountered 10-fold more often than primary brain tumors. Although conventional MRI is a highly utilized and excellent technique for identifying brain metastases, there are some indications where the specificity may not be high enough, such as for example distinguishing radiation induced changes from active tumor. Advanced MRI techniques, SPECT, and PET have been investigated to try to meet these clinical needs (38). The primary PET tracers that may be clinically available for the evaluation of brain tumors include the current workhorse of PET oncology imaging, 18F-FDG, and amino acid radiotracers such as 11C-MET, 18F-FET, 18F-FDOPA, and 18F-FACBC (27, 46); other radiotracers discussed in this chapter that have shown clinical promise include prostate specific membrane antigen (PSMA) ligands (i.e., Ga-68 PSMA-11) and the alkylphosphocholine analogs (i.e., CLR124/CLR1404).

There are some disadvantages of PET imaging which bear mentioning. For example, access to PET technology is limited in some parts of the world due to economic and/or logistic issues, PET scanners are not cheap or low maintenance items, and PET imaging has limitations when it comes to spatial resolution (27, 38, 41). However, there are numerous advantages of utilizing PET in brain tumor imaging which include, for example, co-registration with other imaging technologies, quantitative measurements, and significant potential for improvement in diagnostic accuracy (27, 35). Moreover, depending on the institution, the required PET infrastructure could already be present, and obtaining amino acid PET tracers can sometimes be similar in cost to FDG. There may also be overall cost savings if PET can take the place of other imaging techniques with inferior diagnostic utility (35). In the end, hybrid PET/MRI may hold the most potential for improving clinical outcomes by providing more precise localization of brain metastases for optimal pre-operative planning and post-treatment

monitoring (27, 37). Moreover, PET radiotracers provide a promising future avenue to better care for patients with metastatic disease to the brain by creating the opportunity for theranostics in which the disease could be identified and tracked with a molecular imaging agent and treated with a similar radiotherapy targeting agent.

Conflict of Interest: The authors declare no potential conflict of interest with respect to research, authorship and/or publication of this chapter.

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