Cellular and Molecular Imaging with SPECT and PET in Brain Tumors

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KEYWORDS

• Brain tumor • PET • SPECT • Molecular imaging

KEY POINTS

- Molecular imaging provides functional information based on target detection, which can be helpful in management of brain tumors.
- There are multiple different radiotracers developed based on different mechanisms that can be used in neuro-oncology.
- These radiotracers can detect brain tumors, differentiate low-grade and high-grade lesions, determine eligibility for theranostics, estimate prognosis, and evaluate post-radiation changes.

INTRODUCTION

Brain neoplasms include a diverse group of primary tumors as well as secondary tumors or metastases from neoplasms outside the central nervous system (CNS), which occur more frequently than the primary brain tumors. The incidence rate of primary CNS tumors in adults in the United States is approximately 30 per 100,000 population, with approximately one-third of these tumors being malignant.[1]

Single-photon emission computed tomography (SPECT) and positron emission tomogarphy (PET) are the 2 major tomographic modalities in nuclear medicine that provide functional information regarding different tissues and disorders.[2] Different nuclear medicine radiotracers are utilized for evaluation of brain neoplasms.[3] Although most novel emerging molecular imaging radiotracers are compatible with PET imaging, SPECT remains an alternative modality with lower costs and wider availability.

The emergence of novel radiotracers provides major opportunities in the diagnosis and management of brain tumors. This review delineates the complementary role of conventional and novel molecular imaging radiotracers in neuro-oncology. Most emerging radiotracers are PET agents and, therefore, this review largely focuses on PET imaging agents.

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY

SPECT imaging provide a reasonable imaging alternative to PET, with higher affordability and availability.[4] In SPECT, the gamma camera rotates about the patient and acquires projections at different angles (**Fig. 1**). The main limitation of SPECT imaging is lower resolution and lack of precise anatomic details compared to PET imaging. Recent development of integrated hybrid SPECT/computed tomography (CT), however, has

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Radiol Clin N Am 59 (2021) 363–375
https://doi.org/10.1016/j.rcl.2021.01.005

improved the localization of tumor and increased the diagnostic accuracy.

Technetium-99m or [^{99m}Tc] labeled compounds and thallium-201or [^{201}Tl] are 2 example of SPECT radiotracers that have been evaluated in brain tumors.[5] [^{99m}Tc] labeled compounds are preferred over [^{201}Tl] based on better contrast resolution; less radiation to the patient; universal availability; and favorable gamma emission characteristics of [^{99m}Tc], including the 140-keV gamma ray energy and high photon flux compared to [^{201}Tl].

[^{99m}Tc]methoxy-2-isobutylisonitrile ([^{99m}Tc]MIBI) and [^{99m}Tc]tetrofosmin ([^{99m}Tc]TF) are passively accumulated in mitochondria and are considered markers of cellular transmembrane electrical potentials.[6] These features result in higher uptake in neoplastic cells in comparison with surrounding tissues.[5] [^{99m}Tc]MIBI and [^{99m}Tc]TF can help in improving diagnostic and prognostic accuracy of brain tumors.[5] Alexiou and colleagues showed that [^{99m}Tc]TF can provide helpful information to differentiate recurrence from radiation necrosis[6], with the best results observed in gliomas,[7] particularly when anatomic imaging is equivocal[8] (**Fig. 2**). Semiquantitative analysis of [^{201}Tl] uptake can differentiate tumor recurrence and postradiation necrosis in metastatic brain tumors.[9] Novel SPECT radiotracers are under development for detection of brain tumors. For example, diethylenetriamine pentaacetic acid–conjugated CooP with indium-111 can detect gliomas in 85% of mice.[10]

POSITRON EMISSION TOMOGRAPHY

PET agents play a crucial role in understanding the pathophysiology of neoplasms, developing targeted therapies, and monitoring response to therapy. These agents play a valuable role in diagnosis, classification, staging, image-guided therapy planning, and post-therapeutic evaluation of brain tumors.[11] **Table 1** summarized different PET radiotracers in neuro-oncology. Current and emerging novel radiotracers are discussed within the context of their mechanisms of action.

TRACING GLUCOSE METABOLISM

2-Deoxy-2-[^{18}F]fluoro-D-glucose

2-Deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) is the most commonly used PET radiotracer in oncology. Its half-life is relatively longer than most other positron emitters (approximately 2 hours) and it is widely and readily available. Increased glucose metabolism is associated not only with growth but also with malignant transformation.[40]

The Response Assessment in Neuro-Oncology working group recently provided recommendations in using glucose and amino acid radiotracers in glioma as a complementary modality to MR imaging.[41] To improve the accuracy of [^{18}F]FDG PET in detecting brain tumors, two critical steps are recommended. The first step is to coregister the images with MR imaging if a PET/CT was performed, and the second is to acquire delayed images to improve differentiation of brain neoplasm from cortical uptake.[42] PET/MR imaging provides simultaneous data acquisition which results in gathering functional and anatomic data with significant improvement of spatial and temporal resolution.[42] Few institutions have dedicated PET/MR imaging scanners, however, and,

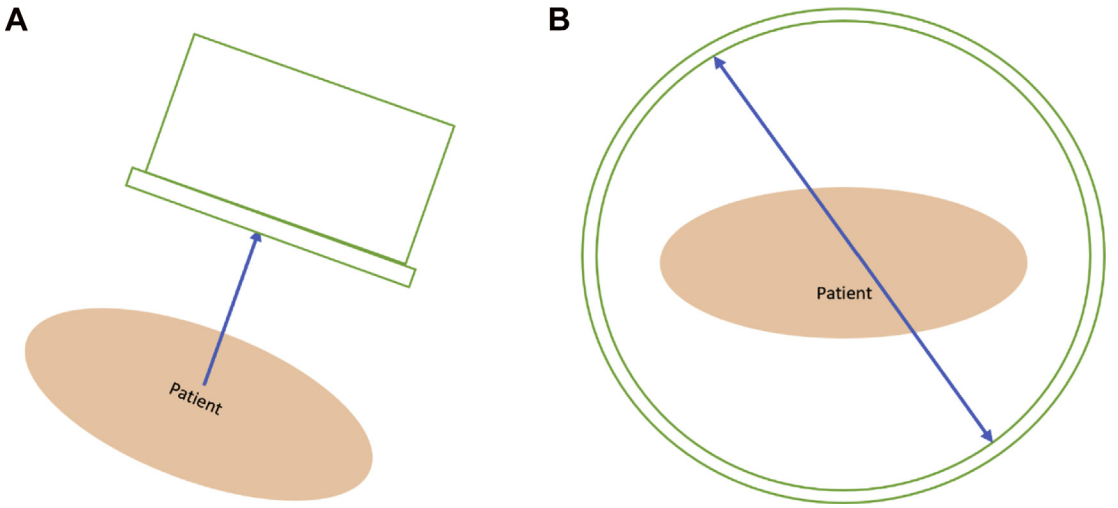

Fig. 1. Schematic acquisition of SPECT (*A*) and PET (*B*). For SPECT, the gamma camera rotates around the patient and acquires images at different angles. In PET, the patient is in the center of a ring of detectors, and positron annihilation results in 2 photons emitted at opposite directions.

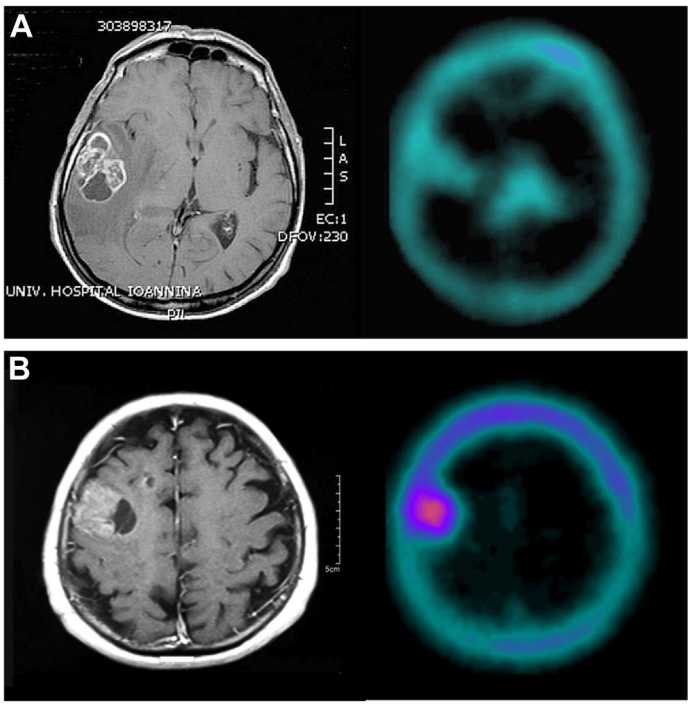

Fig. 2. Postcontrast T1-weighted MR images (*left*) and [^{99m}Tc]TF SPECT images (*right*) in glioblastoma showing low tracer uptake in 1 patient (*A*) and high uptake in another patient (*B*), This research originally was published in the *Journal of Nuclear Medicine*.[6] George A Alexiou, Spyridon Tsiouris, Athanasios P Kyritsis, George Fotakopoulos, Anna Goussia, Spyridon Voulgaris, Andreas D Fotopoulos. The value of 99mTc-tetrofosmin brain SPECT in predicting survival in patients with glioblastoma multiforme. *J Nucl Med*. 2010;51(12):1923-1926.

therefore, the importance of fusion software is critical.

2-Deoxy-2-[^{18}F]Fluoro-D-Glucose PET in Neuro-Oncology

Delineating tumor boundaries

One of the challenges in neuro-oncology is delineation of the tumor margins at the edge of gray matter, which also intrinsically shows high activity. This can be addressed with coregistration with MR imaging or delayed PET imaging (**Fig. 3**).[43] Tumor demonstrates higher [^{18}F]FDG avidity than gray matter on delayed acquisitions due to lower degradation of intracellular [^{18}F]FDG-6-phosphate in tumor than in brain.[43]

Table 1
Selected PET radiotracers and their mechanism of action in neuro-oncology

Tracer	Mechanism	Tumor Type
[^{11}C]acetate	Anabolism by acetyl-CoA synthesis, cell membrane	Glioma,[12] meningioma,[13] meningioma, schwannoma,[14] metastases[15]
[^{11}C]CHO	Phospholipids synthesis	Glioma,[16] CNS metastases,[16] meningioma,[16] schwannoma[17]
[^{11}C]MET	Amino acid uptake (methionine based)	Glioma,[12] germinoma,[18] CNS metastases,[19] meningioma,[20] CNS lymphoma[3]
[^{18}F]FDOPA	Amino acid uptake	Glioma,[21] CNS metastases,[22] meningioma[23]
[^{18}F]FAZA	Hypoxia	High-grade glioma[24]
[^{18}F]FDG	Glucose metabolism	Glioma,[3] CNS metastases,[25] meningioma,[26] CNS lymphoma,[27] oligodendroglioma[28]
[^{18}F]FET	Amino acid uptake (tyrosine based)	Glioma,[29] CNS metastases,[30] meningioma,[31] medulloblastoma,[32] ganglioglioma[32]
[^{18}F]FMISO	Hypoxia	Glioma[33]
[^{68}Ga]DOTA-TATE	somatostatin receptor up-regulation	Meningioma,[34] hemangioblastoma,[35] CNS neuroendocrine,[36] medulloblastoma[37]
[^{68}Ga]PSMA	PSMA	Glioma,[38] metastasis,[38] meningioma[39]

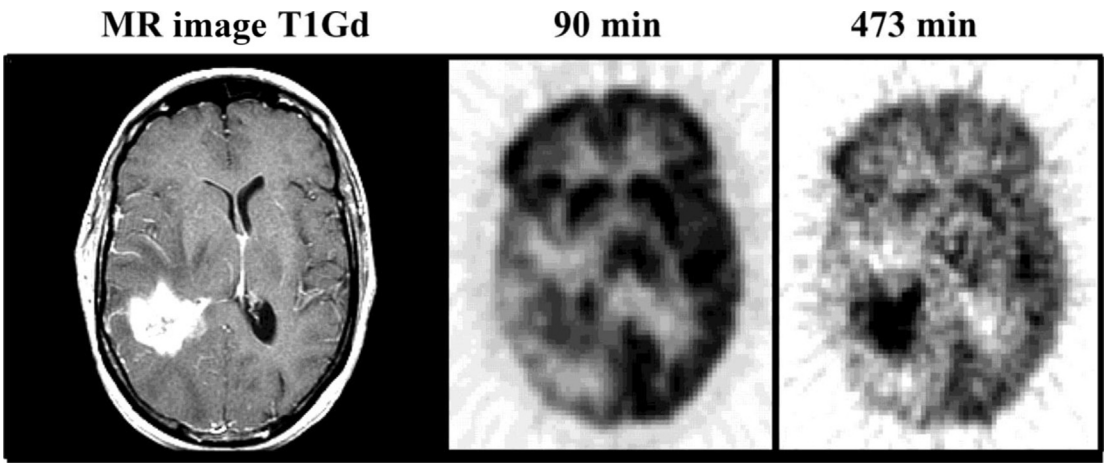

Fig. 3. Recurrent right temporal glioblastoma with enhancing lesion on post gadolinium T1-weighted MR imaging (T1Gd). There is an improvement of TBR in the [^{18}F]FDG PET imaging at the delayed time point in comparison with earlier acquisition. This research originally was published in the *Journal of Nuclear Medicine*.[43] Alexander M Spence 1, Mark Muzi, David A Mankoff, S Finbarr O'Sullivan, Jeanne M Link, Thomas K Lewellen, Barbara Lewellen, Pam Pham, Satoshi Minoshima, Kristin Swanson, Kenneth A Krohn. 18F-FDG PET of gliomas at delayed intervals: improved distinction between tumor and normal gray matter. *J Nucl Med*. 2004;45(10):1653-1659.

Tumor grading

Some studies have shown that [^{18}F]FDG PET can differentiate low-grade and high-grade gliomas based on glioma–to–white matter and glioma–to–gray matter ratios. Tumor–to–white matter ratio of greater than 1.5 and tumor–to–gray matter ratio of greater than 0.6 can differentiate high-grade from low-grade gliomas, with 94% sensitivity and 77% specificity,[44] although other studies have failed to differentiate high-grade and low-grade gliomas based on [^{18}F]FDG uptake.[45]

Determining prognosis

Higher [^{18}F]FDG uptake in a previously known low-grade glioma can indicate anaplastic transformation.[42] [^{18}F]FDG PET can predict survival regardless of histologic classification.[42] Some studies show that [^{18}F]FDG uptake is the most powerful predictor of progression-free survival and overall survival in comparison with other variables, such as histologic grade.[46]

Guiding post-therapy evaluation

One of the major advantages of [^{18}F]FDG PET compared with structural imaging is differentiating radiation necrosis from recurrent disease.[47] This feature is more reliable in gliomas in contrast to metastatic disease. A meta-analysis regarding the diagnostic accuracy of [^{18}F]FDG PET in detecting recurrences in gliomas showed heterogeneous diagnostic accuracies across the studies, with sensitivity of 0.77 (95% CI, 0.66–0.85) and specificity of 0.78 (95% CI, 0.54–0.91). [^{18}F]FDG PET can be used in planning for stereotactic biopsy by improving delineation of higher-grade foci within a heterogeneous tumor. This improves the diagnostic yield of brain biopsy.[48]

AMINO ACID METABOLISM

Amino acids are required in the synthesis of proteins and can indicate level of metabolism and proliferation. Amino acids generally demonstrate a low background uptake in gray matter and white matter, which improves tumor-to-background ratio (TBR). TBR is used to compare the uptake in tumor to the contralateral lobe. The uptake of amino acid–based radiotracers in tumoral cells is based on overexpression of amino acid transporters,[49] which correlates with malignant phenotype and angiogenesis.[50]

Methyl-[^{11}C]-L-Methionine

The most commonly used radiolabeled amino acid in detecting brain tumors is methyl-[^{11}C]-L-methionine ([^{11}C]MET). The relatively short half-life of carbon-11 ([^{11}C]MET), approximately 20 minutes, limits its usage to institutions with an on-site cyclotron. This radiotracer can be synthesized rapidly without requirement for purification.[19] The intracellular uptake happens through transmembrane transport by sodium independent L-transporter based on a concentration gradient. [^{11}C]MET brain uptake generally is lower than brain tumors, resulting in high detection rate and sharp delineation of the tumor.

[^{11}C]MET PET can detect primary gliomas with high sensitivity and specificity, with sensitivities

ranging from 76% to 100%.[19] Besides neoplasms, however, inflammatory cells have increased uptake, making this radiotracer an unideal method in differentiating tumor from inflammation.[51]

The results of quantitative analysis among different [^{11}C]MET PET studies have been controversial in grading primary gliomas. Low-grade gliomas generally show lower uptake in contrast to high-grade gliomas.[19] A meta-analysis in 2019 showed that [^{11}C]MET PET can differentiate low-grade from high-grade gliomas with higher sensitivity than [^{18}F]FDG PET.[52]

Some studies have shown that [^{11}C]MET PET can be used as a prognostic tool with higher uptake values associated with worse outcome. For example, Nariai and colleagues[53] showed significant correlation between survival and pretreatment TBR. In contrast, Ceyssens and colleagues[54] showed that [^{11}C]MET PET does not predict survival in patients with brain tumors.

[^{11}C]MET PET has been shown to improve tumor delineation with higher accuracy in comparison to CT or MR imaging and can identify areas with highest risk of recurrence.[19] This radiotracer can improve biopsy planning by identifying the regions with higher grades and determining better target regions in contrast to structural imaging modalities.[19]

O-(2-[^{18}F]fluoroethyl)-L-Tyrosine

O-(2-[^{18}F]fluoroethyl)-L-tyrosine ([^{18}F]FET) is a tyrosine analogue that can be used in detection of brain tumors. This molecule is not incorporated into proteins; hence, it has greater intracellular stability in contrast to other amino acid radiotracers.[55]

[^{18}F]FET PET can diagnose[29] brain tumors and grade gliomas[52] with higher sensitivities than [^{18}F]FDG. It can differentiate low-grade from high-grade gliomas[29] as well as low-grade and high-grade meningiomas based on TBR.[31] In untreated metastatic lesions, [^{18}F]FET PET uptake is increased in only two-thirds of lesions less than 1.0 cm whereas all lesions greater than 1.0 cm show pathologic uptake independent of tumor size.[30] **Fig. 4** shows [^{18}F]FET uptake in metastatic melanoma lesions, which demonstrate high variability.[30]

This radiotracer can be helpful for target selection and biopsy guidance as well as tumor resection planning.[55] A cost-effectiveness analysis showed that [^{18}F]FET PET and MR imaging may be superior to MR imaging alone in determining the biopsy site in glioma.[56]

[^{18}F]FET also is useful in detection of residual brain tumor after surgery. Early evaluation of the resection status in high-grade glioma is feasible with [^{18}F]FET PET, and PET findings have been shown to correlate with intraoperative assessment with 5-aminolevulinic acid as well as MR imaging results.[57] Multiple studies have shown the role of [^{18}F]FET PET in differentiating recurrence from post therapeutic changes.[55] In a related study, Galldiks and colleagues[58] concluded that [^{18}F]FET PET parameters can differentiate progressive or recurrent glioma from post treatment changes with higher accuracy than MR imaging.

[^{18}F]FET PET also can predict prognosis and survival in gliomas. Early time to peak in dynamic [^{18}F]FET PET is associated with worse outcome in newly diagnosed high-grade gliomas.[59] Maximum and mean TBRs are significant and independent predictors for progression-free survival and overall survival.[60]

l-3,4-Dihydroxy-6-[^{18}F]fluoro-phenyl-alanine

l-3,4-Dihydroxy-6-[^{18}F]fluoro-phenyl-alanine ([^{18}F]FDOPA) is transported into cells through large amino acid transporter and then is decarboxylated by DOPA decarboxylase to [^{18}F]dopamine that is trapped intracellularly in storage granules by vesicular monoamine transporters.[61] Chen and colleagues[62] compared [^{18}F]FDOPA with [^{18}F]FDG PET in 81 patients with brain tumor. [^{18}F]FDOPA had higher sensitivity (96%) in identifying brain tumors compared with [^{18}F]FDG (61%), with similar specificities (43%). [^{18}F]FDOPA is more accurate than [^{18}F]FDG PET for diagnosing low-grade tumors and evaluating recurrent tumors (**Fig. 5**). Moreover, it was able to distinguish tumor recurrence from radiation necrosis.[62]

A recent meta-analysis showed that this radiotracer has pooled sensitivity of 0.90 (95% CI, 0.86–0.93) and pooled specificity of 0.75 (95% CI, 0.65–0.83) for diagnosis of glioma.[21] Pooled sensitivity and specificity to differentiate high-grade from low-grade gliomas were 88% (95% CI, 0.81–0.93) and 73% (95% CI, 0.64–0.81) respectively.

TARGETING CELL MEMBRANE COMPONENTS

[^{11}C]Choline

[^{11}C]choline ([^{11}C]CHO) can be integrated into lecithin, which is a component of cell membrane phospholipid. In neoplasms, there is increased cell membrane turnover, which results in higher choline uptake as a marker of metabolite activity.[42]

In a prospective trial [^{11}C]CHO PET was compared with [^{18}F]FDG PET for various types of malignancies, including 25 patients with brain tumor. [^{11}C]CHO PET was able to differentiate benign and malignant tumors, with area under the curve (AUC) of 0.79, which was significantly higher than [^{18}F]FDG PET (0.58). [^{11}C]CHO PET provides high contrast images of brain tumors in comparison with [^{18}F]FDG PET because of lower background

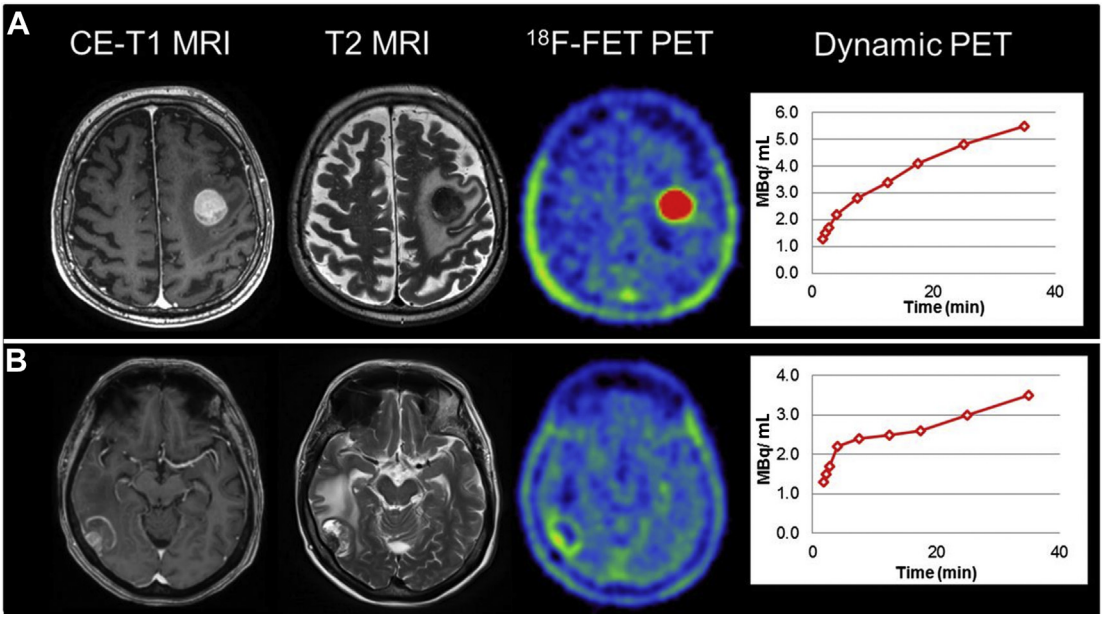

Fig. 4. Contrast enhanced T1-weighted (CE-T1), T2-weighted MR, and [^{18}F]FET PET images for 2 patients with metastatic melanoma (*A*, *B*). There is high variability in [^{18}F]FET PET avidity in metastatic melanoma. This research originally was published in the *Journal of Nuclear Medicine*.[30] Marcus Unterrainer, Norbert Galldiks, Bogdana Suchorska, Lara-Caroline Kowalew, Vera Wenter, Christine Schmid-Tannwald, Maximilian Niyazi, Peter Bartenstein, Karl-Josef Langen, Nathalie L Albert. 18F-FET PET Uptake Characteristics in Patients with Newly Diagnosed and Untreated Brain Metastasis. *J Nucl Med*. 2017;58(4):584-589.

uptake. [^{11}C]CHO PET is superior to [^{18}F]FDG PET in properly delineating the border of brain tumors, likely because of higher background uptake in [^{18}F]FDG PET.[63]

[^{11}C]acetate

The radiotracer [^{11}C]acetate is a precursor of fatty acids in cell membrane, being transformed to acetyl coenzyme A (CoA) and entering the tricarboxylic acid cycle. It can detect high-grade glioma with sensitivity of 90%.[12] In a prospective study, Kim and colleagues[64] showed that [^{11}C]acetate can differentiate low-grade and high-grade gliomas. [^{11}C]acetate may be helpful in detection of meningiomas, assessing tumor extent, and evaluating response to radiosurgery.[13]

TARGETING HYPOXIA

Detection of hypoxia in solid tumors is associated with more aggressive phenotype and worse prognosis. Hypoxia-specific PET can help in therapeutic decision making and provide tumor prognostication.[42] The initial uptake of the radiotracer is determined by blood flow; however, in the later phase (2–4 hours from injection), hypoxia regulates the uptake.[42]

[^{18}F]fluoromisonidazole

[^{18}F]fluoromisonidazole ([^{18}F]FMISO) is the most extensively used and studied hypoxia radiotracer in brain tumors.[33] A major drawback regarding [^{18}F]FMISO is the slow clearance of the unbound radiotracer from normal tissue, resulting in low TBR and slow plasma clearance.[33] There is a positive correlation between radiotracer uptake and expression of biomarkers of hypoxia (carbonic anhydrase IX, hypoxia-inducible factor carbonic anhydrase IX, and hypoxia-inducible factor 1α) and angiogenesis (vascular endothelial growth factor, angiopoietin-2, and relative cerebral blood volume).[65]

In a prospective clinical study in patient with gliomas [^{18}F]FMISO uptake was associated with different grades, with higher uptake in glioblastoma.[65] In another study, hypoxia determined based on [^{18}F]FMISO PET was found to be a negative prognostic marker.[66]

[^{18}F]flouroazomycin arabinoside

[^{18}F]flouroazomycin arabinoside ([^{18}F]FAZA) is one of the most promising hypoxia radiotracers introduced after [^{18}F]FMISO. [^{18}F]FAZA is less lipophilic in comparison with [^{18}F]FMISO, hence its improved biodistribution.[67] [^{18}F]FAZA retention is

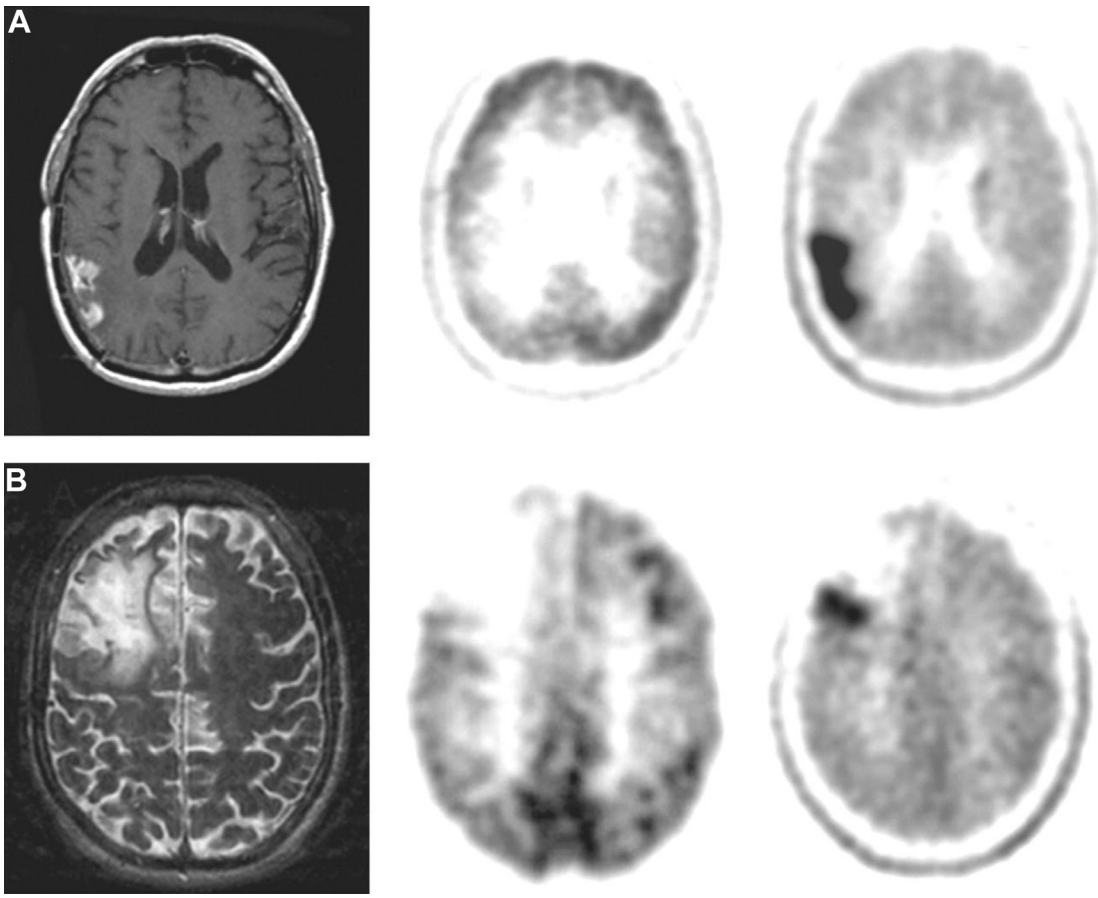

Fig. 5. MR image (*left*), [^{18}F]FDG PET (*middle*), and [^{18}F]FDOPA PET (*right*) for glioblastoma (*A*) and grade II oligodendroglioma (*B*). The lesions show high FDOPA uptake without [^{18}F]FDG avidity. This research originally was published in the *Journal of Nuclear Medicine*.[62] Wei Chen, Daniel H S Silverman, Sibylle Delaloye, Johannes Czernin, Nirav Kamdar, Whitney Pope, Nagichettiar Satyamurthy, Christiaan Schiepers, Timothy Cloughesy. 18F-FDOPA PET imaging of brain tumors: comparison study with 18F-FDG PET and evaluation of diagnostic accuracy. *J Nucl Med*. 2006;47(6):904-911.

dependent on reducing processes, which occur in hypoxic conditions. It has more rapid clearance from normal tissues that results in high TBR.[68] [^{18}F]FAZA is highly representative of hypoxia in glioblastoma.[24]

This radiotracer has been studied for treatment planning and guiding tailored radiotherapy as well as evaluation of tumor response to radiotherapy.[24] Identification of hypoxic regions in tumors can provide guidance by detecting areas with highest aggressive potential.[69]

TRACING SOMATOSTATIN RECEPTOR

Three different Gallium-68 or [^{68}Ga] labeled 1,4,7,10-tetraazacyclo-dodecane-N,N′,N″,N‴-tetraacetic-acid (DOTA) conjugated peptides are available for clinical imaging, namely [^{68}Ga]DOTA-Phe^{1}-Tyr^{3}-octreotide ([^{68}Ga]DOTA-TOC), [^{68}Ga]DOTA-Nal^{3}-octreotide ([^{68}Ga]DOTA-NOC), and [^{68}Ga]DOTA-Tyr^{3}-octreotate ([^{68}Ga]DOTA-TATE).

The somatostatin receptor (SSTR) affinity of these radiotracers is different. [^{68}Ga]DOTA-TATE provides the highest affinity to SSTR2. [^{68}Ga]DOTA-NOC has the broadest SSTR affinity, including to SSTR2, SSTR3, SSTR4, and SSTR5, which makes it an agent of choice to detect intracranial tumors.[70]

Meningiomas express SSTR2, demonstrating excellent TBR uptake.[42] [^{68}Ga]DOTA-conjugated peptides can confirm with presence of meningioma if the MR imaging results are equivocal.[71] One study found that the combination of [^{68}Ga]DOTA-TOC PET/CT and MR imaging changes the target volume definition for radiotherapy in 73% of patients compared with planning with only MR imaging or CT.[72] Moreover, [^{68}Ga]DOTA-conjugated peptides PET can predict

response to radiopeptide therapy in meningioma.[34] **Fig. 6** shows an incidental meningioma in a patient being imaged for neuroendocrince tumor.

Besides meningioma, several studies showed the utility of [^{68}Ga]DOTA-conjugated peptides in CNS neuroendocrine,[36] medulloblastoma, and hemangioblastoma[35] (see **Table 1**). In high-grade glioma, the uptake of this radiotracer is associated with blood-brain barrier disruption, which limits its value in detecting these tumors.[73] Moreover, radiotracer uptake cannot be predicted by SSTR2 expression on immunohistochemistry.

PROSTATE-SPECIFIC MEMBRANE ANTIGEN–EXPRESSING TUMORS

Prostate-specific membrane antigen (PSMA) is a transmembrane enzyme that is overexpressed in prostate adenocarcinoma.[74] The overexpression of PSMA is observed in tumor-associated neovasculature of many solid tumors.[75] PSMA is expressed in primary gliomas and breast cancer brain metastases.[38] These radiotracers are likely to be Food and Drug Administration (FDA) approved in the near future for prostate cancer evaluation.

Glu-NH-CO–NH-Lys-(Ahx)-[^{68}Ga(HBED-CC)] ([^{68}Ga]PSMA-11) and 2-(3-{1-carboxy-5-[(6-[^{18}F] fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid ([^{18}F]DCFPyL) are radiotracers that can be used for a variety of indications in patients with prostate cancer.[76] [^{68}Ga]PSMA-11 can detect brain metastasis in prostate carcinoma.[77] Sasikumar and colleagues[78] compared [^{18}F]FDG and [^{68}Ga]PSMA-11 brain PET in patients with glioblastoma. According to their study, [^{68}Ga]PSMA-11 showed better visualization of recurrent lesions due to its high TBR. There have been reports of incidental meningiomas detected by [^{68}Ga]PSMA-11.[39,79] Similarly, [^{18}F]DCFPyL can detect high-grade gliomas[80] and schwannomas[81] (**Fig. 7**), although there is some question as to the specificity of uptake of PSMA-targeted radiotracers in patients with previously treated brain tumors.[82]

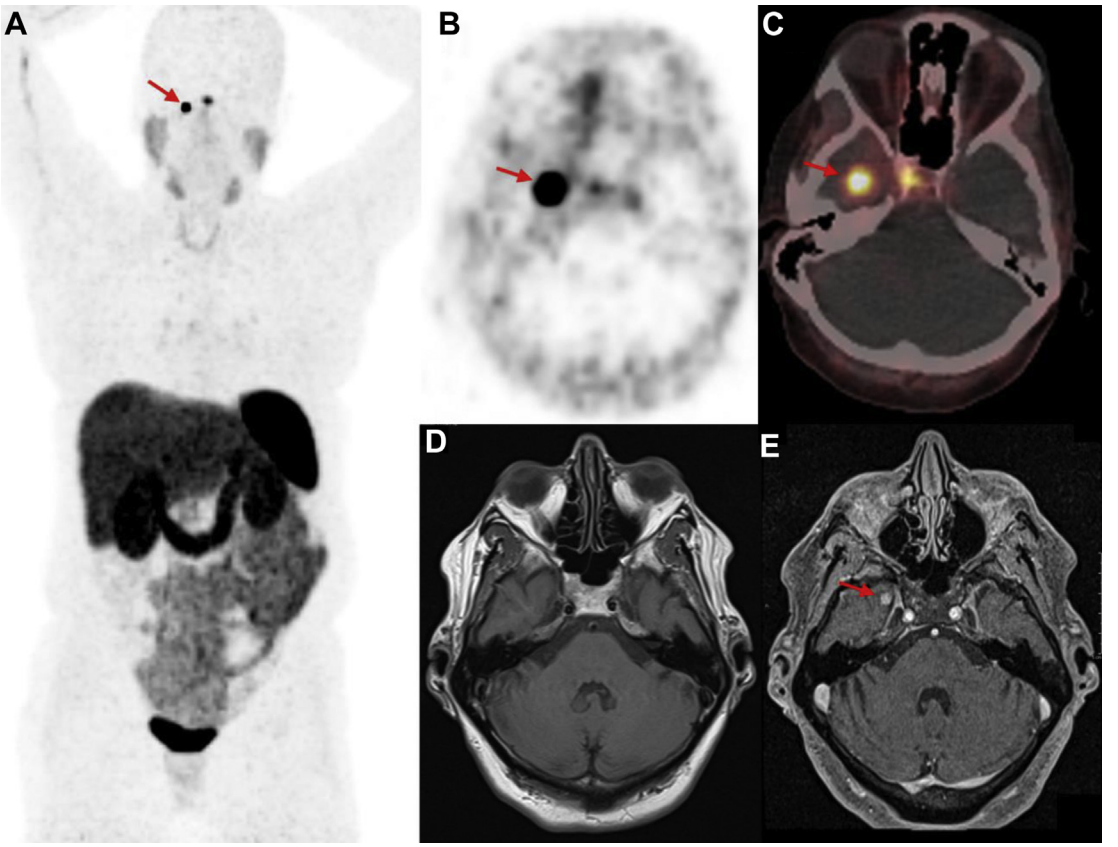

Fig. 6. A 57-year-old woman with incidental note of DOTA-TATE-avid lesion in the right temporal lobe on [^{68}Ga] DOTA-Tyr^3 -octreotide ([^{68}Ga]DOTA-TATE) PET, including coronal view (*A*), axial view (*B*), PET/CT fusion axial view (*C*) Subsequent precontrast MR (*D*) and postcontrast MR (*E*) images show 0.7-cm dural-based enhancing mass in the right middle cranial fossa, with MR characteristics favoring meningioma.

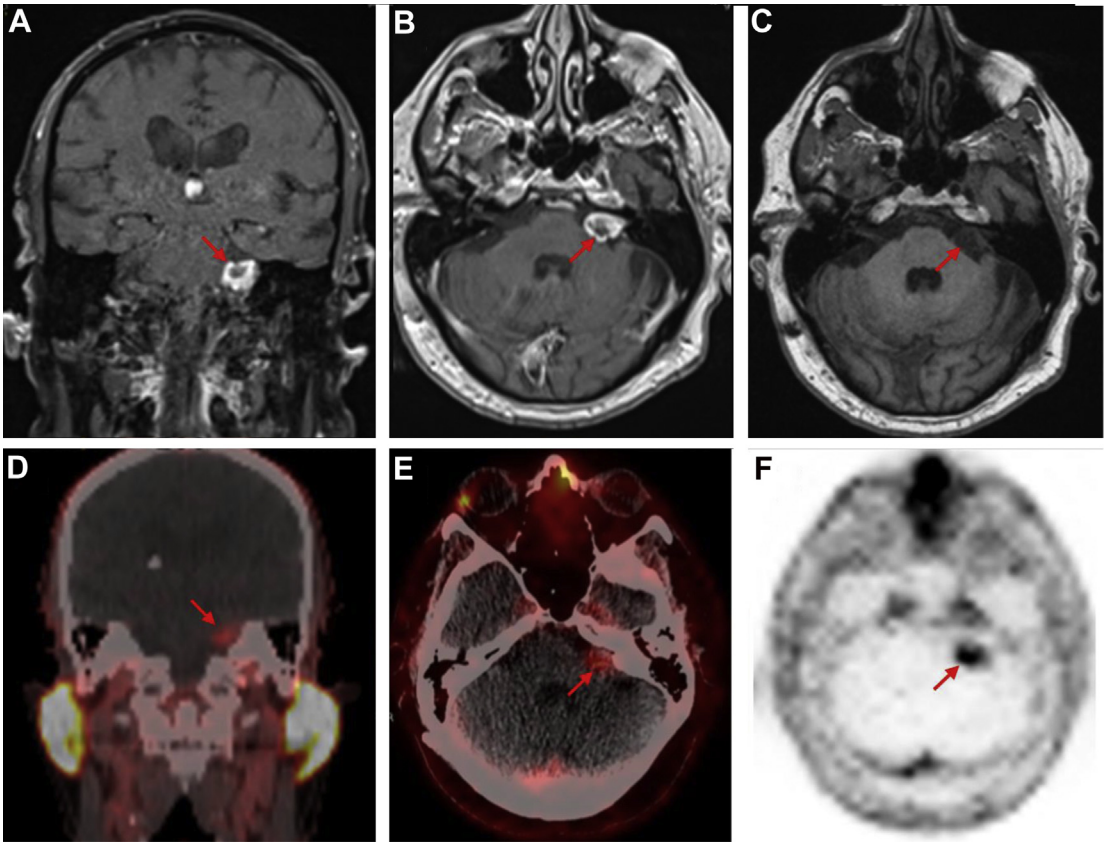

Fig. 7. An 80-year-old man with left cerebellopontine angle lesion (*red arrow*), consistent with a vestibular schwannoma. Coronal (*A*) and axial (*B*) views, postcontrast T1 MR imaging of the brain, show peripherally enhancing lesion in left cerebellopontine angle. Fluid-attenuated axial inversion recovery axial view (*C*) shows low signal intensity within the lesion. Coronal (*D*) and axial (*E*) views, [^{18}F]DCFPyL PET/CT, and axial [^{18}F]DCFPyL PET image (*F*) show radiotracer avidity in the lesion.

SUMMARY

Structural imaging, such as CT or MR imaging, is crucial in initial diagnosis of brain tumors; however, emerging molecular imaging techniques can provide additional information, including tumor grade, tumor composition, and tumor extent. Functional imaging can differentiate tumor recurrence from post-therapeutic changes based on metabolic activity at the surgical bed. Different SPECT and PET radiotracers have been developed that can be used in diagnosis, grading, surgical and radiation planning, post-therapeutic residual tumor detection, recurrence detection, and determining prognosis. Although [^{18}F]FDG is the most commonly used PET radiotracer in neuro-oncology, it has multiple intrinsic limitations, including low TBR and broad differential diagnosis. Other radiotracers, such as amino acid–based agents, provide better TBRs. More novel radiotracers, such as [^{68}Ga]DOTA-conjugated peptide compounds, provide more specific targeting and a narrower differential diagnosis for lesions with avid uptake.

Among the radiotracers discussed previously, only [^{18}F]FDG is approved by the FDA and included in US Pharmacopeia (USP) whereas most are enlisted in European Pharmacopoeia (EP).[83] In Europe, radiotracers are recognized as a special group of medicines. EP is based on the drug quality and is independent of clinical utility or licensing status. In the United States, the clinical use of all radiotracers is regulated by FDA. USP monographs typically are developed based on FDA-approved medicines and are considered as one basis of reimbursements; 8 FDA-unapproved tracers were included in USP monologues until 2014 (including [^{11}C]MET, [^{11}C] sodium acetate, and [^{18}F]FDOPA). These FDA-unapproved drugs were omitted from USP monologues in 2014 based on Society of Nuclear Medicine and Molecular Imaging (SNMMI) committee recommendations in 2013. According to SNMMI, the data regarding these tracers were

unvalidated and the analytical methods were outdated.[84]

CLINICS CARE POINTS

- Different SPECT and PET radiotracers have been developed that can be used in neuro-oncology
- PET provides better imaging resolution; however, SPECT provides greater availability and affordability
- Molecular imaging tracers can be used in diagnosis, grading, therapeutic planning, residual tumor detection, recurrence detection, and determination of prognosis.
- [^{18}F]FDG is the most commonly used PET radiotracer in neuro-oncology, with intrinsic limitations, including low TBR and broad differential diagnosis.
- Others PET radiotracers, such as amino acid–based agents, provide higher TBRs.

DISCLOSURE

L.B. Solnes is a consultant for Progenics and AAA/Novartis Pharmaceuticals.

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