Molecular Imaging of Glial Tumors: Established and Emerging Tracers

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Abstract

Various positron emission tomography (PET) tracers have been developed and extensively studied in the field of neuro-oncology imaging. In the management of brain tumors, accurate delineation of tumor extent, assessment of treatment response, and detection of early recurrence are the most important factors. At present, conventional anatomical imaging paired with amino acid tracer PET imaging is the recommended imaging modality for glial tumor evaluation. Newer PET tracers targeting various structures in the tumor microenvironment have been extensively studied. This review summarizes the established and emerging PET tracers having potential impact on neuro-oncology practice.

Keywords
- FDG
- FET
- FDOPA
- PET/CT
- glioma

Introduction

Gliomas represent the most common histological subtype originating from neuroepithelial cells, that is, astrocytes and oligodendrocytes. Based on their histological and clinicoradiological features, these tumors are graded from low-grade tumors to highly aggressive subtypes.[1] Despite advances in the management of high-grade glial tumors, the overall survival remains poor.[2] Hence, accurate diagnosis with advanced imaging modalities remains the mainstay of management. As it is a well-established fact, multiparametric magnetic resonance imaging (MRI) is the investigation of choice for the initial diagnosis and during further treatment. It has high spatial resolution and better soft tissue delineation, compared with computed tomographic (CT) scan.[3] However, its specificity drops significantly in post-treatment setting (post-surgery and radiotherapy) as there is permanent breach in the blood–brain barrier.[4] Surrogate markers of disease progression on MRI, that is, fluid attenuated inversion recovery hyperintensities and pattern of contrast enhancement, can be influenced by inflammation, infarction, reactive changes, or due to antiangiogenic drugs.[5] Neuro-oncologists often come across such treatment related changes, for example, pseudoprogression, that is characterized by transient increase in the contrast enhancement occurring within 3 to 6 months of treatment, without clinical deterioration, which disappears over a period.[6] Often, features of pseudoprogression overlap with true disease progression on multiparametric MRI and need to be accurately differentiated.[7] To overcome this diagnostic challenge, imaging methods with high accuracy are needed. Positron emission tomography/computed tomography (PET/CT) with various radiopharmaceuticals has been evaluated and has shown definite incremental value in neuro-oncology, since it reflects the true metabolic/molecular feature of brain tumors.[8]

Various prospective studies have highlighted the role of PET imaging. Currently Response Assessment in Neuro-Oncology (RANO) working group recommends the addition of PET imaging with amino acid tracers in the management of high-grade glial tumors.[9] With advent of newer treatment options like targeted therapies and immunotherapy, need for additional information derived from neuroimaging regarding tumor microenvironment is steadily increasing. This review summarizes the role of PET imaging with established tracers which are currently being used in neuro-oncology practices.

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Table 1 Currently used PET tracers in neuro-oncology

PET tracers	Tumor extent	RIN VS Recurrence	T/t Response
Glucose metabolism			
F18-FDG	–	+	–
Amino acid transport			
F18-FET	+	++	++
C11-MET	++	+	++
F18-DOPA	++	++	++
C11-AMT	+	+	–
F18-FACBC	+	–	–
Cellular proliferation			
FLT^3	–	+	++
Hypoxia			
F18-FMISO	Limited data	–	–
F18-FAZA	Available	–	–
Membrane biosynthesis			
F18 choline	–	–	–

Furthermore, few emerging and unique but promising PET tracers are discussed.

Established Tracers and Indications

PET imaging serves as a noninvasive imaging technique that provides information about the metabolic and molecular processes occurring inside the tumor cells. Till date, various tracers have been used clinically, particularly in patients with brain tumors or metastases, with focus on glucose metabolism, amino acid transports, hypoxia, proliferation, angiogenesis, etc. Brief description of radiotracers has been given in ►**Table 1**.

Glucose Metabolism

F-fluorodeoxyglucose (FDG), a fluorinated analogue of glucose, is the most used radiotracer in staging work up of most of the malignancies.[10]

Mechanism of Localization

It enters the tumor cells through GLUT receptors (►**Fig. 1**) and gets metabolized through the glycolysis pathway. Glucose-6-phosphatase is the deficient enzyme in tumor cells, due to which FDG-6-phosphate gets trapped inside the tumor cells, referred to as metabolic trapping (Warburg effect). FDG labeled with PET radioligand, that is, fluorine-18 (F-18) serves as an excellent diagnostic tool.[11,12] High physiological uptake in the gray matter hampers the diagnostic accuracy of FDG PET in differential diagnosis of primary brain tumor from other high-grade intracranial lesions like metastases.[9,13] Various studies and meta-analysis have concluded that FDG PET/CT has high accuracy for the detection of primary central nervous system lymphoma (PCNSL) due to its inherent property of high metabolic activity.[14–16] In patients with index MRI, features suggestive of brain metastases and whole body FDG PET/CT scan can impact therapeutic decision making by detection of primary malignancy on whole body imaging.[17] Uptake patterns on FDG PET have been described in ►**Fig. 2**.

As a tracer, FDG has poor accuracy in detection of glial tumors due to variable uptake by glial cells. It has been concluded that intensity of FDG uptake does not correlate with grade of glial tumor. In post-treatment settings, diagnostic accuracy of FDG is relatively poor compared with multiparametric MRI and amino acid PET.[18] Few retrospective studies have documented the prognostic role of baseline FDG PET/CT in high-grade gliomas (HGGs). It has been shown that lower grade uptake and low value of metabolic parameters on FDG PET/CT are associated with better outcome.[19,20] To conclude, FDG PET/CT can be used in the diagnostic algorithm for high-grade intracranial lesions which have a strong clinico-radiological suspicion of PCNSL or metastases, as it can guide further therapeutic management.

Amino Acid Tracers

There is upregulation of the L-type of amino acid transporter 1 (LAT1) on glial cell surface. Amino acids like DOPA (dihydroxy-phenylalanine), tyrosine, and methionine are transported through LAT1 in spite of an intact blood–brain

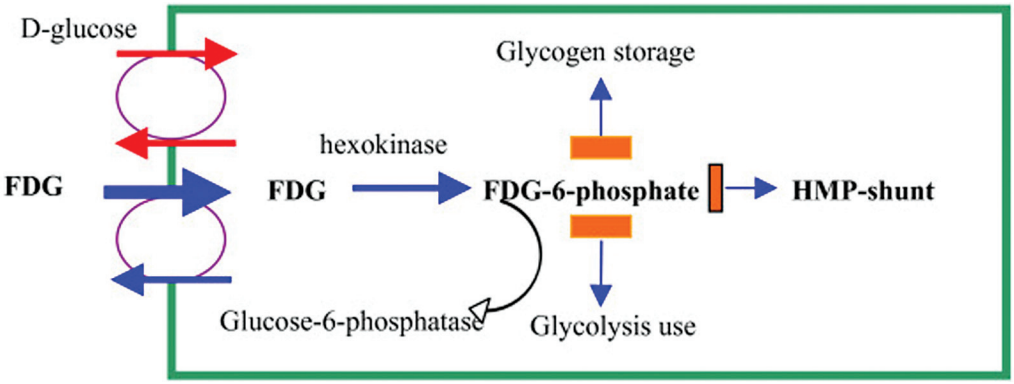

Fig. 1 Mechanism of localization of F-fluorodeoxyglucose (FDG). Courtesy Miele et al, Journal of Experimental & Clinical Cancer Research 2008;27:52 (available via Creative Commons Attribution 2.0 Generic).

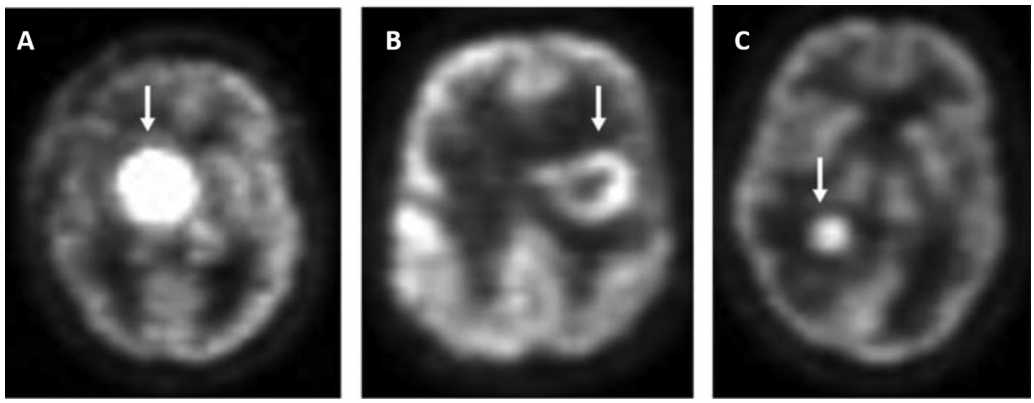

Fig. 2 Imaging patterns of FDG uptake in brain Intense FDG uptake seen in primary CNS lymphoma (**A**-arrow). Peripheral FDG uptake seen in glioma with increased background uptake in rest of the brain (**B**-arrow). Focal FDG uptake in ring enhancing lesion with associated perilesional oedema favours metastasis (**C**-arrow).

barrier.[21–25] Hence these are labeled with positron emitting radionuclides like F-18 and gallium-68 for diagnosis for utility in neuro oncological imaging. Following are the commonly used amino acid tracers, which have shown relevance in clinical practice. ►**Table 1** describes amino acid tracers.

Amino Acid Tracers in Current Neuro-oncology Practice

Differentiation of Neoplasm from Non-Neoplastic Etiologies

In general, neoplastic lesions such as glioblastoma or brain metastases exhibit a considerably higher uptake of radiolabeled amino acids than do non-neoplastic lesions, which makes it suitable for differentiation. A meta-analysis including more than 450 patients from 13 O-(2- [18F] fluoroethyl)-L-tyrosine (18F-FET) PET studies yielded a pooled sensitivity of 82% and specificity of 76% for diagnosing primary brain tumors.[26] In that study, 350 patients had gliomas (84%) of various central nervous system (CNS) World Health Organization (WHO) grades. Eighteen patients had a nonglial brain tumor (5%). Across all tumor types, a mean tumor-to-brain ratio of 1.6 and a maximum tumor-to-brain ratio of 2.1 best separated primary neoplastic lesions from non-neoplastic lesions. Our own institutional experience[27] included 27 patients with radiological differentials HGG and PCNSL in 9 patients, HGG and metastases in 5 patients, and all three differentials (HGG, PCNSL, metastases) in 13 patients, who were referred for FET PET. Tumor to contralateral white mater ratio (T/Wm) was used as a semiquantitative parameter. Most of the patients underwent stereotactic biopsy, while the rest had a follow-up MRI. All high-grade nonglial tumors showed a mean T/Wm of 1.59, which was significantly lower compared with high-grade tumors of glial origin. T/Wm cutoff of 1.9 at showed 93.8% sensitivity and 91% specificity to diagnose HGGs. Thus, FET PET can be reliably used as a problem-solving tool in patients with high-grade brain lesions, in whom MR shows equivocal features.

Delineation of Tumor Extent

Amino acid tracer localization in glial neoplasms is independent of integrity of blood–brain barrier. In terms of volumetric comparison of contrast enhancement with the tumor volume obtained by amino acid PET, there are significant differences in the size, overlap, and spatial correlation of tumor volumes,[27–29] indicating that conventional contrast-enhanced MRI considerably underestimates the active tumor volume. Multiple centers across the world are moving toward FET PET-based radiotherapy planning or adding boost to the FET avid portion of the tumor. Initial studies suggested that amino acid PET-based radiotherapy significantly affects patient survival.[30,31]

Differentiation of Tumor Relapse from Treatment-Related Changes

The current standard-of-care treatment for patients with HGGs (WHO Grade 3 and 4) includes maximal surgical resection followed by radiation therapy with concurrent and adjuvant temozolomide-based chemotherapy, which has shown improved survival.[32,33] At our institution, these patients are routinely followed up in a neuro-oncology clinic at 3 months and then at 1 year with MRI of the brain. We follow Brain Tumor Reporting and Data System (BT-RADS) for response assessment on MRI in gliomas. Patients with MR findings of BT-RADS 3a and 3b are further discussed in a multidisciplinary joint clinic, following which FET PET is done for those with clinicoradiological diagnostic dilemma. We, so far, used a T/Wm cutoff value of 2.5 for differentiating tumor recurrence from post-treatment changes on FET PET.[15] Since we have a regular referral for FET PET, this study aimed at deriving an optimum institutional cutoff reference value for HGGs. Experimental and clinical studies have shown that 18F-FET uptake is highly specific for tumor tissue and is a result of increased LAT expression leading to a carrier-mediated facilitated transport in the glioblastoma tissue, and is thus independent of disruption of the blood–brain barrier.[34] This makes FET an appropriate imaging modality for mapping proliferating glial tissue. The published literature on diagnostic accuracy of 18F-FET PET for distinguishing tumor

recurrence from post-treatment changes is not scarce, but suffers from lack of standardization of protocol, improper patient selection, and fixed imaging time-points.[35–38] Few studies include patients with a variety of grades (II-IV), predominantly astrocytic and oligodendroglial histology, with very few glioblastoma. Variable time-points post-treatment also affect the performance of radiotracers, which is seen is some studies, whereas we focused on those with a follow-up time period of more than 6 months after standard treatment (RT-TMZ) completion to exclude the cases with pseudoprogression. The rationale being pseudoprogression is a vascular phenomenon[39] wherein there is vessel dilatation, platelet-fibrin thrombi, reduced numbers of endothelial cell nuclei and blood–brain barrier leakage, whereas amino acid tracers do not localize through any of these mechanisms. We retrospectively analyzed 72 patients[40] with post-treatment grade 3 or 4 brain gliomas. T/Wm cut-off of 2.5 was used for image interpretation. Imaging findings were confirmed by either histopathologic diagnosis in a multidisciplinary joint clinic or based on follow-up of clinical and neuroimaging findings. Forty-one of 72 patients (57%) showed recurrent disease on FET PET. Thirty-five of them were confirmed to have tumor recurrence; six patients showed post-treatment changes. Thirty-one of 72 patients (43%) showed post-treatment changes on FET PET; 27 were confirmed as post-treatment change and four patients had tumor recurrence on subsequent MRI. An optimum T/Wm cutoff of 2.65 was derived based on receiver operating characteristic analysis with a sensitivity of 80% and specificity of 87.5%. We need to understand the inherent limitation of neuroimaging study is the lack of robust "gold standard," mainly because clinical or radiological progression in glioblastomas can occur within weeks; also, "false positive" results are not always confirmed with biopsy; hence a "multidisciplinary clinic decision" becomes crucial.

Whereas majority of literature on amino acid PET is based on FET PET, DOPA PET is also extensively used. Comparative studies have shown equal accuracy of FET and DOPA PET in assessing treatment-related changes from disease recurrence (►**Fig. 3**).

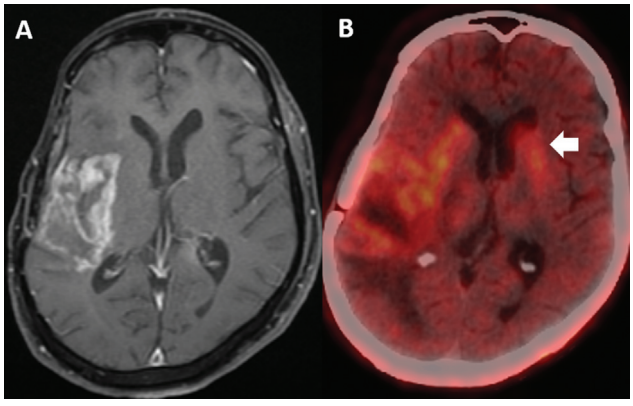

Fig. 3 Representative Case 48/M treated case of High-grade glioma, presented with suspected recurrence. MRI brain revealed thick peripheral contrast enhancement on T1 post contrast in right temporal lobe (**A**), FDOPA PET/CT fused transaxial images show intense FDOPA uptake (higher than striatum- White arrow) in right temporal lobe (**B**).

Table 2 Newer PET tracers in neuro-oncology

PET tracer	Target/mechanism of localization
Ga68-FAPI	Cancer-associated fibroblast (CAFs)
F18-GE 180 (TSPO)	Mitochondrial translocator protein
F18-FBY F18-FBPA F18-FGIn	Amino acid transport
Ga68-RGD	a_vB_3 Integrin family/angiogenesis marker
Ga68-PSMA	Glioma neovasculature
Zr89 labeled EGFR/PD-L1/ VEGFR targeting drugs	Antibody mediated theranostic potential

Other Radiopharmaceuticals

Apart from the conventionally used tracers, there have been multiple other tracers that are being used in practice; however, they find limited utility (►**Table 2**).

F18-choline: Metabolic demand for choline uptake increases in tumor progression, as it is required for cell membrane biosynthesis. As such, choline uptake has been used as a major target for PET imaging.[41] There is extremely low uptake of choline by normal brain parenchyma; hence, there is excellent tumor to background clearance.[42] F-18 choline has shown a high diagnostic accuracy, sensitivity, and specificity with a cutoff of 1.42 for tumor to normal brain uptake ratio in recurrent HGG. It can also be used to predict survival in patients with HGG; however, prospective studies are lacking.[43]

F18-FLT: F-18 Fluoro-thymidine (FLT) has been developed to measure thymidine kinase-1 activity that is involved in DNA synthesis and is a marker of cellular proliferation.[44] It has proven to be an excellent tracer for the assessment of treatment response in patients who have received antiangiogenic drugs like bevacizumab.[45] Prerequisite of disruption of blood–brain barrier is the major disadvantage and other factors, which increase the blood–brain barrier permeability such as radiotherapy and chemotherapy, falsely increase uptake.[46]

Hypoxia Agents

Presence of hypoxia in tumor microenvironment increases risk of tumor growth and metastatic potential. Various PET tracers like F-18 FMISO, FAZA, and FETNIM that target areas of hypoxia have been developed.[47] These traces freely diffuse inside the cells and get reduced to free radicals. In a well-oxygenated state, they can diffuse back. But in hypoxic cells, reduction process continues, leading to accumulation of these tracers. Major advantage of using hypoxia tracers is that it can provide early assessment of tumor progression as hypoxic changes occur relatively early.[48]

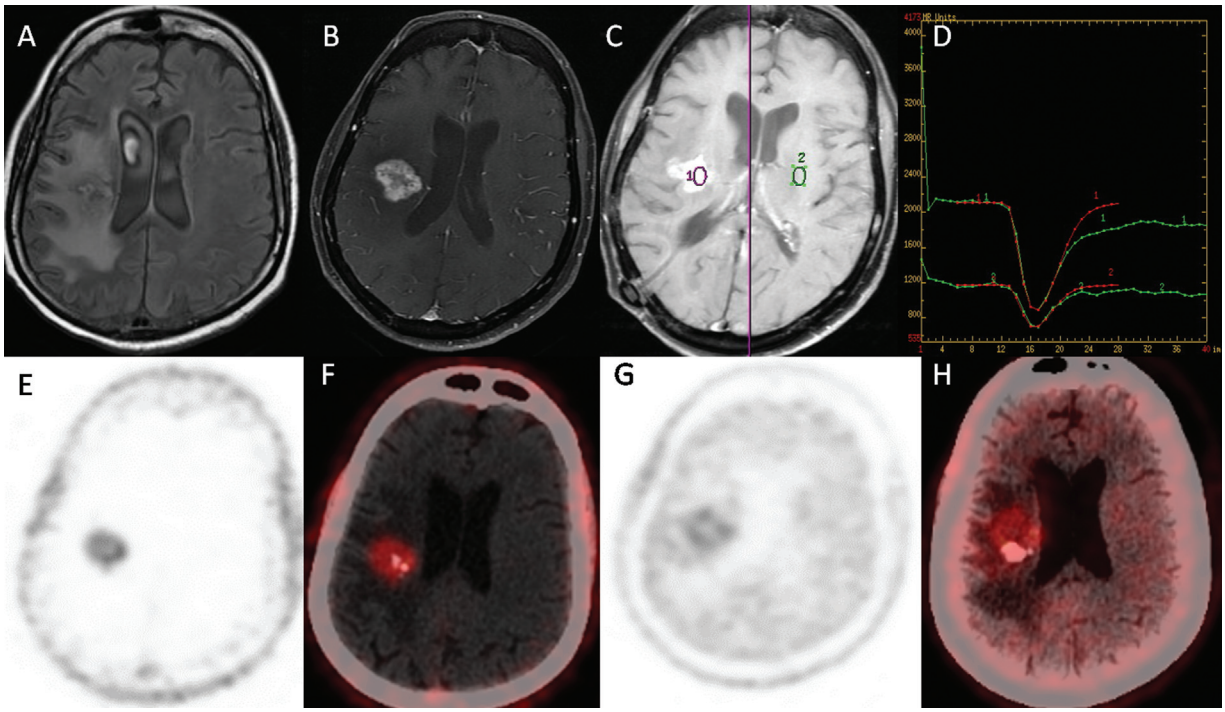

Fig. 4 Representative Case 52/F treated case of WHO grade IV glioma, presented with one episode of seizure, MRI brain revealed T2/FLAIR hyperintense area in right temporal lobe region (**A**). T1 post contrast shows nodular peripheral enhancement (**B**). Perfusion maps show hyperperfusion in the region of interest (**C,D**). 68GA FAPI PET/CT revealed focal intense uptake in nodular lesion in right temporal lobe (**E,F**). FET PET/CT revealed intense tracer uptake with T/w ratio of 5.7 which was suggestive of recurrence (**G,H**).

FAPI: Fibroblast activation protein inhibitor is a serine protease that is overexpressed in cancer associated fibroblasts (►**Fig. 4**). Radiotracers that bind to these proteins (like FAP inhibitors) can be of diagnostic and therapeutic use.[49,50] Further clinical studies are required for establishing their role.

PSMA-11: Prostate-specific membrane antigen, also known as glutamate carboxypeptidase II, is overexpressed in prostate cancer cells. PSMA radioligands have shown diagnostic and therapeutic benefits in prostate cancer. It is documented that PSMA is overexpressed in glial cell neovasculature and hence it can be a potential target of interest for diagnostic and therapeutic purposes in high-grade glial tumors.[51–53]

Conclusion

Multiparametric MRI remains the investigation of choice in the management of glial tumors. However, PET imaging provides additional biological and functional information that cannot be obtained from MRI alone. At present, the algorithm for approach to brain lesions in treatment-naïve patients with indeterminate MRI features involves performing FDG PET/CT, to locate the site of primary or for the detection of primary CNS lymphoma. There is enough evidence to use amino acid PET when MR findings are overlapping or there is a high-index of suspicion of glial neoplasm. PET/CT with amino acid tracers is a preferred imaging modality in post-treatment settings for the detection of glial tumor recurrence and for assessment of treatment response and as prognostic marker. It has also been increasingly used for radiotherapy planning with emerging trials in the pipeline. Newer tracers targeting different components of tumor microenvironment are emerging that needs further validation through large prospective studies and clinical trials in the fields of neuro-oncology.

Conflict of Interest
None declared.

References

1 Hanif F, Muzaffar K, Perveen K, Malhi SM, Simjee ShU. glioblastoma multiforme: a review of its epidemiology and pathogenesis through clinical presentation and treatment. Asian Pac J Cancer Prev 2017;18(01):3–9
2 Liang J, Lv X, Lu C, et al. Prognostic factors of patients with gliomas - an analysis on 335 patients with glioblastoma and other forms of gliomas. BMC Cancer 2020;20(01):35
3 Strauss SB, Meng A, Ebani EJ, Chiang GC. Imaging glioblastoma posttreatment: progression, pseudoprogression, pseudoresponse, radiation necrosis. Radiol Clin North Am 2019;57(06):1199–1216
4 Dhermain FG, Hau P, Lanfermann H, Jacobs AH, van den Bent MJ. Advanced MRI and PET imaging for assessment of treatment response in patients with gliomas. Lancet Neurol 2010;9(09):906–920
5 Kumar AJ, Leeds NE, Fuller GN, et al. Malignant gliomas: MR imaging spectrum of radiation therapy- and chemotherapy-induced necrosis of the brain after treatment. Radiology 2000;217(02):377–384

6 Ahluwalia MS, Wen PY. Antiangiogenic therapy for patients with glioblastoma: current challenges in imaging and future directions. Expert Rev Anticancer Ther 2011;11(05):653–656
7 Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol 2010;28(11): 1963–1972
8 Werner JM, Lohmann P, Fink GR, Langen KJ, Galldiks N. Current landscape and emerging fields of PET imaging in patients with brain tumors. Molecules 2020;25(06):1471
9 Albert NL, Weller M, Suchorska B, et al. Response assessment in neuro-oncology working group and European Association for Neuro-oncology recommendations for the clinical use of PET imaging in gliomas. Neuro-oncol 2016;18(09):1199–1208
10 Almuhaideb A, Papathanasiou N, Bomanji J. 18F-FDG PET/CT imaging in oncology. Ann Saudi Med 2011;31(01):3–13
11 Kawada K, Iwamoto M, Sakai Y. Mechanisms underlying ^{18}F-fluorodeoxyglucose accumulation in colorectal cancer. World J Radiol 2016;8(11):880–886
12 Rahman WT, Wale DJ, Viglianti BL, et al. The impact of infection and inflammation in oncologic ^{18}F-FDG PET/CT imaging. Biomed Pharmacother 2019;117:109168
13 Galldiks N, Langen KJ, Albert NL, et al. PET imaging in patients with brain metastasis-report of the RANO/PET group. Neuro-oncol 2019;21(05):585–595
14 Gupta M, Gupta T, Purandare N, et al. Utility of flouro-deoxy-glucose positron emission tomography/computed tomography in the diagnostic and staging evaluation of patients with primary CNS lymphoma. CNS Oncol 2019;8(04):CNS46
15 Gupta T, Manjali JJ, Kannan S, Purandare N, Rangarajan V. Diagnostic performance of pretreatment 18F-fluorodeoxyglucose positron emission tomography with or without computed tomography in patients with primary central nervous system lymphoma: updated systematic review and diagnostic test accuracy meta-analyses. Clin Lymphoma Myeloma Leuk 2021;21(08):497–507
16 Zou Y, Tong J, Leng H, Jiang J, Pan M, Chen Z. Diagnostic value of using 18F-FDG PET and PET/CT in immunocompetent patients with primary central nervous system lymphoma: a systematic review and meta-analysis. Oncotarget 2017;8(25):41518–41528
17 Purandare NC, Puranik A, Shah S, et al. Common malignant brain tumors: can 18F-FDG PET/CT aid in differentiation? Nucl Med Commun 2017;38(12):1109–1116
18 Dankbaar JW, Snijders TJ, Robe PA, et al. The use of (18)F-FDG PET to differentiate progressive disease from treatment induced necrosis in high grade glioma. J Neurooncol 2015;125(01): 167–175
19 Dev ID, Puranik AD, Purandare NC, et al. Prognostic significance of 18F-FDG PET/CT parameters in IDH-1 wild-type GBM and correlation with molecular markers. Nucl Med Commun 2021; 42(11):1233–1238
20 Patronas NJ, Di Chiro G, Kufta C, et al. Prediction of survival in glioma patients by means of positron emission tomography. J Neurosurg 1985;62(06):816–822
21 Langen KJ, Galldiks N, Hattingen E, Shah NJ. Advances in neuro-oncology imaging. Nat Rev Neurol 2017;13(05):279–289
22 Youland RS, Kitange GJ, Peterson TE, et al. The role of LAT1 in (18) F-DOPA uptake in malignant gliomas. J Neurooncol 2013;111(01): 11–18
23 Papin-Michault C, Bonnetaud C, Dufour M, et al. Study of LAT1 expression in brain metastases: towards a better understanding of the results of positron emission tomography using amino acid tracers. PLoS One 2016;11(06):e0157139
24 Wiriyasermkul P, Nagamori S, Tominaga H, et al. Transport of 3-fluoro-L-α-methyl-tyrosine by tumor-upregulated L-type amino acid transporter 1: a cause of the tumor uptake in PET. J Nucl Med 2012;53(08):1253–1261
25 Okubo S, Zhen HN, Kawai N, Nishiyama Y, Haba R, Tamiya T. Correlation of L-methyl-11C-methionine (MET) uptake with L-type amino acid transporter 1 in human gliomas. J Neurooncol 2010;99(02):217–225
26 Dunet V, Rossier C, Buck A, Stupp R, Prior JO. Performance of 18F-fluoro-ethyl-tyrosine (18F-FET) PET for the differential diagnosis of primary brain tumor: a systematic review and metaanalysis. J Nucl Med 2012;53(02):207–214
27 Puranik AD, Boon M, Purandare N, et al. Utility of FET-PET in detecting high-grade gliomas presenting with equivocal MR imaging features. World J Nucl Med 2019;18(03):266–272
28 Lohmann P, Stavrinou P, Lipke K, et al. FET PET reveals considerable spatial differences in tumour burden compared to conventional MRI in newly diagnosed glioblastoma. Eur J Nucl Med Mol Imaging 2019;46(03):591–602
29 Suchorska B, Jansen NL, Linn J, et al; German Glioma Network. Biological tumor volume in 18FET-PET before radiochemotherapy correlates with survival in GBM. Neurology 2015;84(07):710–719
30 Harat M, Blok M, Miechowicz I, Wiatrowska I, Makarewicz K, Małkowski B. Safety and efficacy of irradiation boost based on 18F-FET-PET in patients with newly diagnosed glioblastoma. Clin Cancer Res 2022;28(14):3011–3020
31 Laack NN, Pafundi D, Anderson SK, et al. Initial results of a phase 2 trial of 18F DOPA PET-guided dose-escalated radiation therapy for glioblastoma. Int J Radiat Oncol Biol Phys 2021;110(05): 1383–1395
32 Weller M, van den Bent M, Hopkins K, et al; European Association for Neuro-Oncology (EANO) Task Force on Malignant Glioma. EANO guideline for the diagnosis and treatment of anaplastic gliomas and glioblastoma. Lancet Oncol 2014;15(09):e395–e403
33 Stupp R, Dietrich P-Y, Ostermann Kraljevic S, et al. Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide. J Clin Oncol 2002;20(05):1375–1382
34 Habermeier A, Graf J, Sandhöfer BF, Boissel JP, Roesch F, Closs EI. System L amino acid transporter LAT1 accumulates O-(2-fluoroethyl)-L-tyrosine (FET). Amino Acids 2015;47(02):335–344
35 Mehrkens JH, Pöpperl G, Rachinger W, et al. The positive predictive value of O-(2-[18F]fluoroethyl)-L-tyrosine (FET) PET in the diagnosis of a glioma recurrence after multimodal treatment. J Neurooncol 2008;88(01):27–35
36 Pöpperl G, Götz C, Rachinger W, Gildehaus FJ, Tonn JC, Tatsch K. Value of O-(2-[18F]fluoroethyl)- L-tyrosine PET for the diagnosis of recurrent glioma. Eur J Nucl Med Mol Imaging 2004;31(11): 1464–1470
37 Pöpperl G, Götz C, Rachinger W, et al. Serial O-(2-[(18)F] fluoroethyl)-L: -tyrosine PET for monitoring the effects of intracavitary radioimmunotherapy in patients with malignant glioma. Eur J Nucl Med Mol Imaging 2006;33(07):792–800
38 Piroth MD, Pinkawa M, Holy R, et al. Prognostic value of early [18F] fluoroethyltyrosine positron emission tomography after radiochemotherapy in glioblastoma multiforme. Int J Radiat Oncol Biol Phys 2011;80(01):176–184
39 Van Mieghem E, Wozniak A, Geussens Y, et al. Defining pseudoprogression in glioblastoma multiforme. Eur J Neurol 2013;20(10):1335–1341
40 Puranik AD, Rangarajan V, Dev ID, et al. Brain FET PET tumor-to-white mater ratio to differentiate recurrence from post-treatment changes in high-grade gliomas. J Neuroimaging 2021;31(06): 1211–1218
41 Contractor KB, Kenny LM, Stebbing J, et al. [11C]choline positron emission tomography in estrogen receptor-positive breast cancer. Clin Cancer Res 2009;15(17):5503–5510
42 Li W, Ma L, Wang X, Sun J, Wang S, Hu X. (11)C-choline PET/CT tumor recurrence detection and survival prediction in post-treatment patients with high-grade gliomas. Tumour Biol 2014; 35(12):12353–12360

43 Bolcaen J, Acou M, Boterberg T, et al. 18F-FCho PET and MRI for the prediction of response in glioblastoma patients according to the RANO criteria. Nucl Med Commun 2017;38 (03):242–249
44 Choudhary G, Langen KJ, Galldiks N, McConathy J. Investigational PET tracers for high-grade gliomas. Q J Nucl Med Mol Imaging 2018;62(03):281–294
45 Chen W, Delaloye S, Silverman DH, et al. Predicting treatment response of malignant gliomas to bevacizumab and irinotecan by imaging proliferation with [18F] fluorothymidine positron emission tomography: a pilot study. J Clin Oncol 2007;25(30): 4714–4721
46 Li Z, Yu Y, Zhang H, Xu G, Chen L. A meta-analysis comparing 18F-FLT PET with 18F-FDG PET for assessment of brain tumor recurrence. Nucl Med Commun 2015;36(07):695–701
47 Bell C, Dowson N, Fay M, et al. Hypoxia imaging in gliomas with 18F-fluoromisonidazole PET: toward clinical translation. Semin Nucl Med 2015;45(02):136–150
48 Yamaguchi S, Hirata K, Toyonaga T, et al. Change in 18F-fluoromisonidazole PET is an early predictor of the prognosis in the patients with recurrent high-grade glioma receiving bevacizumab treatment. PLoS One 2016; 11(12):e0167917
49 Windisch P, Röhrich M, Regnery S, et al. Fibroblast activation protein (FAP) specific PET for advanced target volume delineation in glioblastoma. Radiother Oncol 2020;150:159–163
50 Huang R, Pu Y, Huang S, et al. FAPI-PET/CT in cancer imaging: a potential novel molecule of the century. Front Oncol 2022; 12:854658
51 Wernicke AG, Edgar MA, Lavi E, et al. Prostate-specific membrane antigen as a potential novel vascular target for treatment of glioblastoma multiforme. Arch Pathol Lab Med 2011;135(11): 1486–1489
52 Kunikowska J, Kuliński R, Muylle K, Koziara H, Królicki L. 68Ga-prostate-specific membrane antigen-11 PET/CT: a new imaging option for recurrent glioblastoma multiforme? Clin Nucl Med 2020;45(01):11–18
53 Marafi F, Sasikumar A, Fathallah W, Esmail A. 18F-PSMA 1007 brain PET/CT imaging in glioma recurrence. Clin Nucl Med 2020; 45(01):e61–e62