Curr Treat Options Neurol (2016) 18: 4
DOI 10.1007/s11940-015-0384-z

Neuro-oncology (R Soffietti, Section Editor)

Usefulness of PET Imaging to Guide Treatment Options in Gliomas

Bogdana Suchorska, MD[1,*]
Nathalie Lisa Albert, MD[2]
Jörg-Christian Tonn, MD[1]

Address
[*,1]Department of Neurosurgery, University Hospital Munich, Marchioninistr. 15, 81377, Munich, Germany
Email: bogdana.suchorska@med.uni-muenchen.de
[2]Department of Nuclear Medicine, University Hospital Munich, Munich, Germany

Published online: 27 January 2016

This article is part of the Topical Collection on *Neuro-oncology*

Keywords Glioma · Imaging · PET

Opinion statement

Magnetic resonance imaging (MRI) is the gold standard guiding diagnostic and therapeutic management in glioma with its high resolution and possibility to depict blood-brain-barrier disruption when contrast medium is applied. In light of the shifting paradigms revealing distinct tumor subtypes based on the molecular and genetic characterization and increasing knowledge about the variability of glioma biology, additional imaging modalities such as positron emission tomography (PET) depicting metabolic processes gain further importance in the management of glioma.

Introduction

After onset of neurological symptoms, usually a MRI is performed as diagnostic imaging. In case of a suspected brain tumor, patients usually undergo either surgery or biopsy depending on patient's condition and tumor location as well as resectability. Thereafter, current treatment options in malignant gliomas such as anaplastic astrocytoma or oligodendroglioma WHO III and glioblastoma WHO IV are radiotherapy or/and chemotherapy [1••]. In patients diagnosed with a glioma WHO II, therapeutic options are much more heterogeneous.

In all glioma entities, molecular markers gain rising importance for identification of distinct subgroups with implications for therapy. Furthermore, recent advances in treatment options including antiangiogenic agents as well as substances targeting the immune system require a more sophisticated approach towards diagnosis and treatment monitoring. As a consequence of these emerging therapeutic upheavals, resulting (MR-) imaging phenomena such as pseudoprogression and pseudoresponse cannot be evaluated on the basis of MacDonald criteria

established in 1990 [2]. The establishment of RANO criteria by Wen and colleagues has partly addressed these phenomena by introducing evaluation of additional sequences such as T2 and fluid attenuated inversion recovery FLAIR [3••]. However, though this approach has immensely improved differential diagnosis and standardized evaluation of progression within the setting of clinical trials as well as in daily routine, many problems of neuro-oncological diagnosis remain unsolved with conventional MRI (such as extent of biologically active tumor tissue, intratumoral heterogeneity, differential diagnosis radiation necrosis vs recurrent tumor). Another imaging modality for diagnosis and disease monitoring of glioma is provided by PET. Implementation of PET into planning of surgical procedure and radiotherapy as well as into therapy monitoring is going to improve management in glioma patients. While [^{18}F]FDG is widely used as tracer for solid tumors in general oncology, its usefulness for neuro-oncological issues is limited as described below. Thus, the current review will mainly focus on amino acid tracers.

Tracers

FDG

As most tumors are characterized by enhanced metabolic processes, the introduction of [^{18}F]FGD, a radiolabeled analogue of glucose, has revolutionized oncological imaging in the 80s [4]. [^{18}F]FDG is incorporated into the cell by means of glucose-specific transporters (GLUTs) and cannot be further metabolized due to phosphorylation processes [5]. In contrast to its high explanatory power in somatic malignancies, [^{18}F]FDG is only of limited use in neuro-oncology because of the high glucose uptake in the normal cerebral cortex tissue [6]. Therefore, especially glioma WHO II can often not be discerned from unaffected cortex as they often present as iso- or even hypometabolic entities. Furthermore, though high grade glioma usually shows an elevated [^{18}F]FDG uptake, a high interference exists in the vicinity of gray matter and basal ganglia. Furthermore, [^{18}F]FDG is incorporated via macrophages into inflammatory processes and hence further reduces its value for differential diagnosis in glioma [7]. Hence, the current review will address [^{18}F]FDG only briefly whenever applicable.

Amino acid tracers

Amino acids (AA) play an integral role in cell proliferation and extracellular matrix formation processes in glioma. During the past decades, a large number of radiolabeled tracers were introduced to visualize metabolic processes involving amino acids: [^{11}C]Methionine ([^{11}C]MET), [^{18}F]Fluorotyrosine ([^{18}F]FYT), [^{18}F]Fluoroethyltyrosine ([^{18}F]FET), [^{18}F]Fluoromethyltyrosine ([^{18}F]FMT), and [^{18}F]Fluorodopa ([^{18}F]DOPA). The key difference between natural AA and their artificial radiolabeled analogues is that the latter are not incorporated into the cell [8].

Most widely used AA tracers are [^{11}C]MET, [^{18}F]FET, and [^{18}F]DOPA showing a comparable value for differential diagnosis and grading [9–11]. However, [^{11}C]MET has a very short half-life time of approximately 20 min and thus requires an on-site cyclotron [12]. While [^{18}F]FET is the most common AA tracer used for neuro-oncological imaging in Europe, centers in the USA predominantly use [^{18}F]DOPA. In comparison to [^{18}F]FDG, both [^{18}F]FET and [^{18}F]DOPA provide a higher contrast for differentiation of neoplastic tissue from normal brain [13•, 14]. The value of [^{18}F]FET is somehow limited in

processes located in the vicinity of large (venous) vessels due to pooling phenomena. In contrast, [^{18}F]DOPA is physiologically accumulated in the basal ganglia; thus, differentiation of tumor boarders may be difficult in this region [10, 11]. A common feature of all AA tracers is the uptake via amino acid transporters such as LAT1 and LAT2, which are expressed both in the neoplastic tumor tissue as well as in the BBB [15–18]. However, in difference to MRI contrast media, BBB breakdown is not a prerequisite for AA-tracer uptake. This allows both visualization as well as differentiation of gliomas WHO II–IV with fair specificity and sensitivity as LAT transporter expression is correlated with the tumor grade.

In focus: dynamic AA-PET

The term "dynamic PET" refers to a frame-based analysis technique which explores the tracer uptake behavior over a defined period of time. This approach allows visualization of uptake patterns that might yield additional information on tumor malignancy and metabolic activity. Typical measures of dynamic analysis are time-activity curves (TACs) and time-to-peak (TAC) values. TACs can be increasing or decreasing, depending on the velocity of tracer uptake, while TTP relates to the time when tracer uptake reaches its peak. Decreasing TACs are typically observed in untreated malignant glioma (WHO III and IV) while increasing TACs often occur in gliomas WHO II (an example for increasing and decreasing TAC can be found in Fig. 1) [19–21]. Furthermore, short TTP values can differentiate between malignant gliomas with different disease courses [22•]. So far, the dynamic approach has been established for [^{18}F]FET; similar attempts for [^{11}C]MET and [^{18}F]DOPA failed to provide reliable results, probably reflecting the different uptake characteristics [23, 24].

Proliferation tracer: [^{18}F]FLT

The pyrimidine deoxynucleoside thymidine is a component of double-stranded DNA. Thymidine analogs such as 2-[11C]-thymidine 16 or 3′-deoxy-3′-[^{18}F]-fluorothymidine [^{18}F]FLT have been developed in order to visualize proliferation processes in human tumor cells. Following intake by nucleoside transporters, [^{18}F]FLT is quickly phosphorylated by the enzyme thymidine kinase 1 and thus remains trapped in the cell [25]. Its use in glioma remains limited to monitoring of treatment response in HGG in a research setting, partly due to its complicated synthesis process and partly due to low sensitivity in LGG.

Usefulness of PET for glioma diagnosis and grading

Glioblastomas usually present on MRI with a strong enhancement. However, a proportion of up to 30 % of grade III gliomas does not enhance on T1-contrast-enhanced (CE) weighted sequences [26]. Gliomas WHO II commonly present as a non-enhancing tumor mass visualized on T2-weighted or FLAIR sequences. Yet, a large proportion of the non-enhancing glioma consists of heterogeneous entities harboring "hot-spots" of metabolically highly active and often more malignant tumor

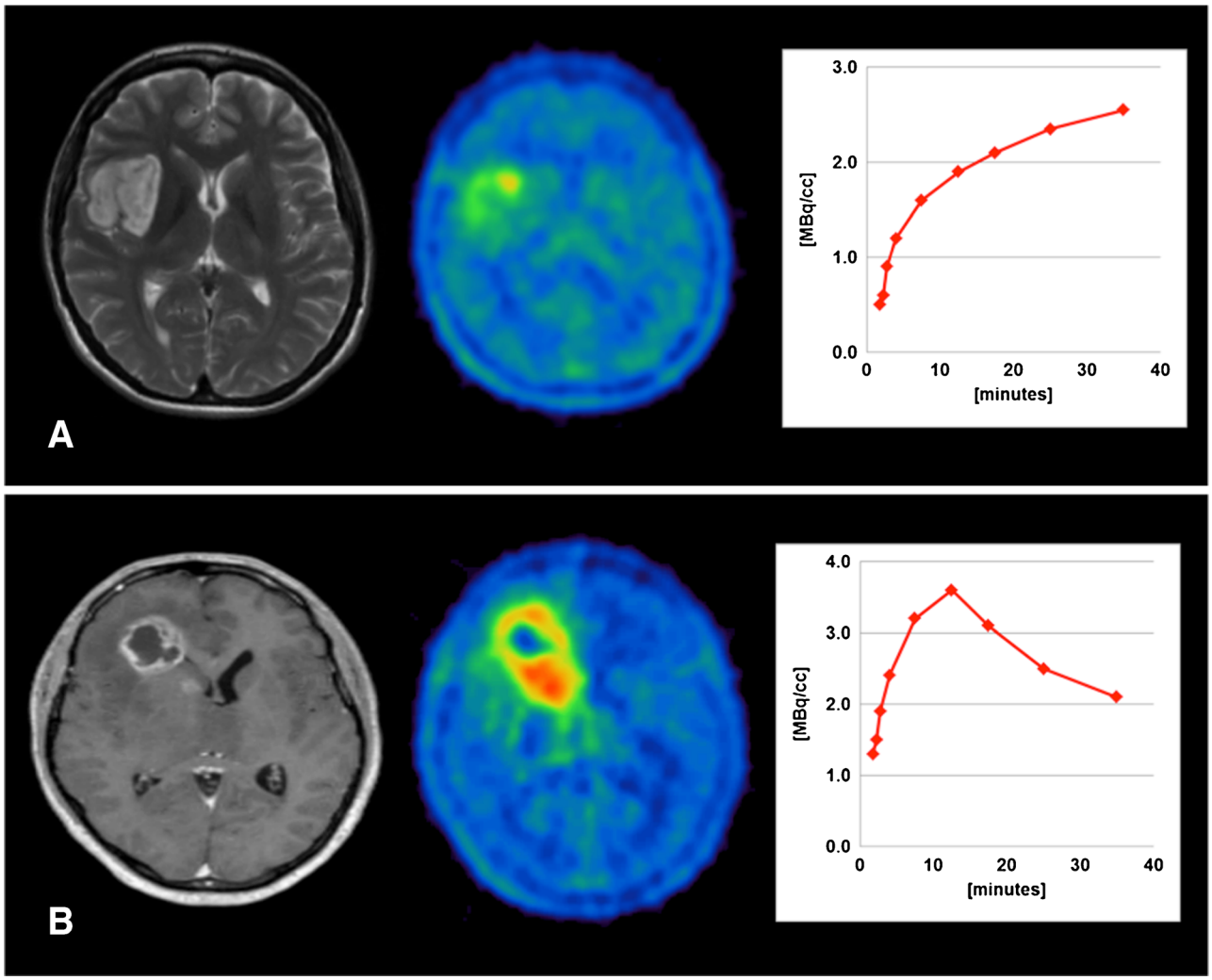

Fig. 1. **a** An example of a LGG patient with a small hot-spot on [^{18}F] FET-PET and "benign" increasing TAC. **b** A HGG patient with larger [^{18}F] FET-based volume than contrast enhancement on MRI and "malignant" decreasing TAC.

parts [27]. Both [^{18}F]FDG and amino acid uptake is usually correlated with tumor grade in glioma with a direct correlation between tumor cell density and tumor proliferation rate [28, 29]. However, many glioma WHO II are iso- or even hypometabolic on [^{18}F]FDG PET and only 3–6 % of patients show an elevated [^{18}F]FDG-uptake [30]. Amino acid tracers such as [^{11}C]MET and [^{18}F]FET have proven to provide a better tumor to brain delineation in non-enhancing glioma [31, 32]. Non-invasive differentiation between glioma and non-tumoral lesions via evaluation of [^{11}C]MET uptake correlated in 79 % with the histological diagnosis [32]. Still, a high overlap of uptake values of both tracers between high grade and low grade glioma exists; here, dynamic [^{18}F]FET-PET was shown to reliably discern between gliomas WHO II versus WHO III and IV with a specificity of 85 % and sensitivity of

71 % [33]. Furthermore, dynamic [^{18}F]FET analysis is helpful for identification of anaplastic foci within homogeneously appearing MRI-suspected LGG [20, 27]. Interestingly, both static and dynamic analysis of [^{18}F]FET uptake is often hampered in oligoastrocytoma (OA) and oligodendroglioma (OD), probably due to the higher vascular density in OA/OD [34].

Usefulness of PET for surgical procedure guidance

As mentioned in the previous section, detection of hot-spots in order to provide a correct tumor classification is of utmost importance. Several studies have shown disparities between MRI-derived pathology and actual histological findings [35–37] in particularly non-enhancing glioma. PET guided biopsy techniques have been evaluated in a number of studies revealing a considerably higher diagnostic yield in PET-based biopsy compared to techniques based on MRI only [38–41]. Microsurgical resection usually aims at a maximum safe removal of the solid tumor mass. However, even here, preoperative identification of the most malignant tumor region via PET can help to optimize the surgical procedure especially in tumors without CE in MRI as the clinically most relevant, anaplastic region within the tumor volume can be selectively sent for pathology and are not at risk to be missed for diagnosis. Thus, incorporation of PET imaging into intraoperative navigation permits tissue sampling from the metabolic hotspot and might help to prevent a misgrading due to sampling error even in open resection [42].

While several studies have demonstrated an additional benefit for pediatric glioma patients undergoing PET-based resection [43, 44], respective data from adults are yet missing. Thus, further prospective studies are needed to explore the value of PET-based resection in glioma.

Usefulness of PET for radiation planning

Due to both the infiltrative nature of glioma growth as well as tumor-associated phenomena such as peritumoral edema, a reliable definition of biologically active tumor volume based on MRI alone may be difficult. A number of studies employing PET for tumor volume definition in radiotherapy have been conducted so far; however, large prospective studies addressing the possible benefit from PET-based radiotherapy are still lacking.

Retrospective studies on PET-based radiation planning in malignant glioma have reported AA-PET based tumor volumes to be on average larger than evaluated by MRI often extending T2/FLAIR changes [45–47]. Furthermore, [^{11}C]MET, [^{18}F]FET, and [^{18}F]DOPA are of comparable utility in discerning tumor tissue from unspecific changes. Conflicting results concerning the influence of PET-based radiation planning on survival have been reported; however, control groups were mostly historical cohorts; thus, these results have to be regarded with caution [48–50]. A huge proportion of studies analyzed failure patterns following PET-based radiotherapy, with similar results: the

predominant failure pattern seems to result in a recurrence localized within the center of the erstwhile tumor, even in the setting of re-irradiation [51–53].

Monitoring treatment including pseudoprogression and pseudoresponse

Monitoring treatment effects and timely identification of treatment failure is a daily challenge in neuro-oncology. AA-PET seems to be an appropriate imaging tool to visualize metabolic changes occurring within the tumor during therapy, an example of [^{18}F]FET-PET-based response following radiochemotherapy can be found in Fig. 2. Several studies using AA-PET have shown a decrease in both tumor uptake and volume to be correlated with response in glioma of grade II–IV [54, 55]. Furthermore, dynamic PET was shown to provide an additional possibility to discern progression from post-therapeutic changes in HGG following multimodal therapy [19]. Notably, most of these studies address treatment response in malignant glioma with more or less homogeneous treatment protocols, while literature on treatment assessment via PET in glioma II is scarce, probably due to the high heterogeneity in treatment protocols. A retrospective study by Roelcke and colleagues evaluating the additional value of [^{18}F]FET-PET in monitoring treatment response of alkylating chemotherapy has shown tumor volume reduction on PET to predict response earlier than MRI alone [55].

Pseudoprogression describes increased contrast-enhancement mimicking tumor progression with subsequent regression. It can occur up to 12 weeks after the completion of radiochemotherapy and was first observed predominantly in methylated glioblastoma with methylated MGMT promoter following standard radiochemotherapy [56]. Pseudoresponse is often observed in patients treated with antiangiogenic agents such as bevacizumab leading to a decrease of contrast medium enhancement on MRI masking presence and even progression of tumor [57, 58]. RANO criteria have taken both of these phenomena into account demanding a repetition of MRI after 4 weeks in questionable cases [3••]. However, this approach consumes valuable time and might postpone important treatment decisions. Amino acid PET has proven to be helpful in identifying pseudoprogression [21, 59, 60]. Pseudoresponse was

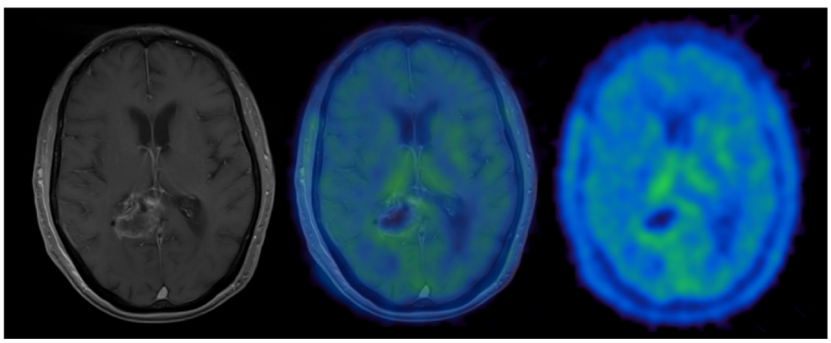

Fig. 2. A glioblastoma patient following radiochemotherapy; while there is still contrast enhancement visible on MRI reflecting BBB disruption or possibly viable tumor cells, no relevant uptake can be observed on [^{18}F] FET-PET corresponding to complete response.

addressed in a study by Hutterer and colleagues investigating [^{18}F]FET-PET in recurrent malignant glioma receiving bevacizumab/irinotecan (BEV/IR). This study revealed to detect treatment failure based on volumetric and uptake changes of FET earlier than by RANO criteria [61]. Both standard and dynamic [^{18}F]FET-PET parameters were useful in identifying BEV/IR non-responders in another trial when compared to an assessment based on RANO criteria only [62]. Furthermore, in a prospective study, Schwarzenberg and colleagues were able to identify treatment responders to antiangiogenic therapy using metabolic volume changes of [^{18}F]DOPA as early as 2 weeks into therapy [63]. [^{18}F]FLT-PET seems to yield comparable results in discriminating responders from non-responders [64]. However, most of the studies mentioned above are retrospective with rather small study populations and need further validation. So far, MRI and AA-PET seem to deliver complimentary information in both pseudoprogression and pseudoresponse. This might become even more important for defining the endpoint of PFS in clinical trials [65••].

Prognosis

Besides established molecular markers providing prognostic as well as predictive information for disease outcome prior to treatment, non-invasively obtained imaging-derived markers are becoming increasingly important in the field of neuro-oncology. Recently, several studies have investigated the prognostic value of PET for outcome in gliomas. Both tumor volume and tracer uptake kinetics reflected by time-activity curves and time-to-peak analysis prior to alkylating chemotherapy and radiotherapy have been shown to be of prognostic value for outcome in malignant glioma [22•, 66•]. Glioblastoma patients with an either intrinsically small initial biological tumor volume (BTV) or tumor volume reduction following surgery prior to concomitant radiochemotherapy have significantly improved overall and progression free survival compared to larger BTV. Similar results were found showing post-resection tumor volume to be prognostic for overall survival in both GBM and anaplastic astrocytoma [67, 68]. Furthermore, two further studies revealed short time-to-peak times and steep time-activity curves at initial diagnosis reflecting fast [^{18}F]FET intake into tumor cells to be associated with worse prognosis in gliomas WHO II as well as III/IV [22•, 69].

Outlook

So far, data from studies comparing the value of different imaging modalities such as magnetic resonance spectroscopy (MRS), perfusion-weighted imaging (PWI) as well as PET have shown the information obtained by the different approaches to be complementary. Thus, recent developments aim at establishing a multimodal approach via simultaneous data acquisition allowing incorporation of both, MRI and PET imaging. This might help to increase explanatory power and diagnostic accuracy both for therapy planning as well for therapy monitoring. Furthermore, another interesting aspect to be explored in the future is the use of new radiolabeled molecules acting not only as diagnostic

markers but also as therapeutic agents. This new evolving field of "theranostics" will open up new possibilities for PET-based therapies and provide further insights into biology of glioma.

Compliance with Ethical Standards

Conflict of Interest

Bogdana Suchorska and Nathalie Lisa Albert each declare no potential conflicts of interest.
Jörg-Christian Tonn served on advisory boards and received honoraria from MerckSerono, Roche and Celldex. Dr. Tonn reports grants from Deutsche Krebshilfe.

Human and Animal Rights and Informed Consent

This article does not contain any trails with animal subjects involved. All research cited in this paper involving any of the authors (B.S. N.L.A and J.C.T) was conducted in accordance to the Helsinki Declaration of 1975 and the local Ethics Committee of the Ludwig-Maximilians University.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1.•• Weller M, van den Bent M, Hopkins K, et al. EANO guideline for the diagnosis and treatment of anaplastic gliomas and glioblastoma. Lancet Oncol. 2014;15(9):e395–403.

Important guideline paper.

2. Macdonald DR, Cascino TL, Schold Jr SC, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol: Off J Am Soc Clin Oncol. 1990;8:1277–80.

3.•• 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: Off J Am Soc Clin Oncol. 2010;28(11):1963–72.

Important guideline paper.

4. Som P, Atkins HL, Bandoypadhyay D, et al. A fluorinated glucose analog, 2-fluoro-2-deoxy-D-glucose (F-18): nontoxic tracer for rapid tumor detection. J Nucl Med. 1980;21(7):670–5.

5. Alavi A, Dann R, Chawluk J, Alavi J, Kushner M, Reivich M. Positron emission tomography imaging of regional cerebral glucose metabolism. Semin Nucl Med. 1986;16(1):2–34.

6. Di Chiro G, DeLaPaz RL, Brooks RA, et al. Glucose utilization of cerebral gliomas measured by [18F] fluorodeoxyglucose and positron emission tomography. Neurology. 1982;32(12):1323–9.

7. Kubota R, Yamada S, Kubota K, Ishiwata K, Tamahashi N, Ido T. Intratumoral distribution of fluorine-18-fluorodeoxyglucose in vivo: high accumulation in macrophages and granulation tissues studied by microautoradiography. J Nucl Med. 1992;33(11):1972–80.

8. Ishiwata K, Vaalburg W, Elsinga PH, Paans AM, Woldring MG. Comparison of L-[1-11C]methionine and L-methyl-[11C]methionine for measuring in vivo protein synthesis rates with PET. J Nucl Med. 1988;29(8):1419–27.

9. Weber WA, Wester HJ, Grosu AL, et al. O-(2-[18F]fluoroethyl)-L-tyrosine and L-[methyl-11C]methionine uptake in brain tumours: initial results of a comparative study. Eur J Nucl Med. 2000;27(5):542–9.

10. Kratochwil C, Combs SE, Leotta K, et al. Intra-individual comparison of (1)(8)F-FET and (1)(8)F-DOPA in PET imaging of recurrent brain tumors. Neuro-Oncology. 2014;16(3):434–40.

11. Becherer A, Karanikas G, Szabo M, et al. Brain tumour imaging with PET: a comparison between [18F]fluorodopa and [11C]methionine. Eur J Nucl Med Mol Imaging. 2003;30(11):1561–7.

12. Huang C, McConathy J. Radiolabeled amino acids for oncologic imaging. J Nucl Med. 2013;54(7):1007–10.

13.• Dunet V, Pomoni A, Hottinger A, Nicod-Lalonde M, Prior JO. Performance of 18F-FET versus 18F-FDG-PET for the diagnosis and grading of brain tumors: systematic review and meta-analysis. Neuro-oncology. 2015. This study provides a consise review on literature available on [^{18}F]FET and [^{18}F]FDG in glioma.

A concise overview on literature available on the two tracers.

14. Chen W, Silverman DH, Delaloye S, et al. 18F-FDOPA PET imaging of brain tumors: comparison study with 18F-FDG PET and evaluation of diagnostic accuracy. J Nucl Med. 2006;47(6):904–11.
15. Youland RS, Kitange GJ, Peterson TE, et al. The role of LAT1 in (18)F-DOPA uptake in malignant gliomas. J Neurooncol. 2013;111(1):11–8.
16. Haining Z, Kawai N, Miyake K, et al. Relation of LAT1/4F2hc expression with pathological grade, proliferation and angiogenesis in human gliomas. BMC Clin Pathol. 2012;12:4.
17. 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(2):217–25.
18. Habermeier A, Graf J, Sandhofer BF, Boissel JP, Roesch F, Closs EI. System L amino acid transporter LAT1 accumulates O-(2-fluoroethyl)-L-tyrosine (FET). Amino Acids. 2015;47(2):335–44.
19. Popperl G, Kreth FW, Herms J, et al. Analysis of 18F-FET PET for grading of recurrent gliomas: is evaluation of uptake kinetics superior to standard methods? J Nuclear Med: Off Publ Soc Nucl Med. 2006;47(3):393–403.
20. Jansen NL, Graute V, Armbruster L, et al. MRI-suspected low-grade glioma: is there a need to perform dynamic FET PET? Eur J Nucl Med Mol Imaging. 2012;39(6):1021–9.
21. Jansen NL, Suchorska B, Schwarz SB, et al. [18F]fluoroethyltyrosine-positron emission tomography-based therapy monitoring after stereotactic iodine-125 brachytherapy in patients with recurrent high-grade glioma. Mol Imaging. 2013;12:137–47.
22.• Jansen NL, Suchorska B, Wenter V, et al. Prognostic significance of dynamic 18F-FET PET in newly diagnosed astrocytic high-grade glioma. J Nucl Med. 2015;56(1):9–15.

First study to show dynamic analysis of [^{18}F]FET uptake via TTP analysis to provide prognostic information on outcome in HGG.

23. Moulin-Romsee G, D'Hondt E, de Groot T, et al. Non-invasive grading of brain tumours using dynamic amino acid PET imaging: does it work for 11C-methionine? Eur J Nucl Med Mol Imaging. 2007;34(12):2082–7.
24. Schiepers C, Chen W, Cloughesy T, Dahlbom M, Huang SC. 18F-FDOPA kinetics in brain tumors. J Nucl Med. 2007;48(10):1651–61.
25. Shields AF, Grierson JR, Dohmen BM, et al. Imaging proliferation in vivo with [F-18]FLT and positron emission tomography. Nat Med. 1998;4(11):1334–6.
26. DeAngelis LM. Anaplastic glioma: how to prognosticate outcome and choose a treatment strategy. [corrected]. J Clin Oncol: Off J Am Soc Clin Oncol. 2009;27(35):5861–2.
27. Kunz M, Thon N, Eigenbrod S, et al. Hot spots in dynamic (18)FET-PET delineate malignant tumor parts within suspected WHO grade II gliomas. Neuro-Oncology. 2011;13(3):307–16.
28. Herholz K, Pietrzyk U, Voges J, et al. Correlation of glucose consumption and tumor cell density in astrocytomas. A stereotactic PET study. J Neurosurg. 1993;79(6):853–8.
29. Kato T, Shinoda J, Oka N, et al. Analysis of 11C-methionine uptake in low-grade gliomas and correlation with proliferative activity. AJNR Am J Neuroradiol. 2008;29(10):1867–71.
30. Kato T, Shinoda J, Nakayama N, et al. Metabolic assessment of gliomas using 11C-methionine, [18F] fluorodeoxyglucose, and 11C-choline positron-emission tomography. AJNR Am J Neuroradiol. 2008;29(6):1176–82.
31. Pauleit D, Floeth F, Hamacher K, et al. O-(2-[18F]fluoroethyl)-L-tyrosine PET combined with MRI improves the diagnostic assessment of cerebral gliomas. Brain. 2005;128(Pt 3):678–87.
32. Herholz K, Holzer T, Bauer B, et al. 11C-methionine PET for differential diagnosis of low-grade gliomas. Neurology. 1998;50(5):1316–22.
33. Popperl G, Kreth FW, Mehrkens JH, et al. FET PET for the evaluation of untreated gliomas: correlation of FET uptake and uptake kinetics with tumour grading. Eur J Nucl Med Mol Imaging. 2007;34(12):1933–42.
34. Jansen NL, Schwartz C, Graute V, et al. Prediction of oligodendroglial histology and LOH 1p/19q using dynamic [(18)F]FET-PET imaging in intracranial WHO grade II and III gliomas. Neuro-Oncology. 2012;14(12):1473–80.
35. Watanabe M, Tanaka R, Takeda N. Magnetic resonance imaging and histopathology of cerebral gliomas. Neuroradiology. 1992;34(6):463–9.
36. Hall WA, Liu H, Martin AJ, Truwit CL. Comparison of stereotactic brain biopsy to interventional magnetic-resonance-imaging-guided brain biopsy. Stereotact Funct Neurosurg. 1999;73(1–4):148–53.
37. Glantz MJ, Burger PC, Herndon 2nd JE, et al. Influence of the type of surgery on the histologic diagnosis in patients with anaplastic gliomas. Neurology. 1991;41(11):1741–4.
38. Levivier M, Goldman S, Pirotte B, et al. Diagnostic yield of stereotactic brain biopsy guided by positron emission tomography with [18F]fluorodeoxyglucose. J Neurosurg. 1995;82(3):445–52.
39. Pirotte B, Goldman S, Bidaut LM, et al. Use of positron emission tomography (PET) in stereotactic conditions for brain biopsy. Acta Neurochir. 1995;134(1–2):79–82.
40. Pirotte B, Goldman S, Massager N, et al. Comparison of 18F-FDG and 11C-methionine for PET-guided stereotactic brain biopsy of gliomas. J Nucl Med. 2004;45(8):1293–8.
41. Pirotte B, Goldman S, David P, et al. Stereotactic brain biopsy guided by positron emission tomography (PET) with [F-18]fluorodeoxyglucose and [C-11]methionine. Acta Neurochir Suppl. 1997;68:133–8.
42. Mert A, Kiesel B, Wohrer A, et al. Introduction of a standardized multimodality image protocol for

navigation-guided surgery of suspected low-grade gliomas. Neurosurg Focus. 2015;38(1):E4.
43. Pirotte B, Acerbi F, Lubansu A, Goldman S, Brotchi J, Levivier M. PET imaging in the surgical management of pediatric brain tumors. Child Nerv Syst: ChNS : Off J Int Soc Pediatr Neurosurg. 2007;23(7):739–51.
44. Kaplan AM, Bandy DJ, Manwaring KH, et al. Functional brain mapping using positron emission tomography scanning in preoperative neurosurgical planning for pediatric brain tumors. J Neurosurg. 1999;91(5):797–803.
45. Grosu AL, Weber WA, Riedel E, et al. L-(methyl-11C) methionine positron emission tomography for target delineation in resected high-grade gliomas before radiotherapy. Int J Radiat Oncol Biol Phys. 2005;63(1):64–74.
46. Kracht LW, Miletic H, Busch S, et al. Delineation of brain tumor extent with [11C]L-methionine positron emission tomography: local comparison with stereotactic histopathology. Clin Cancer Res: Off J Am Assoc Cancer Res. 2004;10(21):7163–70.
47. Munck AF, Rosenschold P, Costa J, Engelholm SA, et al. Impact of [18F]-fluoro-ethyl-tyrosine PET imaging on target definition for radiation therapy of high-grade glioma. Neuro-Oncology. 2015;17(5):757–63.
48. Grosu AL, Weber WA, Franz M, et al. Reirradiation of recurrent high-grade gliomas using amino acid PET (SPECT)/CT/MRI image fusion to determine gross tumor volume for stereotactic fractionated radiotherapy. Int J Radiat Oncol Biol Phys. 2005;63(2):511–9.
49. Miwa K, Matsuo M, Ogawa S, et al. Re-irradiation of recurrent glioblastoma multiforme using 11C-methionine PET/CT/MRI image fusion for hypofractionated stereotactic radiotherapy by intensity modulated radiation therapy. Radiat Oncol. 2014;9:181.
50. Piroth MD, Pinkawa M, Holy R, et al. Integrated boost IMRT with FET-PET-adapted local dose escalation in glioblastomas. Results of a prospective phase II study. Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft … [et al]. 2012;188(4):334–9.
51. Kosztyla R, Chan EK, Hsu F, et al. High-grade glioma radiation therapy target volumes and patterns of failure obtained from magnetic resonance imaging and 18F-FDOPA positron emission tomography delineations from multiple observers. Int J Radiat Oncol Biol Phys. 2013;87(5):1100–6.
52. Weber DC, Casanova N, Zilli T, et al. Recurrence pattern after [(18)F]fluoroethyltyrosine-positron emission tomography-guided radiotherapy for high-grade glioma: a prospective study. Radiother Oncol: J Eur Soc Ther Radiol Oncol. 2009;93(3):586–92.
53. Niyazi M, Jansen NL, Rottler M, Ganswindt U, Belka C. Recurrence pattern analysis after re-irradiation with bevacizumab in recurrent malignant glioma patients. Radiat Oncol. 2014;9:299.
54. Galldiks N, Kracht LW, Burghaus L, et al. Use of 11C-methionine PET to monitor the effects of temozolomide chemotherapy in malignant gliomas. Eur J Nucl Med Mol Imaging. 2006;33(5):516–24.
55. Roelcke U, Wyss MT, Nowosielski M, Rudà R, Roth P, Hofer S, Galldiks N, Crippa F, Weller M, Soffietti R. Aminoacid PET to monitor chemotherapy response, and to predict seizure control and progression-free survival in WHO grade II gliomas. Neuro-Oncology. 2015 [in press].
56. Brandsma D, Stalpers L, Taal W, Sminia P, van den Bent MJ. Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas. Lancet Oncol. 2008;9:453–61.
57. Brandsma D, van den Bent MJ. Pseudoprogression and pseudoresponse in the treatment of gliomas. Curr Opin Neurol. 2009;22(6):633–8.
58. Fink J, Born D, Chamberlain MC. Pseudoprogression: relevance with respect to treatment of high-grade gliomas. Curr Treat Options in Oncol. 2011;12(3):240–52.
59. Galldiks N, Dunkl V, Stoffels G, et al. Diagnosis of pseudoprogression in patients with glioblastoma using O-(2-[18F]fluoroethyl)-L-tyrosine PET. Eur J Nucl Med Mol Imaging. 2015;42(5):685–95.
60. Niyazi M, Jansen N, Ganswindt U, et al. Re-irradiation in recurrent malignant glioma: prognostic value of [18F]FET-PET. J Neuro-Oncol. 2012;110(3):389–95.
61. Hutterer M, Nowosielski M, Putzer D, et al. O-(2-18F-fluoroethyl)-L-tyrosine PET predicts failure of antiangiogenic treatment in patients with recurrent high-grade glioma. J Nucl Med. 2011;52:856–64.
62. Galldiks N, Rapp M, Stoffels G, et al. Response assessment of bevacizumab in patients with recurrent malignant glioma using [18F]fluoroethyl-L-tyrosine PET in comparison to MRI. Eur J Nucl Med Mol Imaging. 2013;40:22–33.
63. Schwarzenberg J, Czernin J, Cloughesy TF, et al. Treatment response evaluation using 18F-FDOPA PET in patients with recurrent malignant glioma on bevacizumab therapy. Clin Cancer Res: Off J Am Assoc Cancer Res. 2014;20:3550–9.
64. 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: Off J Am Soc Clin Oncol. 2007;25(30):4714–21.
65.•• Hutterer M, Hattingen E, Palm C, Proescholdt MA, Hau P. Current standards and new concepts in MRI and PET response assessment of antiangiogenic therapies in high-grade glioma patients. Neuro-Oncology. 2015;17(6):784–800.

An interesting and concise overview on available imaging methods for evaluation of response assessment after antiangiogenic treatment.

66.• Suchorska B, Jansen NL, Linn J, et al. Biological tumor volume in 18FET-PET before radiochemotherapy correlates with survival in GBM. Neurology. 2015;84(7):710–9.

First prospective study to show that PET-derived biological volume prior to radiochemotherapy influences outcome in newly diagnosed glioblastoma.

67. 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(1):176–84.

68. Galldiks N, Dunkl V, Kracht LW, et al. Volumetry of [(1)(1)C]-methionine positron emission tomographic uptake as a prognostic marker before treatment of patients with malignant glioma. Mol Imaging. 2012;11(6):516–27.

69. Jansen NL, Suchorska B, Wenter V, et al. Dynamic 18F-FET PET in newly diagnosed astrocytic low-grade glioma identifies high-risk patients. J Nucl Med. 2014;55(2):198–203.