Review Article

Positron emission tomography imaging in gliomas

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ABSTRACT

Glioma, the most frequent primary brain tumor in adults, is a highly infiltrative tumor exhibiting resistance to most treatments and associated with short survival of patients. Positron emission tomography (PET) imaging using various tracers takes advantage of the increased metabolic rate of neoplastic cells, in order to detect tumors and validate the treatment response. The most frequently used PET tracer, the (18)F-fluorodeoxyglucose (FDG), is useful during the initial and follow-up assessment of patients with gliomas because it can assist in the selection of the initial biopsy site and to assess early response to a given therapeutic intervention. Furthermore, when there is tumor re-growth after an initial remission, FDG-PET can differentiate between true tumor recurrence versus necrosis from radiation therapy. Newly developed PET tracers may exhibit better sensitivity than FDG to diagnose primary brain tumors, but may occasionally produce false positive results in various conditions. In any event, PET is a useful tool in patients with central nervous system cancer during both initial assessment and follow-up.

Key words: Brain tumor, cancer, glioma, positron emission tomography

INTRODUCTION

Gliomas represent the most common primary brain tumors, with poor prognosis even with aggressive therapies such as various combinations of surgery, radiation therapy and chemotherapies.[1,2] Earlier response and progression criteria in recurrent glioma relied on changes in the contrast enhancing magnetic resonance imaging (MRI),[3,4] however, the dramatic response rates seen in therapies involving antiangiogenic therapies as well as other insufficiencies of the previous criteria resulted in development of updated response criteria that take into account the nonenhancing component of the tumor as well as other critical parameters.[4,5] The newly described response assessment in neuro-oncology (RANO) criteria includes comprehensive recommendations to assess response to a therapy taking into account various issues in gliomas, such as imaging changes postsurgical resection of a tumor or locally delivered therapies, issues-related to contrast enhancement of previously unenhanced areas as well as clinical parameters.[6] This field is still evolving since in a recent report the change in ADC histogram skewness may be more sensitive than the response assessment in RANO criteria for evaluation of antiangiogenic therapy.[7]

Nuclear medicine imaging such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) combined with CT are useful for diagnosis and management of a variety of neurological diseases and cancers.[8] SPECT and PET scans may be utilized to assess brain tumor biologic behavior,[9] distinction of radiation-induced necrosis from tumor recurrence and estimation of overall prognosis.[10] Increased tumor uptake of (99 m) Tc-tetrofosmin in SPECT correlated with aggressive behavior and may be an independent prognostic factor in patients with malignant glioma.[11]

In this article, we present an evidence-based practical approach for the use of PET/CT during evaluation and therapy of patients with a malignant primary brain tumor. We reviewed published papers during the last decade and included some older key references and our own experience.

(18)F-FLURODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY

(18)F-flurodeoxyglucose (FDG) PET takes advantage of the increased glucose uptake, a characteristic of

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tumor cells, in order to detect tumors and validate the treatment response [Table 1].

Hypometabolism on FDG PET in brain lesions and stability over a period is indicative of nonmalignancy.[24] When it is difficult to differentiate preoperatively a primary brain tumor from metastasis,[25] FDG PET may be helpful in depicting areas of systemic involvement,[26] or localizing the primary cancer site.[27,28] Occasionally, patients may present with brain lesions, radiologically compatible with brain metastases that after biopsy are proven to be multifocal gliomas.[29,30] In such cases, FDG PET may aid in pinpointing the area of stereotactic biopsy,[31,32] assist in tumor delineation during radiotherapy planning[33] and assessment of treatment response.[34]

In a study of 81 recurrent glioma patients studied by FDG PET, it was found that the higher the FDG uptake by the tumor it was associated with worse survival.[35] In addition, pretreatment uptake of FDG in 25 patients with recurrent gliomas subsequently

Table 1: Representative studies on utility of FDG PET and comparison with other tracers in patients with primary brain tumors

Study	No. of patients	Reason for the exam	Results (%)	Study conclusion
Colavolpe *et al.*[12]	25 patients with recurrent glioma	To assess utility of FDG PET/CT in patients receiving bevacizumab and irinotecan therapy	FDG uptake was the most powerful predictor of both PFS and OS using the RANO criteria	Pretreatment FDG PET predicts survival in recurrent glioma patients following anti-angiogenic therapy
Santra *et al.*[13]	90 patients with possible recurrent glioma	To compare FDG PET/CT with contrast MRI	PET sensitivity: 70 Specificity: 97 MRI sensitivity: 95 Specificity: 23	FDG PET/CT was an accurate modality to detect glioma recurrence
Borbely *et al.*[14]	59 patients with primary and recurrent brain gliomas (50 had MET PET; 33 had FDG PET)	To compare FDG PET with MET PET for *in vivo* grading of malignant gliomas	FDG PET superior to MET PET for grading of gliomas	FDG PET recommended for grading but MET PET may be used for assessing the extent of the tumor
Singhal *et al.*[15]	102 patients with confirmed gliomas were followed for an average of 34.6 months after PET	To compare FDG PET with MET PET and MRI	MET PET superior to FDG PET and MRI in predicting survival in low-grade gliomas	For low grade gliomas MET PET preferred to FDG PET
Yamaguchi *et al.*[16]	26 patients with untreated or recurrent adult gliomas had preoperative FDG (n = 25) and/or MET (n = 22) PET	To compare FDG PET with MET PET	FDG better for tumor grade MET better for delineating the extent of the tumor	Both tracers complement each other to plan the extend of tumor resection
Tripathi *et al.*[17]	15 patients with untreated or recurrent low grade gliomas	To compare FDG PET with FDOPA PET and FLT PET	FDOPA PET superior to both FDG and FLT PET for detection of low grade gliomas	FDOPA PET should be the radiotracer of choice for low grade glioma
Chen *et al.*[18]	25 patients with with untreated or recurrent adult gliomas	To compare FDG PET with FLT PET	FLT PET better to image recurrent high-grade tumors, to correlate with Ki-67 values, and predict tumor progression and survival	FLT a promising tracer of proliferation in high-grade gliomas
Enslow *et al.*[19]	15 recurrent glioma patients	To compare FDG PET with FLT PET	Both FDG PET and FLT PET could differentiate between tumor recurrence and radiation necrosis	FLT PET offers no advantage over FDG PET
Karunanithi *et al.*[20]	28 patients with recurrent gliomas	To compare FDG PET with FDOPA PET for diagnosis of recurrence	FDG sensitivity: 47.6 FDG specificity: 100 FDOPA sensitivity: 100 FDOPA specificity: 85.7	The difference between FDOPA and FDG PET was significant for low grade glioma but not for high grade tumors
Tripathi *et al.*[21]	35 patients with recurrent glioma	To compare FDG PET with MET PET	FDG sensitivity: 81.2 FDG specificity: 88.9 MET sensitivity: 94.7 MET specificity: 88.9	MET should be the radiotracer of choice for recurrent gliomas
Potzi *et al.*[22]	28 patients with recurrent GBM	To evaluate FDG and MET PET for recurrent glioma		FDG PET of limited value; MET PET not superior to conventional imaging
Nihashi *et al.*[23]	Meta-analysis of 26 heterogenous studies	To evaluate the diagnostic accuracy of PET and compare it with conventional imaging modalities	FDG PET and MET PET with acceptable accuracy for diagnosing recurrent glioma	Prospective studies with direct comparisons between various imaging modalities required

PET: Positron emission tomography; CT: Computed tomography; MRI: Magnetic resonance imaging; RANO: Response assessment in neuro-oncology; FDG: (18)F-flurodeoxyglucose; FET: O-(2-(18)F-fluoroethyl)-l-tyrosine; GBM: Glioblastomamultiforme; MET: (11)C-methionine; FDOPA: (18)F-FDOPA; FLT: 3'-Fluoro-3' deoxythymidine; PFS: Progression-free survival; OS: Overall survival; HGG: WHO grades III or IV; LGG: WHO grades I or II

treatment with bevacizumab and irinotecan predicted response to the treatment and correlated with overall survival.[12] Similar predictive value of FDG-PET was reported with other therapies in glioma patients.[36] FDG PET compared to MRI scans with and without contrast enhancement had much higher specificity (97% *vs*. 23%) for detection of recurrence in 90 glioma patients clinically suspicious of tumor growth.[13]

OTHER POSITRON EMISSION TOMOGRAPHY TRACERS AND COMPARISON WITH (18)F-FLURODEOXYGLUCOSE

During the last several years, new PET tracers have been developed for a wide range of biological targets [Table 2].[37]

PET of amino acid transport and metabolism could be a reliable method in assessing a metabolic response after treatment of a tumor or in establishing a treatment-related effect, depending on the rate of the tracer uptake by tumor. Employment of imaging amino acid transport may prove to have an important clinical role in the management of brain tumor patients since it may result in changes in therapeutic management.[62]

For example, application of O-(2-(18)F-fluoroethyl)-L-tyrosine (FET) PET/CT in newly diagnosed brain tumors could predict their biologic behavior in most of the cases.[48,52,63] FET represents an artificial amino acid not incorporates into proteins but transports into active glioma cells.[46] FET-PET may be more accurate than FDG-PET for differentiation of malignant gliomas from low-grade gliomas,[64,65] by their low FET uptake on PET in the low-grade tumors.[66,67] Thus, in a study of 88 patients with an intracerebral lesion observed by MRI, FET PET was performed, followed by biopsy in 60 patients. The sensitivity of FET PET for high-grade tumors (WHO III-IV) was reported 94% and for low-grade tumors (WHO I-II) 68%. However, there were

Table 2: Other PET tracers for patients with gliomas

Tracer	Mechanism	No. of studies	Untreated or recurrent glioma	Advantages	Disadvantages
AMT[38]	Amino acid PET tracer not incorporated into proteins but transported into gliomas via the kynurenine pathway	1	Recurrent	AMT PET could differentiate between tumor and XRT necrosis	False positive results can occur in cortical dysplasia with epileptic focus[39]
MET PET[40]	MET is transported by the LAT1 amino acid transporter into glioma and is incorporated into proteins[41]	5	Upfront[15] Recurrent[41-44]	MET uptake correlated with prognosis[15] MET PET could differentiate between tumor and XRT necrosis[40,42] Correlate with OS and outcome[43,44]	Short half-life (20 min) requiring on site production; MET may accumulate in brain abscesses or inflammation[45]
FET PET	FET is an artificial amino acid transported into active glioma cells but incorporated into proteins[46]	5	Upfront[47,48] Recurrent[49-51]	FET PET could differentiate glioma from nonneoplastic tissue FET PET distinguished active tumor from radiation necrosis;[50,51] dynamic FET uptake could differentiate between high and low grade tumors[49]	Rare false positive in granulomatous conditions and reactive astogliosis[52] or false negative cases[53]
FDOPA PET: (18)F-FDOPA	l-DOPA is the precursor of dopamine and is transported physiologically into the brain and abnormally into the brain tumors[54]	2	Upfront[55] Recurrent[55,56]	Correlation of FDOPA uptake, tumor proliferation and grade Diagnostic accuracy of recurrence similar to MRI[56]	Diagnostic usefulness mostly in upfront gliomas; limited data
FLT PET[57,58]	FLT is an analog of deoxythymidine, which is composed of deoxyribose and the pyrimidine base thymine and phosphorylated by thymidine kinase 1 during DNA synthesis[59]	2	Upfront[57] Recurrent[58]	FLT PET could differentiate between high and low grade tumors FLT-PET responses correlated with OS	FLT may accumulate in benign lesions with BBB disruption[45]
CHO: (18)F-fluoromethylcholine	During glioma cell proliferation choline is trapped into the cells to produce phosphatidylcholine, a necessary constituent of the plasma membrane[60]	1	Various brain lesions (tumors or nontumors)	Higher uptake in malignant tumors	It may also accumulate in various inflammatory processes[61]

PET: Positron emission tomography; MRI: Magnetic resonance imaging; XRT: Radiation therapy; BBB: Blood brain barrier; MET: (11)C-methionine; AMT: Alpha-(11)C-methyl-l-tryptophan; FDG: (18)F-flurodeoxyglucose; FET: O-(2-(18)F-fluoroethyl)-l-tyrosine; FDOPA: (18)F-FDOPA; FLT: 3'-fluoro-3' deoxythymidine; PFS: Progression-free survival; OS: Overall survival

two false-positive cases with postischemic lesions.[52] A study on differences in the dynamics of FET uptake in gliomas could differentiate between recurrent high and low-grade tumors.[49] In another study, it was shown that an FET-PET with a receiver-operating-characteristic curve analysis, a mean tumor-to-brain ratio of 2.5 was highly specific for tumor rather than nontumor tissue.[47] In 10 patients with recurrent glioma treated with a combination of bevacizumab and irinotecan FET PET could predict treatment failure, thus provided additional information from that obtained by MRI response assessment based on RANO criteria.[50] A meta-analysis of 13 studies with 462 newly diagnosed untreated patients with primary brain tumors indicated that FET-PET may be an excellent tool for differentiating tumor for non tumoral lesions.[48]

Another PET tracers that may be employed for evaluation of brain tumors are (18)F-labeled fluoromethylcholine (18F-FCho)[60] and (11)C-methionine (MET) PET.[31,40,50] MET-PET may aid in the differential diagnosis of tumor recurrence versus radiation necrosis although its specificity and sensitivity have been reported both as 75%.[42] In patients with glioma, clinical stability induced by temozolomide chemotherapy correlated to a decline or stability of tumor MET uptake on PET.[43] Furthermore, although the standard MET PET did not correlate with survival, a voxel-wise parametric response map analysis of MET PET correlated with OS in 14 patients with recurrent malignant gliomas treated with specific immunotherapy targeting the Wilms tumor 1gene product.[44] The short half-life (20 min) of (11)C limits its use of MET PET to institutions with an onsite cyclotron. A comparison of MET PET with FET-PET (half-life of 120 min) in 29 patients with recurrent gliomas showed that both tracers differentiated tumor tissue and treatment-related changes with high sensitivity and specificity suggesting that FET PET could be used in places where an onsite cyclotron is unavailable.[68] FET PET may provide more accurate information in respect of treatment response or failure compared with response assessment based on conventional MRI and RANO criteria,[69] and could reliably distinguish between posttherapeutic treatment related effects and tumor recurrence independently on the employed treatment modality.[51]

In addition, there is evidence that FET PET in the management of patients with recurrent glioma treated with a combination of bevacizumab and irinotecan may be cost-effective since it can prevent overtreatment and additional costs, as well as potential side effects to patients.[70]

A comparison study between FDG-PET and MET PET in 59 patients with either untreated or recurrent gliomas demonstrated that FDG-PET was a superior test to *in vivo* predict histologic grade of the tumor compared with MET PET [Table 1].[14] However, in respect to the low-grade gliomas, MET PET appears to better correlate with overall prognosis and survival rather than FDG PET or conventional MRI, suggesting that both tracers may be complementary during evaluation of gliomas before or after therapies.[15] Similar results in another study suggested that both FDG and MET PET provide useful complementary information assisting surgeons to determine the extent of the surgical resection.[16] In a recent study of 35 patients with suspected recurrent gliomas FDG PET and MET PET were performed during the same day and correlated with subsequent histopathology or MRI/modified Rankin scale and clinical follow-up. The results of this study suggested that MET PET should be preferred over FDG PET when available since it demonstrated higher sensitivity for detection of recurrence (94.7% *vs*. 81.2%) and the same specificity.[21] However, one study found that neither FDG PET or MET PET add any additional information over the conventional MRI regarding prognosis of patients with malignant gliomas.[22] A meta-analysis of 26 heterogeneous studies about several PET tracers for diagnosing recurrent gliomas found that FDG-PET had a summary sensitivity of 0.77 and specificity of 0.78 for any glioma histology, and MET PET had a summary sensitivity of 0.70 and specificity of 0.93 for high-grade glioma. Data were limited for FET and 3'-deoxy-3'-[18F] fluorothymidine (FLT) PET. The authors concluded that apart from FDG and MET PET that seem to have utility during evaluation of glioma recurrence, further studies using direct comparisons between PET tracers and imaging modalities are needed.[23]

DOPA: 3,4-dihydroxy-6-(18)F-fluoro-l-phenylalanine (FDOPA) PET tested in a 59 glioma patients (22 with new untreated gliomas and 37 with recurrent tumors) showed that FDOPA uptake was higher in high-grade than in low-grade tumors in newly diagnosed, but not recurrent tumors, suggesting that its usefulness as a noninvasive tumor grading procedure can be only in previously untreated tumors.[55] In recurrent gliomas, FDOPA was able to diagnose the recurrence with a sensitivity of 100% and specificity of 85.7% in contrast to 47.6% and 100% of FDG PET.[20] In that study, the analysis showed superiority of FDOPA PET compared with FDG-PET to diagnose recurrence in low-grade tumors but no statistical difference in high-grade gliomas.[20]

Comparison of FDOPA PET with contrast enhancing MRI scan for detection of tumor recurrence in 35 glioma patients revealed that although both examinations had high sensitivity (100% *vs*. 92.3%), FDOPA PET had much higher specificity (88.9% *vs*. 44.4%) than

MRI.[56] Furthermore FDOPA PET fused with MRI for anatomic localization provides accurate localization of tracer uptake taking advantage of both techniques.[71]

3'-deoxy-3'-[18F]-fluorothymidine is a PET tracer developed for imaging cellular proliferation. In patients with histologically diagnosed primary brain tumors the FLT uptake by the primary tumor could correlate with the grade of malignancy and proliferation index,[72] but occasionally it could result in false positive diagnoses, especially in cases of benign lesions with blood-brain barrier disruption, for example postoperative granuloma.[57] Comparison of FLT PET to MRI with and without contrast in 19 patients with recurrent glioma treated with bevacizumab in combination with irinotecan indicated that both early (1-2 weeks post treatment) and late FLT PET responses (6 weeks) were more significant predictors of overall survival compared with the MRI responses. In this study, metabolic response was defined as more than 25% reduction in tumor FLT uptake compared with baseline.[58] Furthermore, when compared to FDG PET, FLT PET was reported better in imaging recurrent high-grade tumors, correlating with Ki-67 values, and predicting tumor progression and patient survival.[18] Similarly, comparison of FDG with FDOPA and FLT PET in 15 patients with untreated or recurrent low-grade gliomas demonstrated that clearly FDOPA was the tracer of choice for tumor delineation compared with the other 2 tested tracers.[17] However, another small study in 15 patients with recurrent gliomas reported no advantage of FLT PET compared with FDG PET in discriminating between tumor recurrence and radiation necrosis.[19]

FDOPA or FLT PET uptake after bevacizumab treatment may be a useful biomarker for predicting progression-free survival in recurrent gliomas.[73-76]

Alpha-(11)C-methyl-l-tryptophan (AMT) PET utilizes the AMT as PET tracer that accumulates into gliomas through the kynurenine pathway, which leads to the production of nicotinamide adenine dinucleotide (NAD^+) from the degradation of the essential amino acid, tryptophan.[77] In 22 patients with possible recurrent glioma on MRI scan tracer uptake by the tumor could differentiate between recurrent glioma and radiation injury.[38] The (18)F-labeled glycosylated Arg-Gly-Asp peptide is a PET tracer that images the integrin alpha (v) beta (3) expression, which may be important considering the integrin inhibitors as potential therapy for glioblastomas.[78]

LIMITATIONS

(18)F-flurodeoxyglucose although represents the most common radiotracer for PET cancer imaging, it is not tumor-specific, since it shows high uptake in benign conditions such as infections and nonspecific inflammatory tissue.[45,79] In viral encephalitis FDG PET usually demonstrates hypermetabolism but focal areas of hypometabolism may also be observed.[80] Brain abscess may also exhibit FDG hypermetabolism making the differential diagnosis between a metastatic tumor and abscess in a patient with systemic cancer impossible with only this test.[81,82] Tuberculomas may also exhibit FDG hypermetabolism in the periphery and hypometabolism in the center.[83]

Even though, most of the newer PET tracers demonstrated enhanced tumor-specificity compared with FDG, they also had certain limitations; for example, (11)C-choline can be accumulated in various inflammatory processes, MET in brain abscesses and (18)F-FLT in nonmetastatic reactive lymph nodes.[45]

CONCLUSION

(18)F-flurodeoxyglucose PET, as well as PET with other tracers, may be useful for diagnosis of cerebral gliomas in patients that present with a brain mass and no involvement of other organs in conventional imaging. In addition, PET/CT is helpful in selecting the appropriate site for stereotactic biopsy and in monitoring response to various therapeutic interventions. Finally, upon re-growth of the tumor after the initial treatment, PET/CT can differentiate between glioma recurrence *vs*. necrosis from the employed radiation therapy and guide further therapeutic management.

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