[^{18}F]FET PET in Glioma Recurrence

Subjects: Neuroimaging

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[18F]fluoroethyl-tyrosine (FET) is an artificial amino acid taken up into upregulated tumoral cells by the LAT system, independently of blood brain barrier leakage. FET is diffuse in Europe and has been shown to provide high sensitivity and specificity for glioma detection resulting in a reliable diagnostic tool for differentiating tumor recurrence/progression from treatment related changes.

Keywords: FET ; time–activity curves ; MRI

1. [^{18}F]Fluoroethyl-Tyrosine (FET)

[^{18}F]fluoroethyl-tyrosine (FET) is an artificial amino acid taken up into upregulated tumoral cells by Na+ independent transport via the LAT system, independently of BBB leakage [1]. FET is not incorporated into proteins, as with the natural amino acids, and its uptake grade is not directly proportional to tumor differentiation status [2][3][4]. FET is diffuse in Europe and has been shown to provide high sensitivity and specificity for glioma detection and low uptake in the inflammatory and healthy brain [1][5], resulting in a reliable diagnostic tool for differentiating tumor recurrence/progression from TRC. Dynamic FET PET and time–activity curves (TACs) offer additional information on tracer kinetics. As known, in HGG, FET uptake is characterized by an early peak 10–15 min after injection, followed by a decrease in radiopharmaceutical's uptake, similarly to recurrence [6][7]; differently, an LGG shows a typical delayed and steadily increasing tracer uptake similar to TRC [8]. These patterns are usually observed for FET PET and not for other amino acid tracers such as MET and FDOPA. Static PET scan protocols might not reveal the active metabolic tumor and might suffer from a lack of standardized acquisition protocols; thanks to the proprieties of not being metabolized after the entry into the cell, advanced pharmacokinetic analysis of TACs from dynamic FET PET scans, using compartment models, was exploited [5].

Several studies investigated the role of FET in the evaluation of recurrence and a variable diagnostic accuracy ranging between 81% and 99% was reported [9][10]. This wide range could be explained considering the different PET parameters analyzed, e.g., tumor-to-background ratios (TBRmax and TBRmean), acquisition time protocols (static vs. dynamic), the uptake kinetics (time to peak—TTP, in minutes from the beginning of the dynamic acquisition up to the maximum SUV of the lesion) as well as different patient populations, tumor subtypes, and treatments [11]. Notably, guidelines reported a common threshold to assess glioma recurrence on FET imaging defining a TBRmean of 2.0 and a TTP < 45 min [12]. Using these cutoff values, Galldiks and colleagues yielded the best result for identifying tumor recurrence or progression, with a sensitivity of 93%, a specificity of 100%, and an accuracy of 93% [6]. Nevertheless, PET parameters and the relative threshold are not standardized in all studies and different diagnostic performances were reached using different values. For example, in a cohort of 26 patients with GBM, a cutoff value of 1.9 for TBRmax allowed differentiating between true progression and late PSP. Moreover, in the same study, the dynamic acquisition also identified different curve patterns for differential diagnosis. A FET uptake peaking at a midway point (>20–40 min) followed by a plateau or a small descent was described as pattern II; conversely, the uptake peaking early, at 20 min, followed by a constant descent was named pattern III. Curve patterns type II and III resulted in being predictive for true progression and TRC, respectively [11]. However, it is important to underline that, in clinical routine, dynamic FET PET imaging has several limitations. As known, it requires longer acquisition times (50–60 min vs. 10–20 min for a static scan), which reduces patient compliance and could cause motion artifacts, with increasing costs of the investigation [6]. Recently, Bashir et al. performed a static FET PET study in a homogenous population of 146 suspected recurrent GBM patients 20 min after administration, demonstrating that FET parameters were significantly higher in patients with recurrence compared with patients with TRC (TBRmax, 3.2 vs. 1.6; TBRmean, 2.0 vs. 1.6; biological tumor volume—BTV,14.8 cm^3 vs. 0.01 cm^3; $p < 0.0001$). Using a threshold of 2.0 for TBRmax, PET-based classifications of recurrent GBM or TRC were confirmed in 98.8% of patients [10]. In contrast to the reported higher performance of early FET imaging (10–20 min) for the primary diagnosis of glioma, in this setting of recurrent disease, static PET imaging acquired from 30 to 40 min demonstrated a sensitivity and specificity of 80.0% and 84.6%, respectively, at an optimal cutoff of TBR 2.07, providing slightly better discrimination than early

images [7]. Disease progression assessment could also be challenging in recurrent GBM treated with bevacizumab, which is an antiangiogenic agent. Two clinical studies of patients with recurrent HGG undergoing bevacizumab therapy showed an advantage of FET PET over MRI in the early detection of tumor progression. Response to therapy as detected with PET (defined as >45% decrease in tumor volume) was also associated with longer overall and progression-free survival (OS and PFS) [13][14][15]. Although the potential role of FET PET in differentiating TRC from recurrence is well established, the methodology has yet to be standardized to define imaging protocols, as well as both the tumor and the normal brain reference regions, since the differentiation of a viable tumor from TRC is predominantly established by TBR [12]. In a 2019 study, the diagnostic performance of several analytic approaches in the setting of PSP in GBM was evaluated. All TBRs' measures were significantly higher in patients with true tumor progression as compared with late PSP, regardless of the semiquantitative approach applied. Although these results are encouraging and the significance is promising, the need for a consistent method of background activity assessment is requested. A crescent-shaped background volume of interest (VOI), as a reproducible approach for methodological standardization, and an isocontour approach (including multiple voxels with the highest radiopharmaceutical uptake) were proposed to reduce noise, increase reproducibility, and avoid potential pitfalls of reference region definition (e.g., the inclusion of structural changes due to atrophy, trauma, or ischemia) [16][17].

2. Comparison of FET PET with MRI

When FET PET is compared to MRI, the results are not uniform, but the added value of combined data was greatly demonstrated. PWI was often performed to improve the diagnostic accuracy, and the role of dynamic susceptibility contrast (DSC) PWI was demonstrated in HGG [18]. Furthermore, since the neoplastic hypervascularization in glioma might result in a relative increase in the cerebral blood volume (rCBV) compared to normal-appearing brain tissue, several studies analyzed FET PET parameters with PWI-derived parameters. Namely, a recent study addressed the diagnostic value of sequential DSC PWI and dynamic FET PET to differentiate tumor progression from TRC. The results showed rather low sensitivity of the rCBVmax (0.53), compared to the substantially higher FET PET sensitivity of combined static and dynamic (0.96) values. However, the high cutoff of rCBVmax achieved a high specificity, suggesting the additional diagnostic value of a sequential combination of both examinations [19]. Similar results were described by Göttler et al., indicating that the maximum FET uptake might depend more on high blood volumes than on the washout slope [20]. Other study groups reported the increased value of functional imaging over PWI MRI. Verger et al. observed that FET TBRmax was the only parameter that showed a significant diagnostic power to discriminate between TRC and progressive/recurrent glioma, while none of the PWI parameters reached significance. Even though, based on visual analysis, FET PET showed an increased uptake in 76% of recurrent glioma, PWI MRI showed signal abnormalities in only 52%. Surprisingly, in the subgroup of IDH-mutant tumors, PWI appeared to be more reliable than FET PET [21]. This data could be supported by recent evidence describing a significantly higher diagnostics accuracy of FET PET in IDH-wildtype glioma than in IDH-mutant ones. However, further studies are needed to validate these findings [9]. Another matter of discussion remains the poor spatial agreement between the two techniques, with a described considerable distance of hot spots between FET uptake and PWI within the area of tumor recurrence [22]. Moreover, the application of quantitative DWI-derived parameters is inconsistent in this scenario. Some studies reported that TRC show higher apparent diffusion coefficient (ADC) values than recurrent glioma, but some evidence demonstrated opposite results. In an analysis on a hybrid PET/MRI scanner conducted by Lohmeier et al., glioma relapse presented higher ADCmean and TBRmax values than TRC, and both ADCmean and TBRmax achieved reliable diagnostic performance in differentiating glioma recurrence from TRC as also reported by Pika et al. [7][23]. FET PET, PWI, and DWI data were combined by Sogani et al.: the researchers reported significant moderate correlations between TBRmax and rCBVmean, and TBRmean and rCBVmean, suggesting the presence of coupled vascularity and tumor amino acid uptake with mitotic activity and endothelial proliferation. At the same time, negative correlations between TBRmax and ADCmean, and TBRmean and ADCmean were described, suggesting increased FET uptake in areas of high mitotic potential and, consequently, increased cellular density, yielding lower ADC values [24]. Furthermore, PET parameters in combination with MRS data reached a high accuracy: when both the TBRmax was greater than 2.11 (or TBRmean greater than 1.4) and the Cho/Cr ratio was greater than 1.4, an accuracy of 96.9% in diagnosing recurrent glioma was reported [25]. In **Table 1**, researchers describe the main characteristics of the studies regarding FET PET applications in glioma recurrence/differential diagnosis.

Table 1. Summary of the described studies regarding [^{18}F]FET PET in glioma recurrence/differential diagnosis.

Authors [Ref.]	Year	Number of Patients	Glioma Grade (n)	PET Parameter	MRI/Other Imaging Modality Parameter	Main Findings
Galldiks et al. [6]	2015	124	55 grade II 19 grade III 50 grade IV	TBRmax TBRmean TTP	CeMRI	Compared with the diagnostic accuracy of conventional MRI (85%) to diagnose tumor progression or recurrence, a higher accuracy (93%) was achieved by [^{18}F]FET PET when a TBRmean ≥ 2.0 or TTP < 45 min was present (sensitivity, 93%; specificity, 100%; accuracy, 93%; positive predictive value, 100%; p < 0.001).
Pyka et al. [7]	2018	47	3 grade II 16 grade III 27 grade IV	TBR TTP	rCBV ADC	Sensitivities and specificities for static PET were 80 and 85%, 66% and 77% for PWI, 62 and 77% for DWI, and 64 and 79% for PET TTP, respectively. Multiparametric analysis resulted in an AUC of 0.89, notably yielding a sensitivity of 76% vs. 56% for PET alone at 100% specificity.
Popperl et al. [8]	2006	45	26 grade II 7 grade III 12 grade IV	SUVmax TBRmax TTP	ND	TAC slightly and steadily increased in tumor-free patients and in LGG, whereas HGG showed an early peak around 10–15 min after injection followed by a decrease.
Maurer et al. [9]	2020	127	21 grade II 36 grade III 68 grade IV 2 ND	TBRmax TBRmean TTP slope	ND	The highest accuracy for differentiating progression from TRCs was achieved by a combination of TBRmax and slope (sensitivity, 86%; specificity, 67%; accuracy, 81%). The accuracy of [^{18}F]FET PET was higher in IDH-wildtype gliomas than in IDH-mutant ones (p < 0.001)
Bashir et al. [10]	2019	146	146 grade IV	TBRmax TBRmean BTV	ND	TBRmax is a powerful imaging biomarker to detect recurrent GBM (sensitivity 99%, specificity 94%; p < 0.0001). BTV is independently and inversely correlated with OS.
Pöpperl et al. [11]	2004	53	27 grade IV 16 grade III 9 grade II 1 grade I	SUVmax TBRmax	ND	Best differentiation between benign posttherapeutic effects and tumor recurrence was observed at a threshold value of 2.0 for the TBR, with a discriminatory power of 100%. For the absolute values of SUVmax, the best differentiation was seen at a threshold value of 2.2.
Kebir et al. [13]	2016	26	26 grade IV	TBRmax TBRmean TTP	ND	TBRmax and TBRmeanwere significantly higher in patients with true progression than in patients with late PSP, whereas TTP was significantly shorter. ROC analysis yielded an optimal cutoff value of 1.9 for TBRmax to differentiate between true progression and late PSP (sensitivity 84%, specificity 86%, accuracy 85%, p < 0.015).
Galldiks et al. [14]	2012	10	1 grade III 9 grade IV	TBRmax TBRmean TTP	ND	A reduction in TBRmean of ≥17% at follow-up differentiated responders (PFS ≥ 6 months) from non-responders (PFS < 6 months) with excellent sensitivity (83%) and specificity (100%). Moreover, TTP and kinetic patterns at baseline and follow-up differentiated responders from non-responders with a favourable diagnostic performance.
George et al. [15]	2018	13	13 grade IV	Dynamic acquisition	CeMRI	An only moderate correlation between FET PET uptake and CeMRI. FET PET may have a prognostic role in the follow-up of patients with recurrent GBM undergoing antiangiogenic therapy.

Authors [Ref.]	Year	Number of Patients	Glioma Grade (n)	PET Parameter	MRI/Other Imaging Modality Parameter	Main Findings
Hutterer et al. [16]	2011	11	11 grade IV	SUVmax TBRmax	ND	In HGG patients undergoing antiangiogenic treatment, [^{18}F]FET PET seems to be predictive for treatment failure.
Kertels et al. [17]	2019	36	36 grade IV	TBR *	ND	[^{18}F]FET PET is a reliable tool for the detection of late PSP in GBM, irrespective of the analytical approach.
Steidl et al. [20]	2020	104	9 grade II 24 grade III 70 grade IV 1 other	TBRmax slope	rCBVmax	The sensitivity of the rCBVmax was low (0.53), while the sensitivity of the combined TBRmaxand slope values was substantially higher (0.96). In the subgroup of IDH-mutant tumors, PWI appeared to be more reliable than [^{18}F]FET PET.
Verger et al. [21]	2018	31	2 grade II 3 grade III 27 grade IV	TBRmax TBRmean TTP slope	rCBF rCBV	TBRmaxwas the only parameter that showed a significant diagnostic power to discriminate between TRC and progressive/recurrent gliomas. The best cutoff value for TBRmaxwas 2.61, with a sensitivity of 80%, a specificity of 86%, a PPV of 95%, an NPV of 55%, and an accuracy of 81%. [^{18}F]FET PET is superior to PWI for diagnosing progressive or recurrent gliomas.
GoÖttler et al. [22]	2016	30	3 grade II 4 grade III 23 grade IV	TBRmean TTP slope	rCBV	Static and dynamic FET uptake measures and rCBV are interdependent and exhibit only a poor spatial overlap: the mean distance between the tumor hotspots of FET uptake and rCBV was 20.0 +/− 14.1 mm.
Lohmeier et al. [23]	2019	42	40 HGG 2 LGG	SUVmax SUVmean TBRmax TBRmean	rADCmean	The ADCmean in the metabolically most active regions was higher in patients with recurrent glioma than in patients with TRC. The highest accuracy (90%) was achieved when both DWI and [^{18}F]FET PET-derived parameters were combined in a biparametric approach.
Sogani et al. [24]	2017	32	N.S.	TBRmax TBRmean	N rCBV ADCmean Cho/Cr	The diagnostic accuracy, sensitivity, and specificity for recurrence detection using all three MRI parameters were 93.75%, 96%, and 85.7%, respectively. The addition of FET PET TBR values improved these values further to 96.87%, 100%, and 85.7%, respectively.
Jena et al. [25]	2016	26	N.S.	TBRmax TBRmean	N rCBV ADCmean Cho/Cr	The diagnostic accuracy of [^{18}F]FET PET/MRI TBR values for the correct identification of recurrence of brain gliomas reached 93.8% using TBRmax of 2.11 or greater and 87.5% using TBRmean of 1.437 or greater. The highest accuracy (96.9%) was obtained when both the TBRmax was greater than 2.11 (or TBRmean > 1.44) and the Cho/Cr ratio > 1.42.

Legend: PET, positron emission tomography; MRI, magnetic resonance imaging; SUV, standardized uptake value; TBR, tumor-to-background ratio; TTP, time to peak; TAC, time–activity curves; Ce, contrast enhancement; LGG, low-grade glioma; HHG, high-grade glioma; FET, fluoroethyl-tyrosine; PSP, pseudoprogression; N rCBV, normalized relative mean cerebral blood volume; Cho/Cr, choline-to-creatine; rADC, relative apparent diffusion coefficient; CBF, relative cerebral blood flow; TRC, treatment-related changes; PPV, positive predictive value; NPV, negative predictive value; DWI, diffusion weighted MRI; PWI, perfusion-weighted MRI; GBM, glioblastoma multiforme; BTV, biological tumor volume; OS, overall survival; ND, not determined or inconclusive. * different analytical approach (e.g., reference regions) were explored.

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