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ABSTRACT

BACKGROUND AND PURPOSE: Inter- and intratumor heterogeneity and the variable course of disease in patients with glioma motivate the investigation of new prognostic factors to optimize individual treatment. Here we explore the usefulness of standard static and more sophisticated dynamic ^{18}F-fluoroethyltyrosine-PET imaging for the assessment of patient prognosis.

MATERIALS AND METHODS: Thirty-four consecutive patients with untreated, first-diagnosed, histologically proved glioma were included in this retrospective study. All patients underwent dynamic PET scans before surgery (± standard treatment) and were followed up clinically and by MR imaging. Static and dynamic tumor-to-background ratio, TTP, and slope-to-peak were obtained and correlated with progression-free survival.

RESULTS: Twenty of 34 patients experienced progression, with a median progression-free survival of 28.0 ± 11.1 months. Dynamic TTP was highly prognostic for recurrent disease, showing a strong correlation with progression-free survival (hazard ratio, 6.050; 95% CI, 2.11–17.37; $P < .001$). Most interesting, this correlation also proved significant in the subgroup of low-grade glioma (hazard ratio, 5.347; 95% CI, 1.05–27.20; $P = .044$), but not when using established static imaging parameters, such as maximum tumor-to-background ratio and mean tumor-to-background ratio. In the high-grade glioma subgroup, both dynamic and static parameters correlated with progression-free survival. The best results were achieved by defining ROIs around "hot spots" in earlier timeframes, underlining the concept of intratumor heterogeneity.

CONCLUSIONS: ^{18}F-fluoroethyltyrosine-PET can predict recurrence in patients with glioma, with dynamic analysis showing advantages over static imaging, especially in the low-grade subgroup.

ABBREVIATIONS: FET = ^{18}F-fluoroethyltyrosine; LGG = low-grade glioma; HGG = high-grade glioma; HR = hazard ratio; PFS = progression-free survival; ROC = receiver operating characteristic analysis; TBR = tumor-to-background ratio

Glial cell tumors account for approximately 80% of all malignant primary brain tumors. In practice, their biologic behavior differs widely from nearly stationary to rapidly and invasively growing lesions. Naturally, the biologic aggressiveness of the tumor is of particular clinical interest, especially with respect to treatment planning; options range from wait and watch to extensive surgery, radiation, and/or chemotherapy. Optimal treatment for the individual patient depends on a variety of factors and is still a matter of discussion.[1-3] Tumor grading based on histologic properties like cellular proliferation and the presence of necrosis, as described by the World Health Organization classification of brain tumors,[4] is an extensively studied prognostic factor and has, therefore, a major impact on therapeutic decisions. However, in many cases, it is preferable to gain prognostic information before potential surgery. For this purpose, stereotactic biopsies may be performed; nevertheless, these are still invasive procedures and may have sampling errors.

Therefore additional prognostic factors that can be obtained noninvasively have been described or are being investigated.[5,6] Particularly, numerous attempts have been made to use imaging techniques for prognostic stratification. Contrast enhancement in CT and MR imaging indicates disruption of the BBB, which is suggestive of aggressive biologic behavior. Contrast enhancement has been shown to correlate with histologic grading and has also been linked to patient outcome, especially in high-grade gliomas

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(HGGs).[7] However, the method has several drawbacks; low-grade gliomas (LGGs) show contrast enhancement in only about 50% of cases; on the other hand, about one-third of nonenhancing gliomas are still classified as high-grade tumors.[8,9] Newer MR imaging–based techniques, such as perfusion imaging and MR spectroscopy, may contribute to better tumor characterization in the future but are still under clinical evaluation and have their limitations.[10,11]

Prediction of prognosis by assessing tumor glucose metabolism by using ^{18}F-fluoroethyltyrosine (FET)-PET has been proposed, but similar to contrast enhancement, this method is suitable primarily for high-grade tumors because FDG uptake in LGG is, in general, much lower and physiologic background uptake in the brain is considerable.[12] Amino acid PET tracers, on the contrary, are attractive for glioma imaging due to intratumoral upregulation of amino acid transport and low background activity.[13] FET generates a reliable strong signal in high-grade brain tumors and still has an uptake well above background in most low-grade tumors (Fig 1).[14] Another important advantage over FDG is the improved discrimination between malignant and benign lesions because no specific uptake of FET in inflammatory lesions is expected.[15] FET is already used in treatment planning and therapy monitoring,[16,17] and there have been suggestions that it might contribute to assessing patient prognosis.[18] A recent study showed the ability of FET-PET to identify malignant progression in LGG by both static and dynamic analysis of FET uptake.[19] With respect to prediction of tumor grade, dynamic evaluation of FET uptake is superior to static analysis.[20,21] This finding also supports the use of dynamic imaging for prognostication. The aim of this study was to establish the value of FET-PET imaging for predicting tumor progression and progression-free survival (PFS) and therefore to justify its use for optimal patient management.

MATERIALS AND METHODS

Patients

Thirty-four consecutive patients (12 women, 22 men; mean age, 41 years) were included in this study. All patients had first been diagnosed with glioma with no prior treatment and were subsequently referred to surgery, in some cases followed by an appropriate adjuvant treatment (see On-line Table 1 for individual patient data). Written informed consent was obtained before each PET scan as part of the clinical routine. Retrospective analysis of the data was approved by the ethics review board of the Technical University of Munich. Histopathologic diagnosis was established by standard light microscopic evaluation of the resected tumors stained with H&E according to the criteria of the latest World Health Organization brain tumor classification.

The primary end point of the study was tumor progression. Progression-free intervals were calculated starting from the baseline PET examination. All patients were followed up clinically. If no clinical signs of progression emerged, basic MR imaging follow-up intervals were 6 months for LGG and 3 months for HGG.[3] Progression was defined on conventional MR imaging.[22,23] In unclear cases, tumor progression was verified by stereotactic biopsy.

PET Studies

We obtained FET-PET scans before treatment with an ECAT Exact HR+ scanner (Siemens, Erlangen, Germany). To achieve standardized metabolic conditions, patients had to fast for a minimum of 6 hours before scanning. After a transmission scan with Germanium-68 sources (duration, 15 minutes), 190 MBq of FET was injected intravenously. Dynamic studies were acquired from 0 to 40 minutes after injection (128 ×128 matrix, 3D mode) and comprised 16 timeframes (7 × 10 seconds, 3 × 30 seconds, 2 minutes, 3 × 5 minutes, and 2 × 10 minutes). Data were reconstructed by filtered back-projection by using a Hann filter with a cutoff frequency of 0.34 Nyquist and corrected for scatter and attenuation.

Static Data

Maximum and mean tumor-to-background ratios (TBRmax, TBRmean) were calculated by using a 20- to 40-minute summed frame with a circular 1-cm region of interest around the spot of highest tracer uptake and a contralateral background region of interest according to standard criteria.[24]

Dynamic Data

Dynamic data analysis was performed by using a multimodal-multiparametric analytic imaging software (M3P Anima) developed in our institution.[25] Dynamic tumor activity was measured in a 90% isocontour region of interest around the hottest voxel as described previously.[20,21] Before this step, whether FET uptake in the tumor was high enough to allow adequate region-of-interest definition had to be determined. This decision depended, for example, on tumor localization and background homogeneity, but generally, a static TBR of 1.2–1.3 represented the lower threshold for accurate PET-based region-of-interest delineation. Cases that showed no clear tumor uptake above background were excluded from the dynamic analysis. Because a consensus for an optimal region-of-interest definition in dynamic FET uptake analysis does not yet exist, we investigated ROIs on the basis of different timeframes. For comparison, the reference region of interest was defined in averaged frames 11–13 (very early), 12–14 (early), 14–16 (late), and 11–16 (average) and was subsequently transferred to the whole time-series. As with static analysis, the data were normalized against background uptake, which was derived from a cortical region of interest in the opposite non-tumor-bearing hemisphere. In accordance with earlier publications,[20] background data were determined on a summed image (20–40 minutes after injection) to avoid biasing the rather subtle differences in tumor FET kinetics. On the basis of the normalized time-activity curves, we extracted the following dynamic parameters: peak TBR, defined as the highest TBR with time; TTP; and slope-to-peak, defined as the slope of region-of-interest activity from frame 10 to the peak frame (Fig 2).

Statistical Analysis

The above-mentioned parameters were tested for their ability to predict progression by using receiver operating characteristic analysis (ROC). Decision thresholds were considered optimal when the sum of paired values for sensitivity and specificity reached the maximum. In addition, for each method, the total area under the curve was calculated. Kaplan-Meier curves for PFS were estimated, and the distributions of PFS times were compared between groups by using the log-rank test. For relevant measures, hazard ratios (HRs) with 95% CI were estimated by using the Mantel-Haneszel approach. The patients were further divided

into LGG and HGG subgroups, for which the same tests used for the whole group were executed. The Statistical Package for the Social Sciences, Version 22 (IBM, Armonk, New York) and Prism 5 (GraphPad Software, San Diego, California) were used for statistical analysis. Univariate testing was used because the number of events did not allow a multivariate analysis. A 2-sided level of significance of 5% was used for all tests.

RESULTS

Thirteen of 21 patients (61.9%) with LGG and 11 of 13 patients (84.6%) with HGG showed sufficient FET uptake in the tumor to allow accurate region-of-interest definitions as described above. These relations represent the higher sensitivity of FET imaging for high-grade brain tumors. Twenty of 34 patients experienced progression, with a median progression-free interval of 28.0 ± 11.1 months. No deaths occurred before progression was determined; for this reason, progression-free interval and PFS are used synonymously. Kaplan-Meier analysis and log-rank tests revealed no significant differences in PFS between FET-enhancing and nonenhancing tumors with a hazard ratio of 1.44 (95% CI, 0.56–3.72). This finding also held true when dividing the collective into LGG and HGG subgroups. The respective hazard ratios were 1.275 (95% CI, 0.334–4.870) and 0.8223 (95% CI, 0.153–4.417). All FET-positive HGGs showed a static TBR above the published thresholds for high-grade tumors (TBRmax > 2.0, TBRmean > 1.6), and 7 of 21 low-grade tumors (33.3%) had this property.

As described above, dynamic data were evaluated in FET-enhancing tumors only. For this purpose, tumor ROIs based on different timeframes were investigated. Table 1 shows the area under the curve for ROC analyses of peak TBR, TTP, and slope-to-peak calculated in the respective

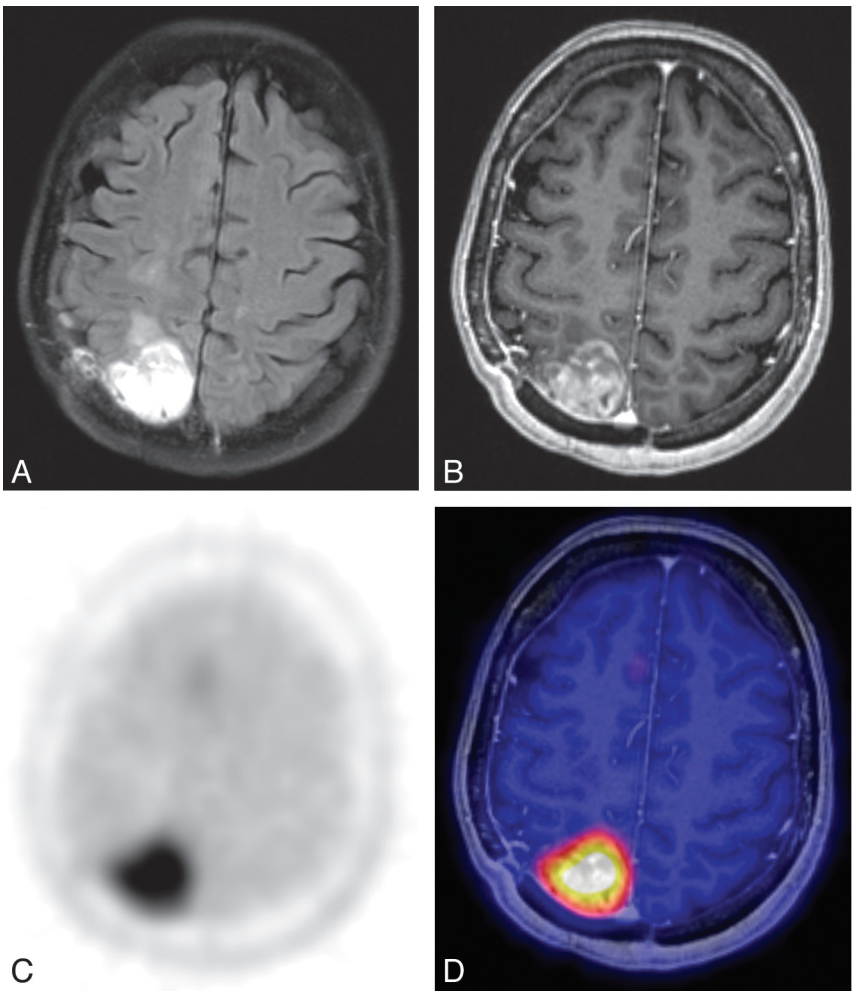

FIG 1. Example of combined FET-PET/MR imaging of a patient with HGG. *A*, T2-weighted FLAIR. *B*, T1-weighted image with Gd-DTPA. *C*, Static FET-PET. *D*, Fused image (*B* and *C*).

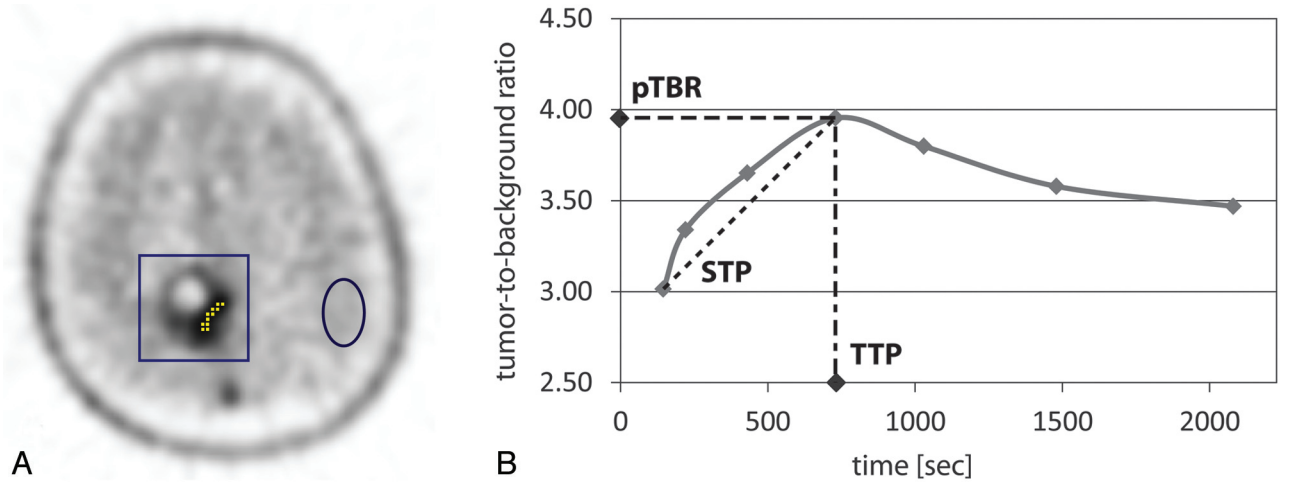

FIG 2. Dynamic FET-PET analysis in a patient with HGG. *A*, Region-of-interest definition with 90% isocontour tumor region of interest (*dots*) and background region of interest (*circle*). *B*, Corresponding time-activity curve with definitions of peak TBR, TTP, and slope-to-peak (STP).

tumor ROIs. These results suggested a region of interest based on early timeframes (frames 12–14 or 5–20 minutes) as the most suitable, and the subsequent analyses were performed by using this definition.

All examined parameters proved valuable for the prediction of PFS in the whole patient collective (Tables 2 and 3 and Fig 3). The property of early FET uptake kinetics as defined by a TTP < 20 minutes (ie, equal or less than frame 14 of 16) demonstrated the best statistical results in Kaplan-Meier/log-rank analysis (HR, 6.05; 95% CI, 2.11–17.37; $P < .001$; Fig 4). Peak TBR and slope-to-peak with thresholds determined by ROC analysis still showed significant results, but lower hazard ratios (HR, 3.39; $P = .023$ and HR, 4.73; $P = .008$). For comparison, static TBR was determined as described above, with results fairly similar to dynamic peak TBR and slope-to-peak (HR, 4.20; $P = .010$). No relevant differences were found between static TBRmean and TBRmax besides the generally higher values of the latter.

In the subgroup of patients with FET-positive LGG, 6 of 13 patients presented with tumor progression. TTP was by far the best parameter predicting PFS, with an HR of 5.347 (95% CI, 1.05–27.20; $P = .044$) in survival analysis. The remaining dynamic parameters, as well as static TBRmean and TBRmax, exhibited lower HRs, which were not statistically significant.

Among high-grade patients, our findings were also suggestive of a relation between progression and the examined uptake parameters. Eleven of 13 patients had progressive disease during the follow-up period. Significant results were obtained for both static and dynamic parameters in the Kaplan-Meier analysis. Peak TBR, TBRmean, and TBRmax exhibited slightly better statistical properties than TTP and slope-to-peak ($P = .022$, .007, and .007 versus $P = .038$ and .040).

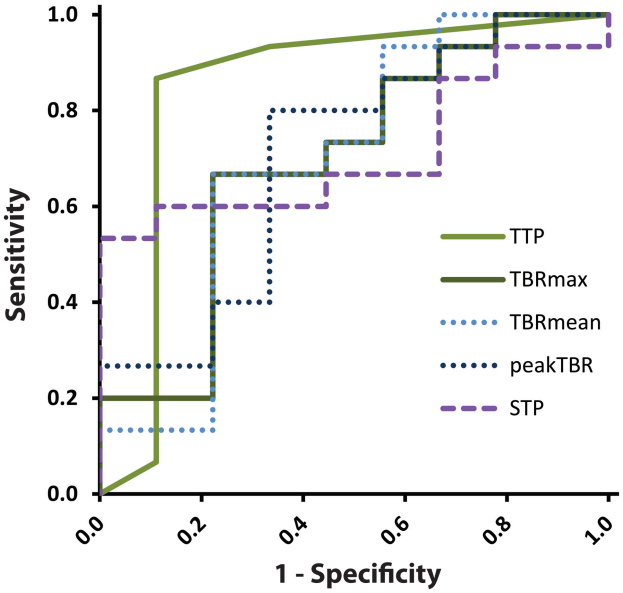

FIG 3. ROC curves for prediction of progression by using TBRmax, TBRmean, peak TBR (pTBR), slope-to-peak (STP), and time-to-peak (TTP).

Table 1: Comparison of different ROI definitions for dynamic FET analysis

ROI Definition (Frames)	TTP[a]	Peak TBR[a]	Slope-to-Peak[a]
11–13 (Very early)	0.844 (.654–.100)	0.719 (.492–.945)	0.659 (.438–.881)
12–14 (Early)	0.848 (.642–1.00)	0.704 (.477–.930)	0.711 (.503–.919)
14–16 (Late)	0.719 (.494–.943)	0.711 (.482–.940)	0.563 (.333–.793)
11–16 (Average)	0.785 (.569–.100)	0.704 (.476–.931)	0.630 (.406–.854)

[a] Shown are area under the curve values for ROC regarding tumor progression.

Table 2: Evaluation of static and dynamic parameters regarding tumor progression

	ROC (AUC)	ROC Threshold
Dynamic		
Time-to-peak	0.848 (.642–1.00)	<20 Minutes
Peak TBR	0.704 (.477–.930)	>2.20
Slope-to-peak	0.711 (.503–.919)	$>7 \times 10^{-5}$/s
Static		
TBRmax	0.696 (.467–.925)	>2.50
TBRmean	0.696 (.456–.937)	>2.30

Note:—AUC indicates area under the curve.

Table 3: Kaplan-Meier analysis/log-rank test

	All	LGG	HGG
Dynamic			
TTP	$P < .001$ HR, 6.05 (2.11–17.37)	$P = .043$ HR, 5.35 (1.05–27.20)	$P = .038$ HR, 4.45 (1.09–18.20)
Peak TBR	$P = .023$ HR, 3.39 (1.19–9.68)	$P = .873$ HR, 0.87 (0.15–5.08)	$P = .022$ HR, 5.84 (1.29–26.4)
Slope-to-peak	$P = .008$ HR, 4.73 (1.50–14.87)	$P = .301$ HR, 2.54 (0.43–14.84)	$P = .040$ HR, 4.86 (1.06–21.92)
Static			
TBRmax	$P = .004$ HR, 4.20 (1.40–12.58)	$P = .847$ HR, 0.84 (0.14–4.95)	$P = .007$ HR, 8.19 (1.78–37.67)
TBRmean	$P = .010$ HR, 4.20 (1.40–12.58)	$P = .847$ HR, 0.84 (0.14–4.95)	$P = .007$ HR, 8.19 (1.78–37.67)

DISCUSSION

In this study, we wanted to clarify the possible role of dynamic FET-PET imaging in assessing the prognosis of patients with first-diagnosed glial cell tumors. The data presented show a correlation of several kinetic parameters and static TBR with PFS. The dynamic parameter TTP proved superior to static TBR, peak TBR, and slope-to-peak and yielded convincing statistic results in the overall patient collective (Tables 2 and 3 and Figs 3 and 4).

TTP also allowed prediction of PFS in the subgroup of low-grade tumors, whereas neither static TBR nor the other dynamic parameters showed a significant correlation with PFS in these patients. An earlier study also proposed a predictive value for static FET uptake in LGG; however, it had an unusually large proportion of patients without initial treatment, with only 3 patients undergoing complete tumor resection.[18] In HGG, on the contrary, we could demonstrate a correlation of PFS with dynamic and static parameters, with static TBR showing slightly better statistical properties in survival curve analysis. These details must be interpreted with care due to the lower number of patients and, in particular, long-time survivors in this subgroup. Similar positive results for static and dynamic FET imaging have been reported by a previous small-sized study focusing on glioblastoma.[26]

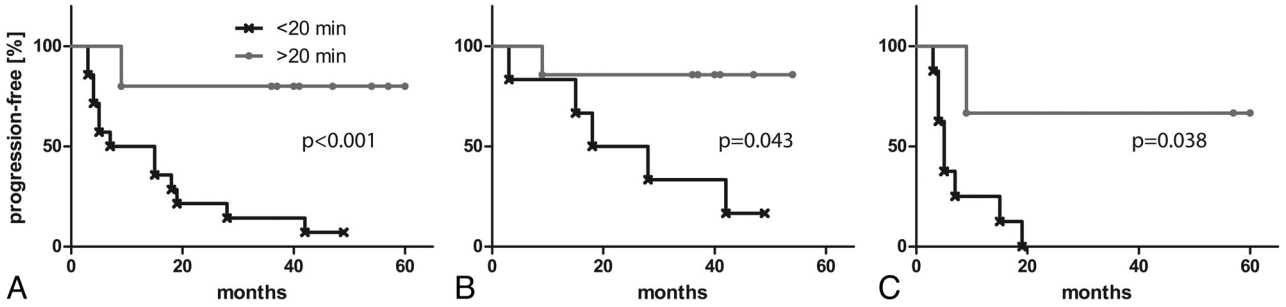

FIG 4. PFS of patients with early and late FET uptake kinetics according to TTP. *A*, All patients. *B*, Patients with LGG. *C*, Patients with HGG.

Our results indicate the presence of certain biologic characteristics in the early-enhancing tumors that go beyond those identified by the H&E staining based on the WHO grading system and that are linked to an unfavorable outcome. The nature of these characteristics has yet to be investigated but may be illuminated by studies that correlate areas identified by time-activity-curve-based analysis or, more demanding, kinetic modeling with new histopathologic markers.[27,28] Until now, whether increased expression of amino acid transporters in tumor cells contributes to rapid FET tracer uptake remains speculative. Another suggestion is an increased vascularity in highly malignant lesions, which would, at least in part, explain both the previously reported steep increase in activity in the beginning and the marked washout in the later timeframes.[20,21]

To obtain the above parameters, we investigated several tumor region-of-interest definitions on different summation timeframes. Time-activity curves deduced from ROIs defined on the earlier timeframes (ie, 5–20 minutes after injection) seem to characterize best the biologic behavior of the tumor, while ROIs defined on the later timeframes perform less well (Table 1). These results are in accordance with earlier publications on tumor grading, which also favored a region-of-interest definition on earlier timeframes.[20] It has already been shown that glial cell tumors exhibit a certain degree of inhomogeneity on the molecular level.[29] Assuming this intratumor variability, the importance of region-of-interest selection can be easily explained because ROIs based on the early timeframes can extract the "hot spots" of biologic aggressiveness, which are expected to show an earlier peak of FET uptake. In the future, a more thorough investigation of this relation should be performed by implementation of a voxelwise analysis of tracer kinetics.

The retrospective design is certainly a limitation of our study. As an additional limitation, the number of events and patients did not allow a multivariate analysis. Prospective studies and larger patient numbers will be necessary before the new predictive parameters presented can be introduced into routine clinical practice.

CONCLUSIONS

In this small, retrospective pilot study, dynamic FET imaging could predict prognosis in glioma and proved superior to static analysis for this purpose, especially in LGG, while both dynamic and static analyses appear useful in HGG. These results underline a previously suggested connection between FET uptake kinetics and tumor biology whose nature still needs to be disentangled.

Disclosures: Florian Ringel—*UNRELATED*: *Consultancy*: BrainLab, *Grants/Grants Pending*: Medtronic, Deutsche Forschungsgemeinsch aft, Deutsche Krebshilfe, B. Braun-Stiftung, *Payment for Lectures (including service on Speakers Bureaus)*: Integra, Medtronic, Ulrich, BrainLab, DePuy Synthes, Update. Hans-Jürgen Wester—*UNRELATED*: *Stock/Stock Options*: SCINTOMICS. Markus Schwaiger—*UNRELATED*: *Consultancy*: Navidea, *Grants/Grants Pending*: Siemens PET, *Payment for Lectures (including service on Speakers Bureaus)*: Siemens, *Stock/Stock Options*: SurcigEye. Stefan Förster—*UNRELATED*: *Consultancy*: Merck KGaA, *Grants/Grants Pending*: Deutsche Forschungsgemeinschaft grant F0886/1-1,* *Payment for Lectures (including service on Speakers Bureaus)*: GE Healthcare. *Money paid to the institution.

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