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Original

FLT-PET in previously untreated patients with low-grade glioma can predict their overall survival

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Abstract

BACKGROUND: Low-grade gliomas (LGG) of the brain have an uncertain prognosis, as many of them show continuous growth or upgrade over the course of time. We retrospectively investigated the role of positron emission tomography with 3'-deoxy-3'--[18F]fluorothymidine (FLT-PET) in the prediction of overall survival and event free survival in patients with untreated LGG. No such information is yet available in the literature.

MATERIAL AND METHODS: Forty-one patients with previously untreated LGG underwent 55 FLT-PET investigations during their follow-up because of subjective complaints, objective worsening of clinical conditions, equivocal findings or progression on magnetic resonance imaging. The time interval before referral for neurosurgical or radiation treatment was considered to be event free survival, the interval until death as overall survival, respectively. Standardized uptake values (SUV) were measured, and a 3-point scale of subjective assessment was also applied. ROC analysis was used to define cut-off values. The log rank test was used for comparison of Kaplan-Meier survival curves.

RESULTS: Eight patients (a total of 9 FLT-PET studies performed) died during follow-up. Progression leading to referral to therapy was recorded in 24 patients (a total of 33 FLT-PET studies). With a cut-off value of SUV_{mean} = 0.236, a median overall survival of 1.007 days was observed in the test positive subgroup while median overall survival for the test negative subgroup was not achieved (p = 0.0002), hazard ratio = 17.6. Subjective assessment resulted in hazard ratio 11.5 (p = 0.0001). Only marginal significance (p=0.0562) was achieved in prediction of event free survival.

CONCLUSIONS: Increased FLT uptake in previously untreated patients with LGG is a strong predictor of overall survival. On the other hand, prediction of event free survival was not successful in our cohort, probably because of high prevalence of patients who needed treatment due to symptoms caused by a space-occupying lesion without respect to the proliferative activity of the tumour.

KEY words: positron emission tomography, 18F-FLT, prognosis, glioma, low-grade glioma

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Background

Gliomas comprise a heterogeneous group of neuroectodermal tumours that arise from the glia, the supporting cells of the central nervous system. Low-grade gliomas refer to tumours in either the grade 1 or grade 2 categories, depending on their histological characteristics. Brain low-grade gliomas include a diverse group of tumours with distinct characteristics, patterns of occurrence, response to treatment, and survival. Patients with low-grade gliomas tend to be otherwise healthy individuals of productive age, and management decisions, such as the timing of the intervention, extent of surgical resection, timing of radiotherapy, and the long-term benefits and risks of chemotherapy, have been controversial [1].

A strong positive correlation between uptake of radiolabeled 3'-deoxy-3'-[^{18}F]fluorothymidine (FLT) and levels of thymidine kinase-1 (TK1) was reported in vitro. Furthermore, it was demonstrated that converting cells from growth arrest to a high growth rate consistently leads to elevated TK1 levels, accompanied by

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increased FLT uptake. Taken together, these data validate FLT as a useful imaging agent for cell proliferation [2].

Positron emission tomography (PET) is a non-invasive imaging modality suitable for imaging FLT tissue distribution in vivo. Several clinically-oriented small-size studies concerning FLT-PET in human brain gliomas have been published to date. A significant correlation of FLT uptake with tumour grade and Ki-67 immunohistochemistry has been found in patients with newly diagnosed and recurrent gliomas [3–5]. The quantitative parameters of FLT uptake correlate with regional variations in cellular proliferation [6] and can help to differentiate between recurrent glioma and radiation necrosis [7, 8]. FLT-PET was used for survival predictions in patients with recurrent malignant glioma early after the start of therapy [9–11]. Overall survival in high-grade glioma was successfully predicted by FLT-PET-derived proliferative tumour volume [12].

No study dealing with prediction of overall survival or event free survival in untreated patients with low-grade gliomas has been found in the literature up to this point. Our work has concentrated on this topic with the aim of providing information that can potentially be used in decision-making for these patients.

Materials and methods

Patients and study design

Between August 2009 and September 2012 a total of 384 FLT-PET brain investigations were routinely performed in 273 patients at a single PET centre. All investigations were based on a clinical indication and were conducted in compliance with the Summary of Product Characteristics (SPC) of commercially available FLT. All patients signed their informed consent forms. Among them, patients with untreated low-grade gliomas were identified from the database for a retrospective analysis.

Inclusion criteria were the availability of feedback from the referring hospital and a diagnosis of low-grade gliomas established at any time prior to FLT-PET. The diagnosis of low-grade gliomas was based on magnetic resonance imaging findings. Typical conventional magnetic resonance imaging findings of low-grade gliomas were defined as relatively well-marginated usually homogeneous tumours that displayed little or no mass effect with minimal or no vasogenic oedema and little or no enhancement after contrast administration [13]. When a repeated magnetic resonance imaging was available, none or minimal enlargement was present over the time. Histologic evaluation was performed before FLT-PET in eight diagnostically uncertain cases and glioma grade II was confirmed.

Exclusion criteria were neurosurgical intervention in the brain except for diagnostic biopsy, results of a biopsy that excluded low-grade gliomas, radiotherapy of the brain or chemotherapy performed prior to a FLT-PET study.

Fifty-five consecutive studies in 41 patients (14 females, 27 males) were identified. The age of the patients at the time of FLT-PET was 19.5–74.5 (M = 43.1, SD = 11.1) years. The indications for FLT-PET in this cohort were subjective complaints, objective worsening of their clinical condition and equivocal magnetic resonance imaging findings. All patients were in good clinical condition; seizures and/or headache represented initial symptoms in majority of patients.

The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All procedures were in accordance with the ethical standards of institutional Ethical Committee on human experimentation.

FLT-PET acquisition and analysis

All patients were investigated early in the morning. Commercially available FLT (3´-[^{18}F]FLT, INJ, RadioMedic s.r.o., Czech Republic) was injected intravenously according to the patients' weight in amounts varying from 161 to 323 (M = 227, SD = 42) MBq.

After an uptake time of 12–24 (M = 16.0, SD = 2.4) minutes, PET data acquisition was initiated using a Biograph 40 TrueV HD (Siemens, Germany) hybrid PET/CT scanner. Prior to this, a native low-dose CT of the head was acquired for the purpose of attenuation and scatter correction of the PET scan. The CT scanning and reconstruction parameters were: 120 kV; 40 eff. mAs; slice 3 mm; pitch 1.2; rotation time 1 s; filtered back projection with H19s PET very smooth kernel, reconstruction increment 2 mm and transversal field of view 300 mm. High resolution PET scanning directly followed the CT scan. PET and CT fields of view matched each other. The PET scanning and reconstruction parameters were: 3D mode; 1 bed position; 15 min. acquisition time; zoom 2; matrix size 256 × 256; iterative reconstruction with point spread function correction TrueX: 4 iteration, 21 subsets and Gaussian filter 2 mm. Transverse slices were archived using the dcm4chee.com picture archiving and communications system.

Neither the original routine reports nor the magnetic resonance imaging images were used for the retrospective FLT-PET analysis. FLT-PET images were blindly re-evaluated using Rover software (ABX GmbH, Germany). Only an approximate tumour location (e.g. left fronto-temporal) was known a priori. In the event of any FLT uptake above normal brain background levels in the known tumour location, an ovoid mask was drawn around this area, excluding the choroid plexus and tissues outside the brain. Automatic region of interest (ROI) delineation was applied within this mask and its volume (Vol_{FLT}), maximum SUV (SUV_{max}), peak SUV (SUV_{peak}) and mean SUV (SUV_{mean}), corrected for partial volume effect, was recorded. For ROI delineation and analysis a complex algorithm of Rover (adaptive thresholding) was used. In cases where the focus of intense FLT uptake occurred outside a known tumour location, it was also incorporated into the analysis. A cubic region of interest (ROI) of 7.8–8.8 ml, representing normal brain background was drawn at a site opposite the tumour if possible, and its SUV_{max}, SUV_{peak} and SUV_{mean} values were recorded. If not possible, i.e. in case of middle-line tumours as well as in case of no tumour appearance, this cubic ROI was arbitrarily placed in the right insular area.

Statistical analysis

To evaluate the prognostic value of FLT-PET, overall survival and event free survival were evaluated as clinical end-points. The date of the first clinical decision to start any therapy (neurosurgery, radiotherapy, chemotherapy) of low-grade gliomas after FLT-PET was recorded as well as the date of the death. The end-point of follow-up was March 2013 when the status (dead or surviving) of all patients was checked in the national register of the health insurance policyholders. Such information is freely accessible to health care institutions.

Overall survival was defined as the interval from FLT-PET investigation until death or end-point of follow-up in surviving pa-

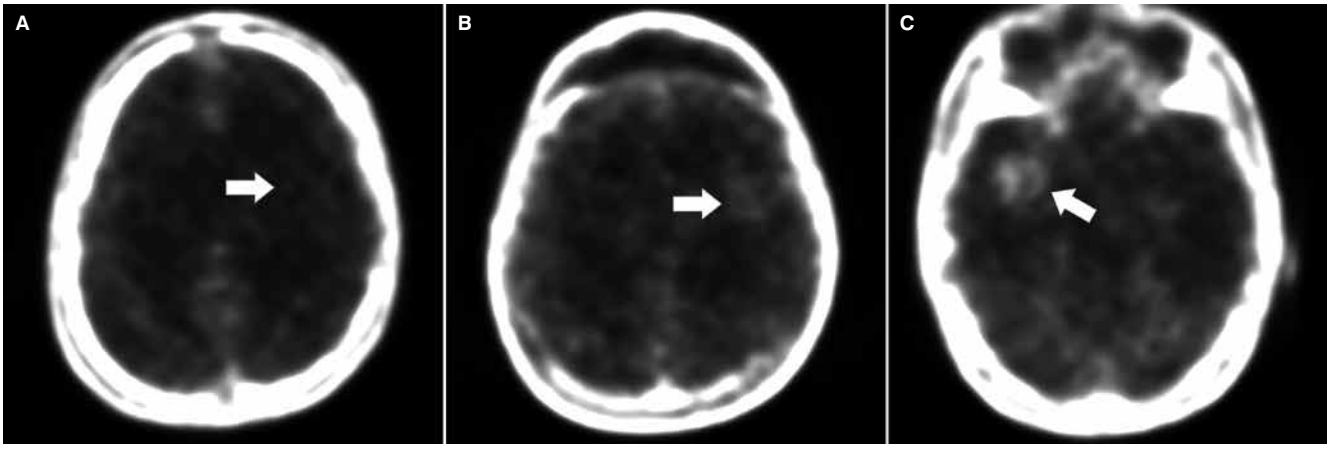

Figure 1. Various categories of subjective assessment (upper threshold was set to 10 % of the image maximum). **A.** Subj = 0, patient is event free for 794 days; **B.** Subj = 1, patient is event free for 1000 days; **C.** Subj = 2, event free survival was 44 days, patient died 1007 days after FLT-PET

tients. Event free survival was defined as the interval from FLT-PET investigation until the first clinical decision to start any therapy for low-grade gliomas or end-point of follow-up.

Measured values of SUV_{max}, SUV_{peak} and SUV_{mean} in the ROI of tumour served for the calculation of the tumour to background ratio (TBR_{max}, TBR_{peak} and TBR_{mean}), where mean background SUV served as a denominator. Total lesion uptake (TLU) was calculated as a product of tumour ROI volume (Vol_{FLT}) and SUV_{mean}. In cases where there was no tumour occurrence, tumour SUV_{max}, SUV_{peak} and SUV_{mean} values were assigned to the values measured in the background ROI; in this situation TBR_{max}, TBR_{peak} and TBR_{mean} were set to 1.0 and TLU and Vol_{FLT} were set to 0.0.

FLT-PET scans were also evaluated subjectively (Subj) using a 3-step scale. In cases where there was no tumour appearance Subj was set to 0 and it represented a negative test (Figure 1A). In findings with faint uptake just above normal brain background in a previously known tumour location Subj was set to 1 and it represented an equivocal test (Figure 1B). In all cases of abnormally elevated uptake of FLT, Subj was set to 2 and represented a positive test (Figure 1C).

The Youden index was used in the ROC analysis to determine the optimal cut-off value of SUV_{max}, SUV_{peak}, SUV_{mean}, TBR_{max}, TBR_{peak}, TBR_{mean}, Vol_{FLT} and TLU for predicting overall survival (dead vs. alive). This cut-off value served to establish the FLT-PET categorization as positive or negative. Survival curves based on FLT-PET categorization were obtained using the Kaplan-Meier approach and were compared using the log-rank test. Hazard ratio was expressed as well.

Probability values of $p < 0.05$ were considered as significant. When applicable, median (M), standard deviation (SD) and the 95% confidence interval (CI_{95}) were calculated.

Results

During the course of the study, nine FLT-PET studies were performed on eight patients, who died 115–1007 (M = 566, SD = 313) days after FLT-PET. Forty-six FLT-PET studies were performed on 33 patients who survived for 234–1410 (M = 682, SD = 341) days after FLT-PET. In the 24 patients the decision to start therapy occurred 15–811 (M = 185, SD = 258) days after 33 investigations and in 17 patients no such decision occurred during follow up of 74–1373 (M = 392, SD = 330) days. After the decision to start therapy, sixteen patients underwent operation, one of them additional radiotherapy and seven of them additional chemo-radiotherapy. Six patients were not surgically treated, four of them underwent radiotherapy and two patients had a combination of radiotherapy and chemotherapy. The record of therapy was not available in two patients. Seven of 24 patients died within 69–963 (median = 269) days after the referral to therapy. Progression of glioma was the cause of death in six of them, in one case the cause of death is not available due to the retrospective nature of the study. One patient did not receive any therapy and died 115 days after FLT-PET examination; the cause of his death is not known.

In the background ROI, mean SUV ranged between 0.083–0.237 (M = 0.152, SD = 0.034) and maximal SUV ranged between 0.175–0.451 (M = 0.292, SD = 0.061).

Overall survival

Stepwise Cox proportional hazards regression was used to identify which of above mentioned parameters are independent predictors of overall survival. SUV_{mean} was identified as the most significant predictor and no other parameter was able to independently improve prediction (overall model fit significance level $p = 0.0001$).

Table 1 shows the results of the ROC analysis. All parameters exhibit a significant ability to predict whether patients survive or die during the course of the study. The performance of SUV_{mean} and Subj is significantly more accurate compared to TLU and Vol_{FLT}. No significant difference was found in the performance of the other parameters. Identified cut-off values were used for the categorization of FLT-PET (positive vs. negative). These categories (positive/negative) were entered into the survival analysis.

Taking $SUV_{mean} = 0.236$ as the cut-off value, 34 investigations were categorized as negative and 21 as positive. Median survival of 1007 days was observed in a test positive subgroup while median survival for a test negative subgroup was not established through the duration of our study. Kaplan-Meier survival curves are presented at Figure 2, with both curves differing significantly ($p = 0.0002$). The hazard ratio is 17.6 with $CI_{95} = 4.3–72.0$.

Table 1. Results of ROC analysis of different parameters in relation to overall survival. Descendent order according to the area under the curve (AUC)

Parameter	Cut-off	Sensitivity (%)	Specificity (%)	AUC	p
SUV_{mean}	0.236	88.9	71.7	0.857	0.0001
SUV_{peak}	0.287	88.9	71.7	0.816	0.0001
Subj	1.000	77.8	80.4	0.812	0.0001
SUV_{max}	0.565	77.8	80.4	0.806	0.0001
TBR_{mean}	2.218	77.8	73.9	0.793	0.0003
TBR_{peak}	1.807	88.9	63.0	0.771	0.0045
TBR_{max}	2.355	88.9	60.9	0.742	0.0182
TLU	0.356	88.9	67.4	0.714	0.0069
Vol	0.479	88.9	63.0	0.685	0.0200

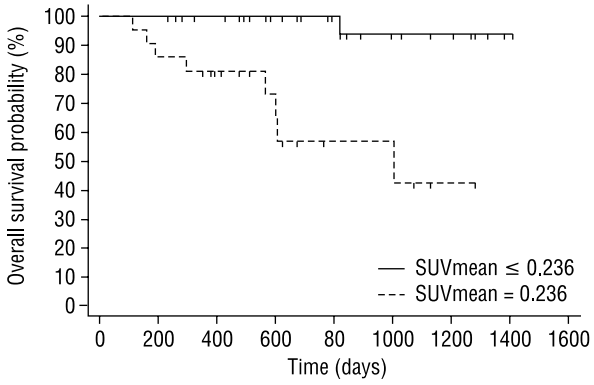

Figure 2. Overall survival: Kaplan-Meier curves for FLT-PET categorized according to SUV_{mean} = 0.236 as a cut-off value. Both curves differ significantly (p = 0.0002)

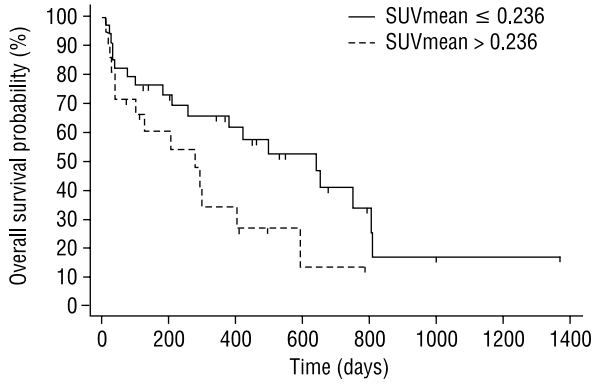

Figure 3. Event free survival: Kaplan-Meier curves for FLT-PET categorized according to SUV_{mean} = 0.236 as a cut-off value. Both curves differ with marginal significance (p = 0.0562)

Event free survival

Stepwise Cox proportional hazards regression identified SUV_{peak} as the most significant predictor of event free survival, but the model fit achieved only a marginal significance level p = 0.0539. At ROC analysis, no parameter exhibits a significant ability to define the moment when any therapy should be started.

Using the same categorization rule as in overall survival analysis, i.e. SUV_{mean} = 0.236 as the cut-off value, median event free survival was 281 days in the test positive subgroup and 643 days in the test negative subgroup. Kaplan-Meier survival curves are presented in Figure 3. Differences between both curves are only marginally significant (p = 0.0562), the hazard ratio is 1.9 with CI_{95} = 0.9–4.1.

Subjective assessment

From a practical point of view, the subjective analysis of these images is of great importance and their predictive value was therefore also analyzed. In 28 cases there was no subjectively detectable FLT uptake higher than natural brain background (category 0). With previous knowledge of approximate localization of the tumour, faint FLT uptake hardly distinguishable from the brain background was found in 11 cases (category 1). Easily identifiable focal pathological FLT uptake was present in 16 cases (category 2). Median overall survival was 1007 days in category 2, while in other categories it was not established during the time span of the study. Kaplan-Meier survival curves are presented in Figure 4. There was no significant difference between overall survival curves of

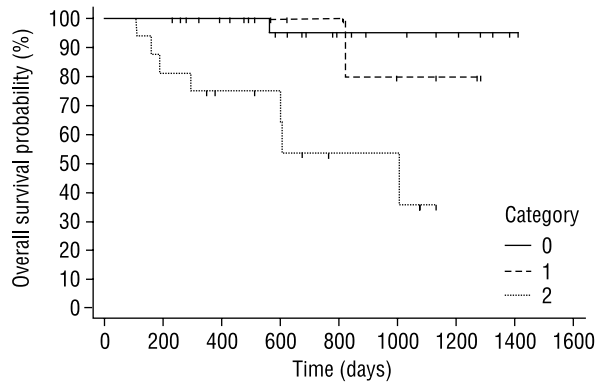

Figure 4. Overall survival: Kaplan-Meier curves for FLT-PET categorized according to subjective assessment. Curves of both categories 0 and 1 significantly differ from category 2

category 0 and 1, while both significantly differed from category 2 (p = 0.005 and p = 0.0445, respectively) with hazard ratios of 15.9 (CI_{95} = 3.5–71.3) and 6.6 (CI_{95} = 1.6–25.6), respectively. When analyzing categories 0 and 1 together against category 2, the hazard ratio for overall survival was 11.5 (CI_{95} = 2.5–54.2).

Median event free survival was 500 days in category 0, 752 days in category 1 and 132 days in category 2. Kaplan-Meier survival curves are presented at Figure 5. No significant differences were found between curves representing event free survival.

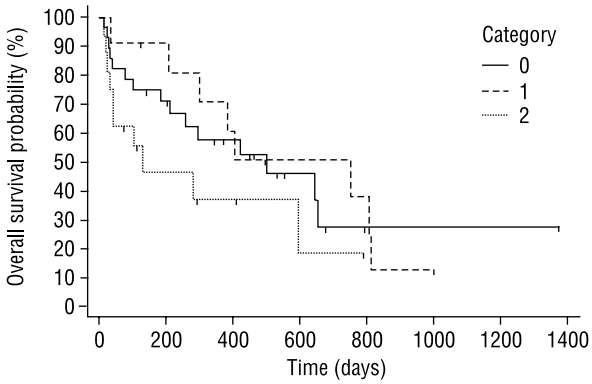

Figure 5. Event free survival: Kaplan-Meier curves for FLT-PET according to subjective assessment. No significant differences were found between curves

Discussion

We are not able to compare our results with results of other studies, as we found no references to any similar study in the literature. No survival analysis dealing with a homogenous group of patients with low-grade gliomas undergoing FLT-PET before therapy is available. Previously published papers have dealt with gliomas of various grades [3–5] or with different timing during their management (before/after therapy). Other studies concentrated on predictions of prognosis in treated high-grade gliomas [9–11]. The lack of comparable studies can be explained by a relatively rare occurrence of low-grade gliomas in the population and the limited availability of FLT-PET. We were able to conduct this study thanks to 1. the close collaboration of two hospitals specialized in neurooncosurgery, where a large proportion of patients with brain tumours are concentrated; 2. commercially and regularly available registered FLT; 3. the full reimbursement of FLT-PET by a national mandatory health insurance system.

It is known that brain tumour uptake is determined on the one hand by the proliferative activity of tumour cells and on the other hand by a nonspecific leakage of FLT through the impaired blood-brain barrier (BBB). Kinetic modelling is essential to distinguish both processes and SUV measurement is not sufficient for the assessment of net proliferative activity [14]. This is of great importance in high grade gliomas and especially after treatment, when impairment of the BBB occurs regularly. On the other hand impairment of the BBB is a rare finding in untreated low-grade gliomas on magnetic resonance imaging. Taking this fact into consideration and because kinetic modelling is not applicable to daily routine, we did not apply it.

Besides dynamic studies concentrated on kinetic modelling of FLT, an uptake time of 60 minutes was used in the majority of the remaining studies. We routinely apply a 15 minute uptake time based on findings by Chen et al. [16] that FLT uptake in gliomas is rapid, peaking at 5–10 minutes after injection and remaining stable for up to 75 minutes. The advantage of this approach is to lower the fraction of FLT conjugated with glucuronide [16] and, theoretically, to lower the unspecific uptake due to an impaired BBB.

We decided to use the date when neurosurgery, radiotherapy or chemotherapy was recommended as the considerable event, i.e. time of progression. This date was easily retrievable from the information system and we consider it to be the most objective approach, because the decision is based on multidisciplinary neurooncologic consultation. The weakness of this approach is the partial influence of FLT-PET itself on disease management decision-making, because its results were also considered at consultation. We found only marginally significant relation between FLT-PET and event free survival.

FLT-PET represents a very strong predictive factor for overall survival. Based on this, we believe FLT-PET also has a predictive power for event free survival in general, but we were unable to clearly demonstrate this in our study. We assume that this was due to a high prevalence of patients with mass effect at the time of the FLT-PET investigation, who all consequently received treatment that disregarded the FLT-PET result. To demonstrate the predictive value of FLT-PET for event free survival, we would need to enlarge the cohort of those patients who have no clinical symptoms at the time of FLT-PET.

Conclusion

We have brought evidence that FLT-PET can predict overall survival in previously untreated patients with suspicious or histologically confirmed low-grade glioma. Patients without any identifiable FLT uptake or with hardly distinguishable FLT uptake in the tumour region have good prognosis, while patients with clearly visible pathologic FLT uptake have a 12 times higher risk of death despite the standard treatment. The prediction value of the subjective assessment was not significantly improved by a semi-quantitative assessment, including SUV_{mean}. Based on this work, we can recommend inclusion of FLT-PET into further clinical studies aiming to identify the most important predictors of survival in patients with untreated low-grade gliomas.

On the other hand we were not able to bring robust data to confirm FLT-PET as a test capable of predicting event free survival. We assume that this difference can be explained by the fact that patients undergoing FLT-PET often had symptoms derived from space-occupying lesions only and were therefore referred for treatment which disregarded the FLT-PET result.

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Disclosure

No potential conflict of interest relevant to this article was reported.

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