Benefit of Static FET PET in Pretreated Pediatric Brain Tumor Patients with Equivocal Conventional MRI Results

Nutzen der statischen FET-PET bei multimodal behandelten pädiatrischen Hirntumorpatienten mit uneindeutigen MRT Befunden

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ABSTRACT

Background MRI has shortcomings in differentiation between tumor tissue and post-therapeutic changes in pretreated brain tumor patients.

Patients We assessed 22 static FET-PET/CT-scans of 17 pediatric patients (median age 12 years, range 2–16 years, ependymoma n = 4, medulloblastoma n = 4, low-grade glioma n = 6, high-grade glioma n = 3, germ cell tumor n = 1, choroid plexus tumor n = 1, median follow-up: 112 months) with multimodal treatment.

Method FET-PET/CT-scans were analyzed visually by 3 independent nuclear medicine physicians. Additionally quantitative FET-Uptake for each lesion was determined by calculating standardized uptake values (SUVmaxT/SUVmeanB, SUVmeanT/SUVmeanB). Histology or clinical follow-up served as reference.

Results Static FET-PET/CT reliably distinguished between tumor tissue and post-therapeutic changes in 16 out of 17 patients. It identified correctly vital tumor tissue in 13 patients and post-therapeutic changes in 3 patients. SUV-based analyses were less sensitive than visual analyses. Except from a choroid plexus carcinoma, all tumor entities showed increased FET-uptake.

Discussion Our study comprises a limited number of patients but results corroborate the ability of FET to detect different brain tumor entities in pediatric patients and discriminate between residual/recurrent tumor and post-therapeutic changes.

Conclusions We observed a clear benefit from additional static FET-PET/CT-scans when conventional MRI identified equivocal lesions in pretreated pediatric brain tumor patients. These results warrant prospective studies that should include dynamic scans.

ZUSAMMENFASSUNG

Hintergrund Die MRT ist in der Differenzierung zwischen Tumorgewebe und therapieassoziierten Veränderungen bei vorbehandelten Hirntumorpatienten limitiert.

Patienten Wir untersuchten retrospektiv 22 FET-PET/CT Untersuchungen von 17 multimodal behandelten pädiatrischen Patienten (medianes Alter 12 Jahre, Spannbreite 2–16 Jahre, Ependymom n = 4, Medulloblastom n = 4, niedriggradiges Gliom

n = 6, hochgradiges Gliom n = 3, Keimzelltumor n = 1, Choroid-Plexus Tumor n = 1, mediane Beobachtungszeit: 112 Monate).
Methode 22 FET-PET/CT Scans/Läsionen wurden unabhängig visuell von 3 Nuklearmedizinern bewertet. Zusätzlich wurde für jede Läsion die quantitative FET-Aufnahme durch Berechnung von standardisierten Aufnahmewerten (SUV) bestimmt (SUVmaxT/SUVmeanB, SUVmeanT/SUVmeanB). Als Referenz dienten die Histologie oder die klinische Verlaufsbeurteilung.
Ergebnisse Die statische FET-PET/CT unterschied bei 16 von 17 Patienten zuverlässig zwischen Tumorgewebe und therapieassoziierten Veränderungen: 13 Patienten mit vitalem Tumorgewebe sowie 3 Patienten mit posttherapeutischen Veränderungen. Die SUV-basierte Analyse war weniger sensitiv als die visuelle Analyse. Alle untersuchten Tumorentitäten außer einem Choroid-Plexus Karzinom zeigten eine gesteigerte FET-Aufnahme.
Diskussion Die Ergebnisse unterstreichen die Möglichkeit der Erkennung unterchiedlicher Tumorentitäten bei Kindern. Hierbei erscheint eine Diskriminierung zwischen Residual-/Rezidivtumor und therapieassoziierten Veränderungen möglich.
Schlussfolgerung Das klinische Vorgehen wurde durch den Einsatz der statischen FET-PET/CT Untersuchungen bei uneindeutigen MRT-Untersuchungen vorbehandelter pädiatrischer Hirntumorpatienten vereinfacht. Dieser Nutzen sollte in prospektiven Studien durch Einsatz von dynamischen FET-PET/CT Untersuchungen gesichert werden.

Introduction

Brain tumors represent almost a quarter of all neoplasms in childhood and adolescence. They display strong heterogeneity in histology. Relapsing tumors remain a clinical challenge and are generally associated with a dismal prognosis [3, 32]. Magnetic resonance imaging (MRI) is the gold standard imaging tool for the detection of brain tumors because of its high sensitivity and specificity [31]. During and after multimodal treatment, i. e. surgery, chemotherapy and radiotherapy, the diagnostic significance of MRI declines due to therapy-associated changes such as necrosis, edema, hemorrhage or inflammatory changes [2, 12]. In a series of pretreated adult patients with malignant brain tumors, the specificity of MRI to reliably detect vital tumor tissue dropped to 50–75 % [17, 24]. Positron emission tomography (PET) is a metabolic imaging tool aiming at overcoming these limitations by its significant increased specific uptake in vital tumor cells. The most frequently used PET tracer is the F18-labeled glucose derivate 2-[F18]fluoro-2-deoxy-d-glucose (FDG). However, in brain tumor patients sensitivity of FDG is limited by the high rate of glucose metabolism in grey matter of the brain, which results in an unfavorable signal-to-background ratio [22, 29]. Metabolic imaging studies in patients with brain tumors employing radiolabeled amino acids showed a significantly improved discrimination and delineation of tumor tissue from the surrounding brain parenchyma in comparison with FDG [22, 29]. Among these amino acid tracers O-(2-[F18]fluoroethyl)-L-tyrosine (FET) found a widespread use [35]. In several clinical studies in adult patients the uptake of FET in various CNS tumors was significantly higher than in healthy brain tissue [9]. PET using this FET was demonstrated to have an added value to MRI for the differentiation of suspected brain lesions and detection of recurrent brain tumors [21, 24, 25, 33]. Until now, few studies included pediatric patients to evaluate the benefit of this promising diagnostic tool [4, 6, 7, 11, 19–22, 27, 33]. Apart from the current analysis, only 3 studies focused on the special situation in children [4, 17, 20] whereas the remainder included children just sporadically beside adult patients. As each of these studies employed different examination protocols and different criteria for evaluating FET-PET scans, comparison of these studies is somewhat limited. Considering the differences between brain tumors in children and adults with respect to tumor entity, incidence, therapy and prognosis as well as the high heterogeneity of brain tumors in children and young adolescents [10], the available FET-PET data on adult patients cannot be applied to pediatric patients.

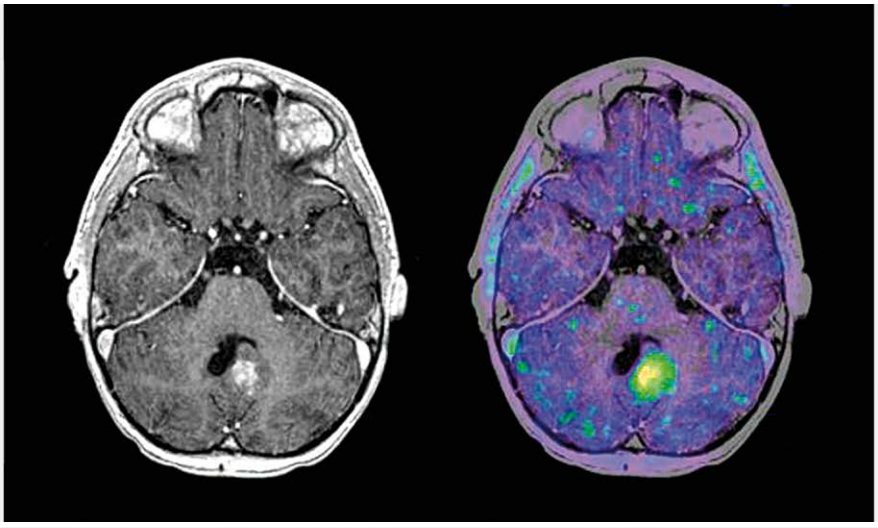
Facing the challenging situation in pretreated brain tumor patients as mentioned above, in this retrospective analysis we asked whether FET PET is able to reliably detect vital brain tumor tissue in children and adolescents during and after treatment when conventional MRI indicates suspicious or equivocal lesions.

Patients and Methods

In order to obtain long-term follow-up data (median follow-up 9.3 years, range 60–126.5 months) we analyzed FET-PET/CT examinations that were carried out from May 2005–2010 in children and young adolescents during therapy or surveillance when lesions occurred on routine MRI indicating possible residual tumor tissue or tumor progression demanding a decision on further management. In these challenging situations FET-PET/CT was performed as a non-invasive diagnostic method for compassionate use to help with clinical decisions. All FET-PET/CT examinations were carried out after informed consent of patients and/or their legal guardians.

In this retrospective analysis we included children and young adolescents with age 1 year to ≤ 18 years and when histology (second look surgery) or data on clinical- and neuroradiological follow-up of at least 48 months (or death due to tumor progression within 6 months following FET-PET/CT investigation) were available to evaluate FET-PET/CT results. A total of 17 patients (15 males, 2 females, median age: 12 years, range: 2–16 years) during or at the end of their cancer treatment met these inclusion criteria. The local ethics committee approved the retrospective analysis and there was no conflict with the declaration of Helsinki. Eight patients, i. e. patients #2, #3, #5, #6, #9, #14, #15, and #17 were part of the analyses of our previous publication on target selection for neurosurgery using FET-PET scans [20].

Two patients underwent FET-PET examination at 2 different time points, which were assessed separately: In patient #9 (medulloblastoma) the first FET PET/CT was done because of a stable but tumor suspicious lesion at the primary tumor location seen in routine MRI during ongoing chemotherapy (9 months after partial



▶ **Fig. 1** T1-weighted MRI after intravenous application of gadolinium-containing contrast agent (left) and fused FET-PET/MRI (right) of pretreated pediatric brain tumor patient #9 (lesion #11).

tumor resection; 2 months after completion of radiotherapy, ▶ **Fig. 1**). A second FET-PET/CT scan was carried out because of a suspected recurrence on the routine MRI scan after the end of therapy. In patient #7 (pilocytic astrocytoma WHO I) the first FET PET/CT scan was performed at suspected tumor progression 23 months after subtotal tumor resection. After proven progression and decision for radiotherapy, a second FET-PET/CT scan was performed 14 months after the end of radiotherapy – again at suspected tumor progression.

In two patients (#4, #13) MRI revealed multiple lesions suspicious for active tumor tissue: patient #4 (anaplastic ependymoma WHO III) two lesions, patient #13 (anaplastic astrocytoma WHO III) three lesions.

In total we analyzed 22 lesions seen on routine MRI in 17 patients that were rated as equivocal, i. e. as non-specific for vital tumor. Evaluation of FET-PET/CT scans was based on histology (second look surgery) for 10 lesions (of 10 patients) and on clinical- and neuroradiological follow-up for 12 lesions (of 9 patients, 5 patients died due to tumor progression within 6 months following FET-PET/CT investigation and 4 patients were observed for at least 60 months; ▶ **Table 1**). Data actualization ended May 2019.

FET-PET/CT- Investigation

Patients followed a protein-deficient diet for a period of 12 h prior to FET-PET/CT investigation. FET-PET/CT scans were performed 10 min after intravenous injection of 70–200 MBq O-(2-[F-18]-fluoroethyl)-l-tyrosine (FET) in a weight adapted fashion, with acquisition of helical CT data immediately preceding acquisition of 3D emission data (10 min per bed position with a 16 cm axial field of view (FOV); one, and if required 2 bed positions/subject covering the entire head) using the Siemens Biograph 16 scanner. PET/CT data were reconstructed iteratively (OSEM algorithm) using a 128 × 128 matrix.

FET-PET/CT - Analysis

For this retrospective analysis three independent nuclear medicine physicians visually analyzed all FET-PET/CT-images blinded to clinical information and based on the procedure guideline for brain tumor imaging using labelled amino acid tracers of the European Association of Nuclear Medicine [30]. Evaluation was done patient- and lesion-based. For anatomical orientation FET-PET/CT images were either fused with MRI data using the "3D volume viewer" implemented in the Siemens LEONARDO workstation, or compared in a "side-by-side" analysis (median time interval of MRI to FET-PET/CT: 2 days; 21 of 22 PET-scans were carried out within 2 weeks after routine MRI; one PET-scan (patient #9) 79 days after MRI). The nuclear medicine physicians documented whether FET-uptake was elevated within or outside the lesion(s) suspicious for tumor on MRI and rated the lesion(s) on a 6-point rating scale: 6: definitely positive; 5: probably positive; 4: possibly positive; 3: possibly negative; 2: probably negative; 1: definitely negative for tumor tissue [21]. When rating results of these three observers differed, majority decision was made (▶ **Table 2**).

For quantification of FET-uptake, circular regions-of-interest (ROIs) were placed onto the tumor suspicious lesion(s) and mirrored onto the non-tumor-bearing hemisphere or in case of midline lesions onto unaffected remote brain tissue for comparison. Standardized uptake value (SUV) ratios for tumor (T) and unaffected brain tissue (B) (SUV_{maxT}/SUV_{meanB}, SUV_{meanT}/SUV_{meanB}) were calculated by dividing the maximum and mean SUV (SUV_{maxT}, SUV_{meanT}) of the tumor by the mean SUV in the unaffected brain tissue (SUV_{meanB}) according to Pauleit et al.[22]. Based on our study population we performed the ROC analysis to define a threshold for SUV_{maxT}/SUV_{meanB} in order differentiate between vital tumor tissue and post-therapeutic changes.

Evaluation of FET-PET/CT results

Evaluation of FET-PET/CT scans was based on histology (second look surgery) in 10 lesions of 10 patients and on clinical- and neuroradiological follow-up in 12 lesions of 9 patients (▶ **Table 1**). A pediatric neurooncology board evaluated clinical and neuroradiological follow-up. According to surveillance protocols, patients' disease status was classified as progressive disease (worsening symptoms and/or progressive lesion on MRI: > 25 % increase of tumor

▶ **Table 1** FET-PET/CT lesions of pretreated pediatric brain tumor patients.

Les	Pat	Sex	Age [years]	Primary tumor	Indication	Histology	Clinical course	Follow-up time [months]	Time: end of therapy - FET-PET [months]	Therapy before PET		
										Surgery	CTX	RTX
1	1	M	12	AE III	β	-	PD	2.9 †	7.4	STR	+	+
2	2	M	12	MB	α	GBM		-	107.6	STR	+	+
3	3	M	11	MB	α	MB * * *		-	8.3	STR	+	+
4§1	4	F	5	AE III	α	-	PD	2.9 †	13.4	STR	+	+
5§1	4					-	PD					
6	5	M	16	DNT	α	DNT * *		-	12.7	GTR		
7	6	M	13	GG II	α	GG II *		-	4.7	STR		
8	7	M	15	PA	α	PA *		-	23.0	STR		
9	7	M	16	PA	α	-	PD	60.3	13.3	STR		+
10	8	M	16	mGCT	α	-	SD	101.5	20.0	GTR	+	+
11	9	M	5	MB	γ	MB *		-	#	STR	+	+
12	9	M	7	MB	α	-	SD	126.5	17.3	GTR	+	+
13	10	M	2	AE III	α	-	SD	122.6	7.9	STR	+	+
14	11	M	9	GBM	γ	-	PD	4.4 †	#	GTR	+	+
15	12	F	16	GBM	γ	-	PD	4.8 †	#	STR	+	+
16§2	13	M	14	AA III	γ	-	PD	0.6 †	#	BIO	+	+
17§2	13					-	PD					
18§2	13					-	PD					
19	14	M	7	AE III	β	AE III * / * * *		-	34.3	STR	+	+
20	15	M	8	CPC III	β	CPC III * * *		-	#	STR	+	
21	16	M	14	PA	ε	PA *		-	0.6	STR		
22	17	M	13	PA	α	PA * *		-	0.5	GTR		

Les ID of lesion, **Pat** patient, **Clinical course** clinical and neuroradiological follow-up according to McDonald criteria, **Follow-up time** follow-up time after FET-PET examination, **PA** pilocytic astrocytoma WHO I, **DNT** dysembryoplastic neuroepithelial tumor WHO I, **GG II** ganglioglioma WHO II, **mGCT** malignant germ cell tumor, **AE III** anaplastic ependymoma WHO III, **AA III** anaplastic astrocytoma WHO III, **CPC III** choroid plexus carcinoma WHO III, **MB** medulloblastoma, **GBM** glioblastoma multiforme, **PD** progressive disease, **SD** stable disease, **GTR** gross total resection, **STR** subtotal resection, **CTX** chemotherapy, **RTX** radiation therapy, §1,2 lesions belong to one FET-PET examination , # FET-PET in the time of chemotherapy, † death caused by tumor progression, * progression, * * local recurrence, * * * metastasis, **α** identification of residual or recurrent tumor tissue after completed therapy, **β** suspected tumor progression after completed therapy, **γ** suspected tumor progression during ongoing therapy, **ε** identification of vital tumor tissue for planning radiation therapy.

volume), stable disease (at least stable clinical performance and constant lesion on MRI, i. e. < 25 % change of tumor volume), partial response (at least stable clinical performance and partial remission on MRI, i. e. > 50 % decrease of tumor volume) or no tumor (at least stable clinical performance and complete remission (CR) on MRI, i. e. no evidence of tumor tissue). Evaluation of tumor tissue on MRI was carried out according to McDonald criteria [16]. FET-PET/CT-results were classified as true positive (positive rating and progressive disease (PD) according to histology and/or follow-up), false positive (positive rating but no progressive disease (PD) according to histology and/or follow-up), true negative (negative rating and no progressive disease (PD) according to histology and/or follow-up) and false negative (negative rating but progressive disease (PD) according to histology and/or follow-up).

Statistical analysis

The R software (Version 2.15.3, The R Foundation for Statistical Computing) was used for statistical analysis. Due to small sample size, non-parametric distributions of data were assumed and median and ranges were used as descriptive parameters. Differences for SUVmaxT/SUVmeanB and SUVmeanT/SUVmeanB were tested for tumor vs. lesions of undetermined clinical significance with the unpaired Mann-Whitney-U-test. To evaluate the visual analyses of all 3 independent observers as a group average rating scores were calculated for FET-PET/CT lesions of each patient. A rating score of four or higher was considered positive for tumor tissue; a rating score of three or less was considered negative for tumor tissue. Due to the small number of patients this study had rather explorative character and the diagnostic value of FET-PET/CT is presented as a descriptive data analysis. Inter-rater reliability of visual FET-PET/CT analysis was assessed using Fleiss' kappa. κ -values between 0 and 0.2 indicate slight, between 0.21 and 0.4 fair, between 0.41 and 0.6 moderate, between 0.61 and 0.8 substantial and between 0.81 and 1 almost perfect agreement. Statistical significance was assumed at a p-value less than 0.05.

▶ **Table 2** Results of FET-PET/CT analysis.

Les	Pat	Diagnosis	MRI Lesion location	MRI KM-uptakte	PET/CT Results (3 reviewers) *	PET/CT Results (majority decision)	SUVratio SUVmaxT/SUVmeanB (threshold 2.3)	SUVratio SUVmeanT/SUVmeanB (threshold 1.6)	Clinical decision	Comparison PET/CT and reference
1	1	AE III	Distant	+	6/6/6	Positive	2.6	1.9	BSC	TP – FU
2	2	GBM	Distant	+	6/6/6	Positive	3.9	2.3	Resection	TP – H
3	3	MB	Distant	+	5/4/4	Positive	1.8	1.4	Resection	TP – H
4	4	AE III	Local	+	6/6/4	Positive	2.7	2.2	BSC	TP – FU
5	4	AE III	Distant	+	5/6/6	Positive	2.4	1.7	BSC	TP – FU
6	5	DNT	Local	+	6/6/6	Positive	5.8	3.7	Resection	TP – H
7	6	GG II	Local	-	6/6/6	Positive	3.6	2.5	Resection	TP – H
8	7	PA	Local	-	6/5/6	Positive	3.6	2.3	Resection	TP – H
9	7	PA	Local	+	5/5/6	Positive	3.4	2.3	WW	TP – FU
10	8	No tumor	Local	-	2/1/1	Negative	2.1	0.8	WW	TN – FU
11	9	MB	Local	+	6/6/6	Positive	2.9	2.1	Resection	TP – H
12	9	No tumor	Local	-	5/1/1	Negative	1.9	0.9	WW	TN – FU
13	10	No tumor	Local	-	1/2/1	Negative	2.2	1.4	WW	TN – FU
14	11	GBM	Local	+	6/6/6	Positive	3.6	2.4	BSC	TP – FU
15	12	GBM	Local	+	5/6/6	Positive	2.3	1.4	BSC	TP – FU
16	13	AA III	Local	+	6/6/6	Positive	3.3	2.1	BSC	TP – FU
17	13	AA III	Distant	-	6/6/6	Positive	3.4	1.9	BSC	TP – FU
18	13	AA III	Distant	+	6/6/6	Positive	3.6	2.1	BSC	TP – FU
19	14	AE III	Local	+	6/6/6	Positive	3.4	2.2	Resection	TP – H
20	15	CPC III	Local	+	2/1/4	Negative	1.6	0.9	Resection	FN – H
21	16	PA	Local	-	6/6/6	Positive	4.4	2.7	Radiation	TP – H
22	17	PA	Local	+	6/6/6	Positive	1.9	1.6	Resection	TP – H

Les ID of lesion, * PET/CT-scans visually analyzed by three independent reviewers _/_/_ and classified as "definitely positive" (6), "probably positive" (5), "possibly positive" (4), "possibly negative" (3), "probably negative" (2), and "definitely negative" (1) for tumor tissue. **WW** watch and wait, **BSC** best supportive care, **FU** follow-up, **H** histology, **TP** true positive, **FP** false positive, **TN** true negative, **FN** false negative, **PA** pilocytic astrocytoma WHO I, **DNT** dysembryoplastic neuroepithelial tumor WHO I, **GG II** ganglioglioma WHO II, **AE III** anaplastic ependymoma WHO III, **AA III** anaplastic astrocytoma WHO III, **CPC III** choroid plexus carcinoma WHO III, **MB** medulloblastoma, **GBM** glioblastoma multiforme, **Distant** lesion location distant to primary tumor site, **Local** lesion location at primary tumor site.

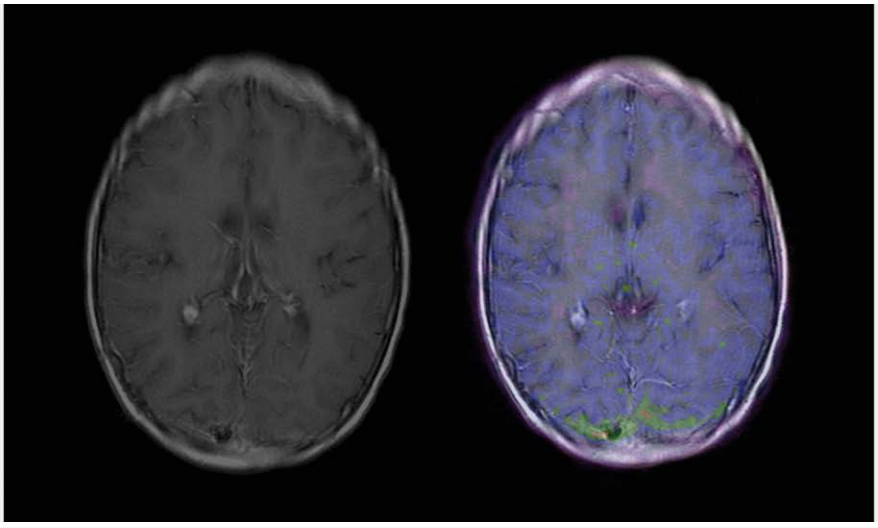
Results

Visual analysis of FET-PET/CT-scans (qualitative analysis)

In 19 FET-PET/CT-scans of 17 pediatric patients a total of 22 suspicious lesions were visually analyzed. No increased FET-uptake was identified outside the suspicious lesion sites seen on routine MRI. Nineteen of these 22 lesions were proven as vital tumor tissue by histology and/or follow up (▶ **Table 2**). Eighteen of these 19 tumor lesions were correctly identified by FET-PET/CT by visual analysis. One of these 19 tumor lesions was rated false negative (Patient #15, choroid plexus carcinoma WHO III, ▶ **Fig. 2**). The remaining 3 suspicious lesions (lesion #10, #12, #13) were correctly identified by FET-PET/CT as unspecific post-therapeutic changes. In total, FET-PET/CT correctly differentiated between vital tumor tissue and post-therapeutic changes in 21 out of 22 lesions (95 %). This results in a reliable identification, i. e. accuracy in detecting the viable tumor tissue in 16 out of 17 patients (94 %). For this retrospective analysis all FET-PET/CT-images were rated by three independent nuclear medicine physicians using a six-point rating scale [21] (▶ **Table 2**). The inter-rater reliability yielded just a 'fair' agreement with a value of $\kappa = 0.37$. Reducing the evaluation on the presence or absence of tumor tissue (positive: ratings ≥ 4, negative: ratings ≤ 3) inter-rater reliability yielded 'substantial' agreement ($\kappa = 0.76$). Inconsistent rating results were seen in patient # 9 and #15 (▶ **Table 2**).

SUV analysis of FET-PET/CT-scans (quantitative analysis)

SUV_{maxT}/SUV_{meanB} trended to be higher in tumor lesions (median 3.4, range 1.6–5.8) when compared to the lesions of undetermined clinical significance (median 2.1, range 1.9–2.2), but this difference did not reach statistical significance ($p = 0.15$). ROC analysis among our study population indicated a threshold of 2.3 for SUV_{maxT}/SUV_{meanB} to differentiate between tumor tissue and lesions of undetermined clinical significance. Based on this threshold we identified 16 out of 19 tumor lesions (84 %), i. e. two less than based on visual analysis. Non-tumor lesions, i. e. without determined clinical sig-



▶ **Fig. 2** T1-weighted MRI after intravenous application of gadolinium-containing contrast agent (left) and FET-PET/CT scan (right) of pretreated pediatric brain tumor patient #16 (lesion #21).

nificance (lesion #10, #12, #13) were also reliably identified by SUV_{maxT}/SUV_{meanB} -based analysis. SUV_{meanT}/SUV_{meanB} trended to be also higher tumor lesions (median 2.1, range 0.9–3.7) when compared to non-tumor lesions (median 0.9, range 0.8–1.4) without reaching statistical significance ($p = 0.09$; ▶ **Table 2**). In ROC analysis a threshold of 1.6 for SUV_{meanT}/SUV_{meanB} allowed identification of 16 out of 19 tumor lesions (84 %) – two less than based on visual analysis (s. above). Lesions without determined clinical significance (lesion #10, #12, #13) were again reliably identified by SUV_{meanT}/SUV_{meanB} -based analysis. In comparison to SUV_{maxT}/SUV_{meanB}, SUV_{meanT}/SUV_{meanB} recognized lesion #22 (patient #17) as true positive, whereas lesion #15 (patient #12) as false negative. Visual FET-PET/CT-analysis ascertained both lesions correctly as true positive. In this study we saw no significant differences in FET-uptake between low-grade and high-grade tumors (SUVmax LGG: range 1.9–4.6, median 2.8; SUVmax HGG: range 1.4–5.9, median3.5 ($p = 0.57$); SUV_{maxT}/SUV_{meanB} LGG: range 1.9–5.8, median 3.6, SUV_{maxT}/SUV_{meanB} HGG: range 1.6–3.8, median 2.9 ($p = 0.09$)).

Discussion

In this small pediatric brain tumor patient cohort additional static FET-PET/CT-scans reliably distinguished between tumor tissue and lesions of undetermined clinical significance, i. e. most probably unspecific post-therapeutic changes in 21 out of 22 lesions (accuracy 95 %). FET-PET/CT identified correctly vital tumor tissue in 18 lesions and unspecific post therapeutic changes in 3 lesions. These results are in line with data published on pretreated adult and pediatric patients with brain tumor and reflect the potential of FET-PET/CT as an add-on tool to increase sensitivity and specificity when dealing within equivocal MRI data [17, 18, 20, 23, 24]. Despite promising results in adult patients with gliomas, up to now it remains unclear, whether FET shows sufficient and specific uptake in the wide plethora of brain tumor entities seen in children and adolescents. In our cohort a choroid plexus carcinoma WHO III did not show sufficient FET-uptake (Patient #15) and was rated false negative by visual analysis as well as by quantitative analysis (SUV_{maxT}/SUV_{meanB} ratio of 1.6 and a SUV_{meanT}/SUV_{meanB} ratio of 0.9).

Dunkl et al. published the largest number of children and young adolescents (n = 49), on FET-PET/CT-scan in pediatric brain tumor patients [4]. Eighteen of these 49 patients underwent FET-PET/CT examination because of suspected tumor progression or recurrence. They found a sensitivity of 75 % and a specificity of 90 %. We previously analyzed the helpfulness of FET-PET in 26 pediatric patients with suspected brain tumor on MRI for target selection prior to surgery. Using this perspective, FET-PET examination yielded a false negative result while two were false positive, resembling a sensitivity of 83 % and a PPV of 91 % [20]. Marner et al. examined 22 pediatric brain tumor patients after tumor resection with hybrid FET-PET/MRI and reported an increased specificity (100 %) and PPV (100 %) compared to MRI alone (specificity 75 %, PPV 75 %) [17]. Their data corroborate the rather explorative character of FET-PET evaluation, because of the strong heterogeneity of their patient population, i. e. Dunkl et al. included 18 patients with 11 different tumor entities [4], whereas in our previous study we examined 13 patients with 8 different tumor entities[20], Marner et al. performed FET-PET on 22 patients with 12 different tumor entities [17] (in the present series we included 8 different tumor entities in 17 patients). These studies demonstrate the urgent and warranted need to continue clinical research with FET-PET in children and young adolescents with brain tumor in order to define the diagnostic value of this promising tool in this rare and heterogenic patient group.

Various SUV ratios have been reported for differentiation between tumor and non-tumor lesions [17, 21, 23, 24]. In the present study we compared SUV_{maxT}/SUV_{meanB} with SUV_{meanT}/SUV_{meanB}. Both types of approach reached a similar sensitivity (16/19 lesions, 84 %) and specificity (3/3 lesions, 100 %), but were less sensitive compared to visual analysis (18/19, 95 %). According to our clinical experience, SUV-ratio analysis may support visual analysis and may

help to increase inter-observer-reliability, but did not reach significance in our study cohort.

In recent years a plethora of features were investigated to extract more predictive data from FET-Uptake, in addition to already established and still crucial features like anatomical localization and change in FET-uptake over time. A highly promising approach seems to be the dynamic FET-PET/CT analysis based on time-activity curves for the whole 40 min of examination. A recent study by Albert et al. with dynamic FET PET/CT analyzed the outcome in different subgroups, separated by the most common genetic markers found in glioma. The time-to-peak identified patients with favorable outcome even within tumor grades established in the WHO classification of 2016 [15, 28]. Further development of hybrid PET/MR scanners enabled simultaneous recording of anatomical and functional images using perfusion and diffusion weighted imaging in addition to metabolic imaging [14]. Song et al. demonstrated when using hybrid FET-PET/MRI that FET-PET delineated histologically proven primary or recurrent tumor volume outside contrast enhancement on MRI, adding vital information for treatment planning (e. g. biopsy, resection, radiation) [26]. Marner et al. showed an increased specificity when employing hybrid FET-PET/MRI in early postoperative detection of residual tumor tissue in pediatric brain tumor patients compared to MRI alone [17]. The additional information derived from perfusion weighted imaging (PWI), diffusion weighted imaging (DWI) with apparent diffusion coefficient (ADC) maps and FET-PET leads to visualization of different cerebral volumes. The combination of these different parameters (e. g. static and dynamic FET-PET, static FET-PET and ADC) seems to further improve diagnostic accuracy when differentiating recurrent tumor from treatment related changes [34]. This type of multifactorial analysis of various parameters of FET-PET/MRI data may further increase diagnostic accuracy, e. g. predicting IDH genotype of gliomas [13].

However, the high accuracy of static FET-PET-imaging in our study more than sufficed to make proper clinical decisions, albeit in patient #15, such as watch and wait, palliative care with symptom-oriented therapy, or even taking another surgical approach. In patient #15 the decision was to continue treatment and assess response at an earlier stage, i. e. within 8 instead of 12 weeks due to the discrepancy between MRI and static FET-PET/CT. Eventually, the following MRI revealed PD and subsequent surgery confirmed the progression of vital tumor tissue.

In this study we observed no significant differences in FET-uptake between low-grade and high-grade tumors based on SUV-analysis ("Results", ▶ **Table 2**). There was a tendency to a higher FET-uptake in high grade tumors, which is in accordance with the literature [5, 11, 33]. Next, the lesion # 9 of PA patient #7 helped to decide to watch and wait as volume of the PET-positive lesion had become smaller and the SUV_{maxT}/SUV_{meanB} became smaller. Eventually, the tumor became progressive 61 months later. This highlights the special challenge when assessing vitality of LGG with FET-PET as these may switch their balance of oncogene induced senescence [1] and progress after long periods of stable disease [8].

In this series of 22 FET-PET/CT-lesions we noted the challenge of consistent rating results across all visual observers. For this retrospective analysis we asked three independent nuclear medicine physicians to visually analyze all FET-PET/CT-images without any further clinical information. We used a six-point rating scale which was published 2005 by Pauleit D. et al. [21]. Based on this rating scale, there were discordances of two and more rating points in 2 out of 22 lesions (patient #9 and #15, ▶ **Table 2**). In patient #9 observer one rated post-therapeutic changes as "probably positive" (5), while observer two and three rated the same lesion as "definitely negative for tumor tissue" (1); a clinical and neuroradiological follow-up of 55 months revealed no evidence for tumor tissue. In patient #15, observer three rated a choroid plexus carcinoma WHO III as "possibly positive" (4), while observer one and two rated "probably negative" (2) or "definitely negative for tumor tissue" (1). A second look surgery after further progression on MRI revealed vital tumor tissue. Overall, the inter-rater-reliability of visual FET PET/CT scan analysis by these three independent observers reached a κ-value of 0.37 indicating just a fair agreement. Reducing the evaluation on the presence (definitely positive, probably positive, possibly positive) or absence (possibly negative, probably negative, definitely negative) of tumor tissue the inter-rater reliability yielded at least a slightly better agreement ($\kappa = 0.76$). Despite the excellent results of visual FET-PET analysis in general, this experience also reflects the challenge of observer-independent evaluation.

Conclusion

In this retrospective analysis in pretreated children and adolescents with brain tumor we demonstrated the benefit of an additional FET-PET/CT-scan when conventional MRI did not provide sufficient data for a therapeutic decision. Visual analysis of FET-PET/CT-scans helped to differentiate between vital tumor tissue (residual tumor, progress, and relapse) and lesions without determined clinical significance in 16 out of 17 studied patients. Nevertheless, at this early stage of FET-PET use in children and adolescents we became aware of the challenge to obtain consistent visual rating results across different observers; the inter-rater-reliability reached just a 'fair' agreement. Additional dynamic data and use of PET/MRI scanners may be helpful to support visual interpretation; their usefulness should be investigated by further studies. Above all, these encouraging results indicate the possible clinical value of FET-PET as a promising diagnostic tool for pediatric patients suffering from brain cancer.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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