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RESEARCH ARTICLE

Influence of Dexamethasone on O-(2-[^{18}F]-Fluoroethyl)-$_L$-Tyrosine Uptake in the Human Brain and Quantification of Tumor Uptake

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Abstract

Purpose: O-(2-[^{18}F]fluoroethyl)-L-tyrosine ([^{18}F]FET) is an established positron emission tomography (PET) tracer for brain tumor imaging. This study explores the influence of dexamethasone therapy on [^{18}F]FET uptake in the normal brain and its influence on the maximum and mean tumor-to-brain ratio (TBR).

Procedures: [^{18}F]FET PET scans of 160 brain tumor patients were evaluated (80 dexamethasone treated, 80 untreated; each group with 40 men/40 women). The standardized uptake value of [^{18}F]FET uptake in the normal brain (SUV_{brain}) in the different groups was compared. Nine patients were examined repeatedly with and without dexamethasone therapy.

Results: SUV_{brain} of [^{18}F]FET uptake was significantly higher in dexamethasone-treated patients than in untreated patients (SUV_{brain} 1.33 ± 0.1 *versus* 1.06 ± 0.16 in male and 1.45 ± 0.25 *versus* 1.31 ± 0.28 in female patients). Similar results were observed in patients with serial PET scans. Furthermore, compared to men, a significantly higher SUV_{brain} was found in women, both with and without dexamethasone treatment. There were no significant differences between the different groups for TBR_{max} and TBR_{mean}, which could have been masked by the high standard deviation. In a patient with a stable brain metastasis investigated twice with and without dexamethasone, the TBR_{max} and the biological tumor volume (BTV) decreased considerably after dexamethasone due to an increased SUV_{brain}.

Conclusion: Dexamethasone treatment appears to increase the [^{18}F]FET uptake in the normal brain. An effect on TBR_{max}, TBR_{mean}, and BTV cannot be excluded which should be considered especially for treatment monitoring and the estimation of BTV using [^{18}F]FET PET.

Key words: PET, Brain tumors, Amino acids, [^{18}F]Fluoroethyltyrosine, FET, Dexamethasone, Tumor-to-brain ratio

Introduction

Brain tumor diagnostics with positron emission tomography (PET) using radiolabeled amino acids such as O-(2-

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[^{18}F]fluoroethyl)-L-tyrosine ([^{18}F]FET) is gaining increasing interest and has recently been recommended by the Response Assessment in Neuro-Oncology (RANO) working group at every stage of management of patients with brain tumors [1, 2]. Amino acid PET using [^{18}F]FET provides important additional information to conventional MRI especially with respect to delineation of tumor extent, the differentiation of treatment-related effects from tumor progression and for treatment monitoring [3–14].

Treatment with dexamethasone is the current standard therapy for patients suffering from brain edema, as it rapidly restores brain homeostasis and the integrity of the blood brain barrier (BBB), and thus reduces symptoms [15, 16]. Recently, we were able to show that dexamethasone treatment reduces the permeability of the BBB in rat gliomas but does not change [^{18}F]FET uptake in the tumors [17]. Furthermore, we observed that restoration of the BBB after antiangiogenic therapy of rat gliomas with bevacizumab did not influence [^{18}F]FET uptake in the tumors [18]. These observations indicate that [^{18}F]FET uptake in brain tumors is widely independent of the permeability of the BBB and that viability of tumor tissue during therapy is more reliably reflected by [^{18}F]FET uptake than by contrast-enhanced MRI.

In another experimental study, however, we found some evidence that the tumor-to-brain ratio (TBR) decreased after dexamethasone treatment caused by an increased tracer uptake in normal brain tissue and not by reduced [^{18}F]FET uptake in the tumor [19]. Since it can happen that a patient during chemotherapy is once treated with dexamethasone and once not, changes of TBR of [^{18}F]FET uptake could be misinterpreted and interfere with the assessment of response to chemotherapy. Moreover, the biological tumor volume (BTV) is determined by a predefined threshold above background and could be influenced by an increased standardized uptake value in normal brain tissue (SUV_{brain}) after dexamethasone treatment.

The aims of this study were to explore the effect of dexamethasone treatment on [^{18}F]FET uptake in normal brain of patients with gliomas and, consequently, to estimate the possible impact on TBR_{mean}, TBR_{max}, and BTV.

Methods

Patients

Out of 1170 patients who were referred to our institution from November 2014 to August 2016 for tumor diagnostics using [^{18}F]FET PET, 160 patients were selected consecutively according to the following criteria: (1) no dexamethasone prior to PET scans for at least 2 weeks (80 patients) and (2) dexamethasone treatment for at least 2 weeks prior to the PET scans in doses ranging from 0.5 to 24 mg/day. The groups contained a balanced sex distribution, *i.e.*, 40 men and 40 women per subgroup. Further information on mean age, dose of dexamethasone, histological or suspected diagnosis, and, if appropriate, specific pretreatment of the different groups are provided in Table 1. Nine patients were scanned multiple times (two to four times) with and without dexamethasone therapy. The ethics committee of the University of Aachen approved the retrospective data evaluation. There was no conflict with the Declaration of Helsinki. All subjects gave prior written informed consent for the PET investigation and the use of the data for scientific evaluations.

PET Imaging with [^{18}F]FET

The tracer was produced in-house as described elsewhere [20]. All patients fasted for at least 4 h before PET scanning according to the German guidelines for brain tumor imaging using radiolabeled amino acid analogues [21] and were asked to take their drugs as usual, including dexamethasone, on the day of the PET scan. PET imaging was performed in 80 patients (20 per group) on an ECAT Exact HR+ PET scanner (Siemens Medical Systems, Erlangen, Germany) in three-dimensional mode (axial field of view, 15.5 cm; image resolution, 6 mm) and in 80 patients (20 per group) simultaneously with MR imaging using a BrainPET insert (Siemens Medical Systems, Erlangen, Germany). The BrainPET is a compact cylinder that fits in the bore of the Magnetom Trio MR scanner (Siemens Medical Systems, Erlangen, Germany) (axial field of view, 19.2 cm; optimum image resolution, 3 mm) [22]. The dynamic PET studies were acquired up to 50 min after intravenous injection of approximately 3 MBq/kg body weight [^{18}F]FET. Reconstruction parameters were as similar as possible considering the different reconstruction environment of the two PET scanners. For the Exact HR+ scanner, iterative reconstruction with 16 subsets and 6 iterations without any filtering was applied, while for the BrainPET, an iterative reconstruction with 32 iterations and 2 subsets with a final image Gaussian filtering of 2.5 mm^3 was used; attenuation correction for the ECAT HR+ PET scan was based on a transmission scan, and for the BrainPET scan on a template-based approach [23]. The data were reconstructed dynamically with different frame lengths: 5×60 s, 5×180 s, and 6×300 s covering the 50 min whole scan time and allowing a time-activity curve for the analysis.

PET Data Analysis

The volume-of-interest (VOI) analysis and the calculation of the BTV were based on the averaged PET data from 20 to 40 min post-injection using PMOD (Version 3.505, PMOD Technologies Ltd.). [^{18}F]FET uptake in the tissue was expressed as standardized uptake value (SUV) by dividing the radioactivity concentration (kBq/ml) in the tissue by the radioactivity amount (kBq) injected per gram of body weight. To determine the SUV_{brain}, a three-dimensional elliptic VOI of 15.5 was placed contralateral to the tumor in

Table 1. Patient population and distribution of diseases

	Men w/o	Women w/o	Men under dexamethasone	Women under dexamethasone	*P* value
n	40	40	40	40	
Age	52.5 ± 10.9	48.7 ± 12.7	51.8 ± 10.5	53.1 ± 11.2	n.s.
Dexamethasone (mg)	–	–	9.0 ± 6.8	7.3 ± 5.2	n.s.
HGG	28	18	25	21	n.s.
LGG	8	14	3	5	n.s.
Metastasis	2	2	10	11	n.s.
Unclear/other	2	6	2	2	n.s.
Pretreatment					
Surgery	26	20	26	25	n.s.
Radiotherapy	21	17	30	32	n.s.
Chemotherapy	19	18	22	22	n.s.
SUV_{brain}	1.06 ± 0.16	1.33 ± 0.19	1.31 ± 0.28	1.45 ± 0.25	< 0.001*#
SUV_{wm}	0.85 ± 0.12	1.08 ± 0.17	1.02 ± 0.22	1.21 ± 0.19	≤ 0.005*
AUC_{cortex}	24.82 ± 3.56	30.78 ± 4.33	30.58 ± 6.46	33.59 ± 5.62	< 0.001*
TBR_{mean}	2.02 ± 0.54	1.92 ± 0.53	2.08 ± 0.44	1.93 ± 0.33	n.s.
TBR_{max}	2.67 ± 1.07	2.40 ± 1.13	2.68 ± 1.17	2.38 ± 0.78	n.s.

**P* values for male *vs.* female patients and dexamethasone treatment *vs.* no dexamethasone treatment (w/o)
#For post hoc/subgroup *P* values, see Fig. 3

normal appearing perisylvian cortex representing almost exclusively gray matter. Another 2D ROI (6.7 cm^2) was placed in the centrum semiovale representing exclusively white matter, to test for different effects of dexamethasone in gray and white matter (SUV_{wm}). Furthermore, the area under curve (AUC) of the time-activity curve of FET uptake in the brain VOI was determined. The maximum tumor SUV was determined by a 2-ml VOI centered on the maximal tumor uptake, mean tumor SUV, and BTV by a three-dimensional auto-contouring process using a tumor-to-brain ratio (TBR) of 1.6 as described previously [24]. TBR_{mean} and TBR_{max} were calculated by dividing the mean and maximum SUV in the tumor VOIs by the mean SUV of normal brain.

Statistics

Descriptive statistics are provided as mean and standard deviation (SD). A *t* test was performed to test a difference between the two scanners. Distribution of patients in the different subgroups was evaluated by Fisher exact tests for 2 × 2 contingency tables. Two-way (TW) ANOVAs with all pairwise multiple comparison procedures (Holm-Sidak method) were performed to detect differences between dexamethasone-treated and untreated patients as well as between men and women without correction for multiple testing. Data without normal distribution were tested with the Mann-Whitney Rank Sum test (TBR_{mean} and TBR_{max}). *P* values of 0.05 or less were considered significant. Pearson product correlations were performed for testing correlations between two variables. Statistical analysis was performed using SigmaPlot for Windows, Version 12.5.

Results

SUV_{brain} of [^{18}F]FET uptake was significantly higher in dexamethasone-treated patients than in untreated patients (SUV_{brain} 1.33 ± 0.10 *versus* 1.06 ± 0.16 in male and 1.45 ± 0.25 *versus* 1.31 ± 0.28 in female patients; both $P < 0.001$). The effect was likewise significant in white matter (Table 1). Furthermore, a significantly higher SUV_{brain} was found in women than in men, independently of dexamethasone treatment (Table 1, Fig. 1). Similar results were obtained when using AUC as a quantitative parameter for comparison. SUV_{brain} and AUC_{brain} values did not differ significantly between the ECAT HR+ PET scanner and the BrainPET scanner (*t* test: $P = 0.234$ and 0.233, respectively).

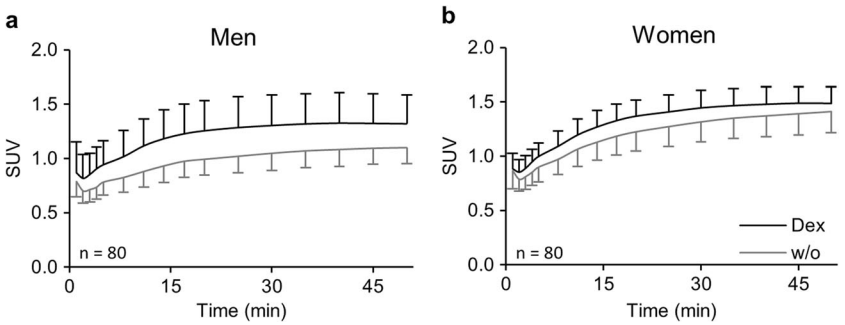

Fig. 1. Time-activity curves (mean SUV with SD) of dexamethasone-treated (Dex) and non-treated (w/o) **a** men and **b** women. Under dexamethasone therapy, the mean SUV increases in men more than in women.

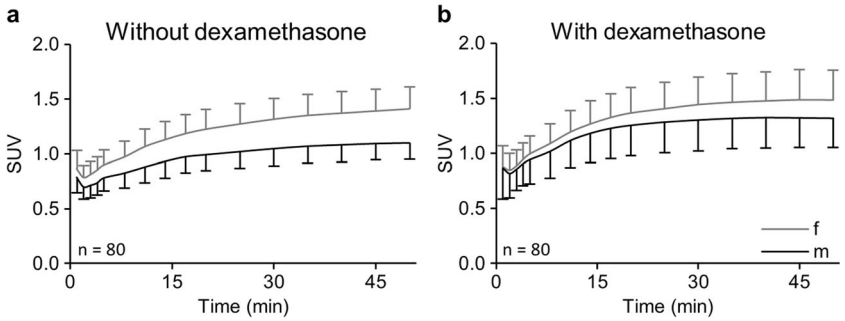

Fig. 2. Time-activity curves (mean SUV_{brain} with SD) of female (f) and male (m) patients **a** without dexamethasone therapy and **b** with therapy. The mean SUV of female patients is higher than the mean SUV of male patients, regardless of therapy

In the nine patients who were scanned multiple times (two to four times) with and without dexamethasone therapy, the SUV_{brain} values were highest in all but one case during dexamethasone therapy (Fig. 2, Table 2).

All pairwise multiple comparison procedures found significant differences between subgroups, that is, men without dexamethasone had the lowest [^{18}F]FET uptake in normal brain tissue and women with dexamethasone showed the highest uptake (Fig. 3), with a difference of 37 % between the two groups.

A slight correlation was found between SUV_{brain} and dexamethasone dose in men ($P < 0.01$; $r = 0.44$), but not in women (Fig. 4a). There was no correlation between SUV_{brain} and body mass index (BMI) (Fig. 4b), dose of [^{18}F]FET, or age (data not shown) in men or women.

The influence of changing SUV_{brain} of [^{18}F]FET uptake after dexamethasone treatment is further illustrated in one male patient with brain metastasis who underwent a [^{18}F]FET PET scan during dexamethasone therapy (4 mg/day) and 9 weeks later a second scan without dexamethasone (Table 3). No other treatment or medication was administered during this time. During follow-up, the tumor size remained unchanged on MR images, clinical symptoms remained stable (Fig. 5), and the maximum SUV of FET uptake in the tumor did merely change (−3 %). In contrast, the SUV_{brain} was 19 % higher during dexamethasone therapy leading to a drop of the TBR_{max} by 18 %. Calculation of BTV using the threshold-based method yielded a 70 % smaller BTV with dexamethasone than without, leading to a 14 % higher SUV_{mean} in the corresponding tumor VOI (Table 3). Thus, the higher SUV_{brain} during dexamethasone treatment was compensated by a higher SUV_{mean} in the tumor VOI and the TBR_{mean} was less dependent on dexamethasone therapy (−4 %) than the TBR_{max} (−18 %).

Table 2. SUV brain of nine patients with and without dexamethasone scanned multiple times. Except of the last patient, the SUV during dexamethasone therapy was always higher than the SUV without therapy

Patient, sex	FET PET	SUV_{brain}	Dexamethasone
1, m	1	1.33	Yes
	2	1.12	No
2, f	1	1.61	No
	2	1.28	No
	3	1.62	Yes
	4	1.93	Yes
3, m	1	1.57	Yes
	2	1.48	No
	3	1.23	No
4, f	1	1.38	No
	2	1.95	Yes
5, m	1	1.20	No
	2	1.72	Yes
6, f	1	1.36	No
	2	1.89	Yes
	3	1.38	No
7, m	1	1.32	No
	2	1.12	No
	3	1.49	Yes
8, f	1	1.13	No
	2	1.43	Yes
9, f	1	1.35	No
	2	1.28	Yes

Discussion

The aim of this retrospective study was to evaluate whether dexamethasone treatment changes [^{18}F]FET uptake in normal brain tissue and might influence PET parameters such as tumor $SUV_{mean/max}$, tumor volume, and $TBR_{mean/max}$, which are important for diagnosis, grading, treatment planning and control, and follow-up.

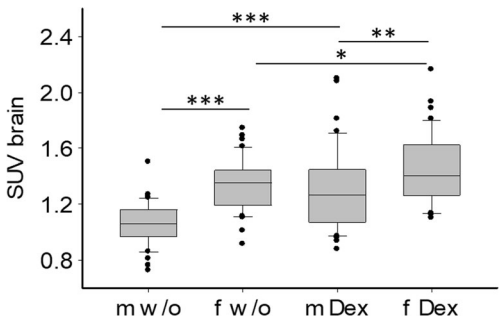

Fig. 3. The boxplot diagram shows significant differences between the subgroups. Men not receiving dexamethasone (m w/o) show lowest SUV in healthy brain tissue, women under dexamethasone therapy (f dexamethasone) have highest uptake. *$P \leq 0.05$; **$P \leq 0.01$; ***$P \leq 0.001$.

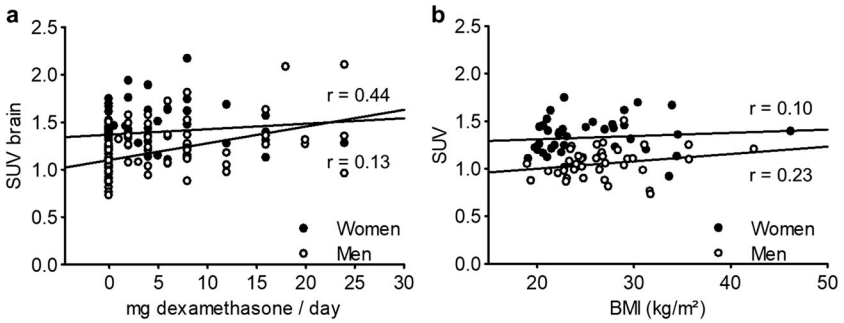

Fig. 4. Correlation plots of **a** SUV_{brain} *vs.* dose of dexamethasone per day and **b** SUV *vs.* body mass index (BMI), separately for men and women. SUV_{brain} *vs.* dose of dexamethasone correlated in men ($P < 0.01$; $r = 0.44$), but not in women.

We observed that dexamethasone treatment increased [^{18}F]FET uptake in normal brain tissue in both men and women (+ 24 and 9 %, respectively). This effect was identical for gray and white matter. The difference in SUV_{brain} could be demonstrated not only in the mean values of the different subgroups, but it was also clearly detectable in eight out of nine patients, who underwent repeated [^{18}F]FET PET with and without dexamethasone treatment. There was no correlation between SUV_{brain} and the dose of dexamethasone in women and a very poor correlation in men (Fig. 4a). This is not unexpected because the Cushing threshold for dexamethasone is only 1–2 mg/day and high metabolic effects can be expected at low doses. Thus, an all or nothing effect on SUV_{brain} can be expected at doses used for brain tumor patients. Hence, the increase of [^{18}F]FET uptake in normal brain tissue under dexamethasone therapy is a reproducible phenomenon which might interfere with the quantification of [^{18}F]FET uptake in brain tumors especially for treatment monitoring of chemotherapy if dexamethasone therapy is initiated or interrupted in the meantime.

The key question in this context is whether [^{18}F]FET uptake in the brain and the tumor is affected by the drug in the same way. As mentioned above, our data from animal experiments suggest that [^{18}F]FET uptake in the tumor is not increased by dexamethasone treatment in contrast to brain tissue and that the TBR thereby changes [19]. For humans, this question cannot easily be answered by comparing [^{18}F]FET uptake in the brain tumors of different patients with and without dexamethasone treatment since the tracer uptake varies largely between different types of brain tumors, causing high standard deviation when calculating statistics (Table 1). Repeated measurements in the same patients with and without dexamethasone in a short time interval with stable disease would be required, which we have not performed for ethical reasons. Nevertheless, the data of one patient with a brain metastasis and a short time interval between two [^{18}F]FET PET scans with and without dexamethasone medication confirmed the hypothesis of a different influence of dexamethasone therapy on tracer uptake in the tumor and normal brain tissue. Maximum SUV of [^{18}F]FET uptake in the tumor remained constant (− 3 %) while SUV_{brain} was 19 % higher during dexamethasone therapy leading to a drop of the TBR_{max} by 18 % (Table 3, Fig. 5). In addition, the threshold-based determination of BTV using a value of 1.6 above background resulted in a change in volume of 70 %.

Interestingly, Herholz and colleagues [25] reported a lower TBR_{max} of the amino acid tracer L-[^{11}C]methionine ([^{11}C]MET) uptake in high grade gliomas after corticoid therapy but no SUV data are reported. It is tempting to speculate that the lower TBR of amino acid uptake during corticosteroid treatment was caused by higher [^{11}C]MET uptake in the brain tissue, rather than lower [^{11}C]MET uptake in the tumor.

Based on the results from our previous animal experiments, we tested the short term effect of dexamethasone on [^{18}F]FET uptake in a group of six healthy male rats which yielded the same increase of [^{18}F]FET uptake of approx. Twenty percent after 48 h of dexamethasone treatment (see supplementary table 1). This small time span argues against the involvement of long-term effects due to corticoid treatment and cross-effects with other medication.

Table 3. [^{18}F]FET PET parameters of a patient with a brain metastasis investigated twice, during dexamethasone treatment (Sep/15) and without (Nov/15)

	Dexamethasone 09/15	No dexamethasone 11/15	Difference under dexamethasone treatment (%)
SUV_{brain}	1.33	1.12	+ 19
Tumor volume (ml) (threshold based)	2.72	8.99	− 70
Tumor SUV_{mean} (threshold based)	2.35	2.06	+ 14
Tumor SUV_{max}	2.07	2.14	− 3
TBR_{mean}	1.77	1.84	− 4
TBR_{max}	1.56	1.91	− 18

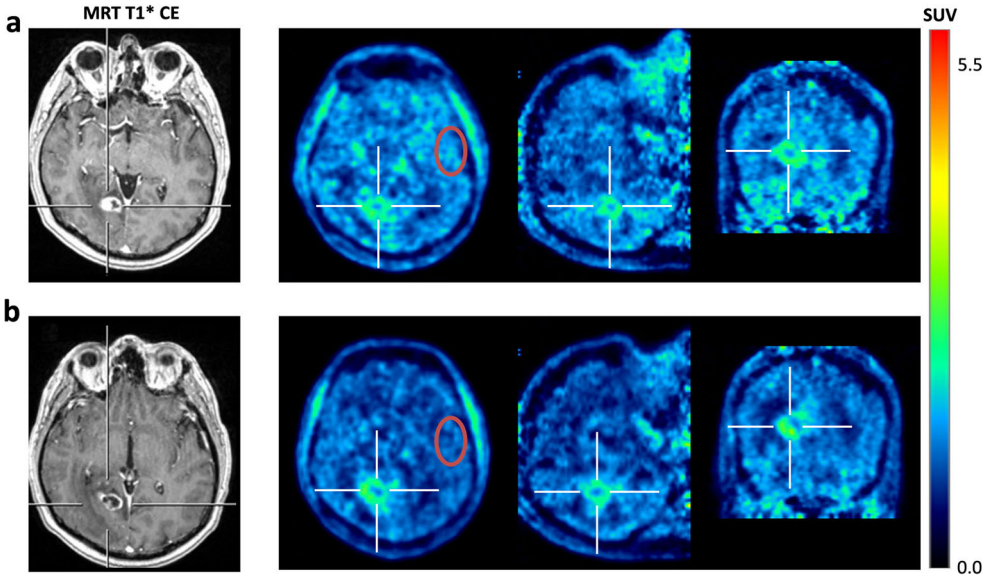

Fig. 5. Contrast-enhanced MR images and corresponding [^{18}F]FET PET SUV images of a male patient with brain metastasis at an interval of 10 weeks. Visually, no significant tumor growth could be observed in MR or PET images. (a) At the time of first PET scan, the patient received dexamethasone. (b) Nine weeks later, dexamethasone was already discontinued and background activity was visually lower, resulting in higher tumor volume due to threshold-based VOI definition (Table 2).

The cause of the phenomenon is still unknown. It has been shown that glucocorticoids induce increased protein breakdown and consumption of leucine [26, 27], while the transport system LAT1 itself has been shown to be unaffected in rat kidneys by glucocorticoids [28]. [^{18}F]FET, like leucine, is a substrate of the LAT transporter and uptake might be upregulated due to increased amino acid consumption and oxidation. This effect might be different in tumor cells, which already have an increased metabolism.

Furthermore, we observed higher [^{18}F]FET uptake in the healthy brain tissue of women than of men. Sex-specific differences in metabolism is a well-known phenomenon and leads to discussions in pre-clinical as well as in clinical studies [29–31]. Sex-specific metabolism might also be the reason for different increase of brain SUV after dexamethasone therapy in men in women. As there was no correlation for brain SUV and BMI (Fig. 4b) and a poor correlation for brain SUV and BMI in another patient population evaluated in our group [32], we assume that the high sex-specific differences are more likely due to differences in metabolism than to different volume of distribution caused by a higher percentage of muscle mass in men which shows increased FET uptake [33].

Our study is limited by its retrospective nature and the fact that the effects of dexamethasone treatment on TBR and BTV could be directly demonstrated in a single patient only. Therefore, a prospective study in the same patients is needed to confirm these effects. Nevertheless, the effect of dexamethasone treatment on TBR and BTV has been clearly demonstrated in animal experiments which in conjunction with this study represents important information for clinicians in this field.

Conclusion

In conclusion, dexamethasone treatment increases [^{18}F]FET uptake in the normal brain. An effect on TBR_{max}, TBR_{mean}, and BTV cannot be excluded which should be considered in particular during treatment monitoring with [^{18}F]FET PET and if BTV is used for treatment planning.

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Compliance with Ethical Standards. The ethics committee of the University of Aachen approved the retrospective data evaluation. There was no conflict with the Declaration of Helsinki. All subjects gave prior written informed consent for the PET investigation and the use of the data for scientific evaluations.

Conflict of Interest

The authors declare that they have no conflict of interest.

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