Journal of Nuclear Medicine, published on August 5, 2021 as doi:10.2967/jnumed.121.262051

Impact of ^{18}F-FET PET/MR on clinical management of brain tumor patients

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Word Count: 4937

Financial Support: The work did not receive financial support by third parties.

Running Title: Impact of ^{18}F-FET PET/MR in brain tumors

ABSTRACT

Multiparametric PET-MRI with the amino-acid analog ^{18}F-FET enables the simultaneous assessment of molecular, morphologic, and functional brain tumor characteristics. Although it is considered the most accurate non-invasive approach in brain tumors, its relevance for patient management is still under debate. Here we report the diagnostic performance of ^{18}F-FET PET/MR and its impact on clinical management in a retrospective patient cohort. **Methods:** We retrospectively analyzed brain tumor patients who underwent ^{18}F-FET PET/MR between 2017 and 2018. ^{18}F-FET PET/MR examinations were indicated clinically due to equivocal standard imaging or clinical course. Histological confirmation or clinical and standard imaging follow-up served as the reference standard. We evaluated ^{18}F-FET PET/MR accuracy in identifying malignancy in untreated suspect lesions (category new diagnosis) and true progression during adjuvant treatment (category detection of progression) in a clinical setting. Using multiple regression, we also estimated the contribution of single modalities to produce an optimal PET/MRI outcome. We assessed the recommended and applied therapies before and after ^{18}F-FET PET/MR and noted if the treatment changed based on the ^{18}F-FET PET/MR outcome. **Results:** We included 189 cases in the study. ^{18}F-FET PET/MR allowed the identification of malignancy at new diagnosis with an accuracy of 85% and identified true progression with an accuracy of 93%. Contrast enhancement, ^{18}F-FET PET uptake, and tracer kinetics were the major contributors to an optimal PET/MR outcome. In the previously equivocal patients, ^{18}F-FET PET/MR changed the clinical management in 33% of the untreated lesions and 53% of the tumor progressions. **Conclusion:** Our results suggest that ^{18}F-FET PET/MR helps clarify equivocal conditions and profoundly supports brain tumor patients' clinical management. The optimal

modality setting of ^{18}F-FET PET/MR and the clinical value of a simultaneous examination need further exploration. At a new diagnosis, multiparametric ^{18}F-FET PET/MR might help prevent unnecessary invasive procedures by ruling out malignancy; however, adding static ^{18}F-FET PET to an already existing MR examination seems to be of equal value. At detection of progression, multiparametric ^{18}F-FET PET/MR may increase therapy effectiveness by distinguishing between tumor progression and therapy-related imaging alterations.

Key Words: multiparametric ^{18}F-FET PET/MR, brain tumor, accuracy, clinical impact, human

INTRODUCTION

Positron emission tomography (PET) with radiolabeled amino-acid analogs like ^{18}F-fluor ethyl tyrosine (^{18}F-FET) is an advanced non-invasive imaging method for various disease-related indications of brain tumors (*1-5*). Combining it with magnetic resonance imaging (MRI) using a hybrid scanner may further improve its diagnostic validity (*6,7*). However, excellent diagnostic performance does not necessarily correlate with better patient outcomes. In order to determine a diagnostic procedure's actual clinical utility, its impact on clinical management, patient-relevant outcomes, and cost-effectiveness must be assessed additionally (*8,9*).

There is limited evidence evaluating the impact of PET on clinical decisions (*10*). Single studies reported clinical management changes in a significant proportion of patients (*11-14*). Ideally, scientific studies should compare the clinical consequence of a new procedure with an established diagnostic test in a randomized controlled design (*9,10*). This can be challenging due to several reasons. First, the patient outcome depends mainly on applied therapies. Extensive sample sizes will be needed to filter out a diagnostic procedure's small and multifold impact in a patient cohort with various therapeutic approaches (*15-17*). Also, an artificial patient selection may not reflect the disease's actual prevalence and distribution of clinical manifestations (*15*). Amino acid PET/MR in brain tumors currently serves as add-on diagnostics in patients with equivocal findings in clinical routine MRI. A direct comparison of both modalities would not be helpful. Therefore, several authors recommend performing studies in a routine clinical setup (*15,16*).

Summarized, defining the impact of an imaging procedure like PET/MR is challenging but essential to establish an efficient application in clinical routine. We aimed to investigate the clinical consequences of multiparametric ^{18}F-FET PET/MR in brain tumors by performing a structured evaluation of its diagnostic performance and impact on clinical management under real-world conditions.

MATERIALS AND METHODS

Patients and Data Collection

The institutional review board approved this retrospective study, and all subjects signed a written informed consent. We retrospectively reviewed all ^{18}F-FET PET/MR brain tumor examinations and disease outcomes in our institution in 2017 and 2018. Our institution treats over 600 newly diagnosed brain tumor patients per year. ^{18}F-FET PET/MR serves as a second-line diagnostic procedure performed only upon recommendation by a multidisciplinary tumor board in a minority of cases at both initial diagnosis or during the disease course. Thus, ^{18}F-FET PET/MR is predominately performed in patients presenting with uncertain MRI features or an equivocal clinical course after or during treatment. We evaluated all clinical data from the patient reports of each medical specialty and the multidisciplinary neuro-oncological tumor board. We recorded patient age and sex, the tumor pathology, periods between examinations, and follow-up duration. We also documented the medical history, including treatment recommendations immediately before the ^{18}F-FET PET/MR examination, and the subsequent disease course, including pathological examinations, subsequent therapies, clinical status, and imaging follow-up. In single cases, we could not retrieve retrospectively precise information about the treatment recommendations before ^{18}F-FET PET/MR. Clinical specialists of the tumor board (FP, MR, CS) reviewed these cases for the study and determined the appropriate treatment recommendation.

^{18}F-FET PET/MR Examinations and Data Analysis

All ^{18}F-FET PET/MR examinations were performed on a hybrid 3T-PET/MR scanner (Biograph mMR, Siemens Healthineers, Erlangen, Germany) due to clinical indication. An ultrashort echo time MRI sequence provided by the vendor was used for PET attenuation correction (AC). The diagnostic MRI comprised sequences according to the standardized brain tumor protocol, dynamic susceptibility perfusion (DSC-MRI), and ^{1}H-MR spectroscopy (MRS) (*18-20*). Multi-slice DSC-MRI was assessed during the first pass of a bolus of 0.1 mmol/kg Gadobutrol (Gadovist, Bayer Healthcare, Leverkusen, Germany, injection rate of 3 ml/s), 3 minutes after a pre-bolus of 0.25 mmol/kg Gadobutrol. MRS was performed as a 2D multivoxel chemical-shift imaging technique based on a point-resolved spectroscopy MR sequence with an echo time of 135 ms over a central slice of the tumor, including contrast-enhancing parts if present. We used syngo.via® (Siemens Healthcare, Erlangen, Germany) to semi-automatically calculate the cerebral blood volume from the perfusion raw data (including software-based leakage correction) and to assess the spectroscopy data. For the ^{18}F-FET PET, a 40-min dynamic emission recording in 3D mode consisting of 16 frames was started on injection of approximately 185 MBq ^{18}F-FET. Dynamic and static PET data were reconstructed according to our clinical protocol using an 3D ordererd subset expectation maximization algorithm and corrections for attenuation, scatter, random and dead time. ^{18}F-FET PET images analysis was performed as described previously and included the evaluation of both dynamic data (0-40 min p.i.) and static images (summation of PET images between 20-40 min p.i.) (*21*). ^{18}F-FET tracer kinetics and maximum tumor-to-background ratio (TBRmax) were assessed using a dedicated

software package (Hermes Medical Solutions, Stockholm, Sweden) following the current Joint EANM/EANO/RANO practice guidelines (*22*). To minimize MR-related AC artifacts (especially for the kinetic analysis), we used a threshold-based segmentation with high thresholds, only defining the most metabolic active areas (*23*). The final interpretation of the multiparametric imaging results was produced by a board-certified neuro-radiologist and nuclear medicine specialist in a clinical-routine consensus session blinded to the future clinical course. Consensus reading routinely includes several measures: the presence of MR contrast enhancement, visual hyperperfusion in DSC-MRI, visually increased Cholin/N-acetyl-aspartate ratio in MRS, TBRmax in static ^{18}F-FET PET, and presence of a washout curve in the kinetic PET analysis. For evaluating the accuracy of single modalities, we focused on the presence of the results mentioned above from the original PET/MR reports.

Our patient cohort was divided into two main categories following the indication of ^{18}F-FET PET/MR: newly diagnosed tumors and progressive disease during or after post-operative therapy. To evaluate ^{18}F-FET PET/MR prediction metrics, we used histological confirmation or the disease course based on follow-up examinations as ground truth. At the new diagnosis, we rated if malignancy (World Health Organization (WHO) grades III and IV) was present or not. At detection of progression, we defined two dichotomic outputs: true progression or remission. In cases with follow-up as the reference standard, malignancy or true progression was defined by the continuing imaging expansion of a tumor beginning within three months after ^{18}F-FET PET/MR - the standard period until the first imaging follow-up, or by patient death within six months. The absence of malignancy or progression was defined as clinically stable disease or regression without therapy for at least six months. We judged other follow-up constellations as

not assessable, e.g., remission under continued or new therapy. Here, therapeutic effect on a vital tumor cannot be differentiated from the natural course of therapy-related changes. To estimate the impact of PET/MR on clinical management, we tabulated the treatment changes after the disclosure of the imaging results (see Table 1). We assessed if ^{18}F-FET PET/MR was causative for a treatment change. For example, we rated ^{18}F-FET PET/MR as decisive if MRI could not determine true progression based on the RANO criteria (*24,25*), but not if a treatment change was recommended before the examination but realized only afterward.

Statistical Analysis

We tabulated a confusion matrix using the ^{18}F-FET PET/MR respectively single modalities outcomes and the reference standard and calculated commonly used performance metrics. Missing measurements (for example, due to technical failure) were counted as false outcomes since they did not help solve the diagnostic question. For calculating the diagnostic performance of static ^{18}F-FET PET, we used the established cut-off value TBRmax=2.5 at new diagnosis (*22*). At detection of progression, we performed receiver operating characteristics analysis for the optimal TBRmax cut-off value, as there is no general recommendation covering a heterogeneous patient cohort. We calculated the contribution of single modalities for predicting best the reference outcome by multiple logistic regression analysis. We noted the percentage of cases with treatment changes based on ^{18}F-FET PET/MR. JMP 15.1 (SAS, Cary, CN, USA) and statpages.org served as tools for the statistical calculations. Besides, we used sankeymatic.com for building the Sankey diagrams.

RESULTS

Patients

A total of 172 brain tumor patients (median age 53 years, range 4-86 years, 71 females) received 201 ^{18}F-FET PET/MR examinations in the years 2017 and 2018. Seventeen patients underwent two, six patients three, and 149 patients one examination. Finally, we included 189 ^{18}F-FET PET/MR examinations for evaluating the impact on clinical management and 158 for assessing the diagnostic performance (see Figure 1 with a flow chart, Supplemental Table 1 for the specific tumor pathologies, and Supplemental Table 2 for the imaging characteristics of the lesions). Histological confirmation served as the reference standard in 32% of the cases (51/158, median interval to the PET/MR 17 days, range 0-113 days), and clinical and imaging follow-up in 68% (107/158, median duration 14 months, range 0-45 months). Overall, ^{18}F-FET PET/MR reached an accuracy of 91% (95% confidence interval (CI) 85-95%) and changed the clinical management in 47% of the cases (88/189, CI 40-54%).

^{18}F-FET PET/MR at a New Diagnosis

This category included 58 ^{18}F-FET PET/MR examinations. The indications leading to ^{18}F-FET PET/MR consisted of: grading of inhomogeneous masses with predominantly low-grade features (24%, 14/58); grading in tumor-locations at risk for surgery complications (14%, 8/58), identification of hotspots for biopsies (16%, 9/58); or differentiation of glioma from other entities (47%, 27/58). The accuracy of ^{18}F-FET PET/MR for identifying malignancy reached 85%,

and the clinical management changed in 33% of the cases (19/58, CI 22-46%, see Table 2 and Figure 2 for details).

^{18}F-FET PET/MR at Detection of Progression

A total of 131 ^{18}F-FET PET/MR examinations were performed during the disease course. The mean disease duration was 2¼ years, and 79% (104/131) of the patients had undergone surgery. The number of previously received treatments was tabulated as follows: one standard adjuvant therapy, either combined radio-chemotherapy, radiation, or chemotherapy (27%, 36/131); one advanced immunotherapy or experimental treatment (2%, 3/131); two or more standard adjuvant therapies (15%, 19/131); standard and advanced therapy (21%, 28/131); or no adjuvant therapy within the last year (34%, 45/131). The medical history leading to ^{18}F-FET PET/MR was categorized as follows: baseline status before a new therapy (9%, 12/131); first progression under the current therapy through MR imaging (53%, 70/131) or with clinical symptoms (2%, 3/151); slight ongoing imaging progression (13%, 17/131); alternating imaging progression and regression (4%, 5/131); and ongoing imaging progression initially rated as therapy-associated change (18%, 24/131). ^{18}F-FET PET/MR reached an accuracy of 93% in identifying true progression and changed the clinical management in 53% (69/131, CI 44-61%) of the cases (see Table 2 and Figure 3 for details).

The largest subgroup in this category constituted 62 IDH-wildtype high-grade gliomas (anaplastic astrocytomas WHO grade III and glioblastomas WHO grade IV). Here, the prevalence of true progression was 90%, which was detected with an accuracy of 96% (CI 87-100%) through

of ^{18}F-FET PET/MR. Subsequently, the clinical management changed in 47% of these patients (29/62, CI 35-59%).

Contribution of Single Modalities to an Optimal Disease Prediction

MRS was the modality with the most artifacts (26%, 49/189), often because of unfavorable lesion localization for the acquisition or measurement missing the hotspot in large lesions (Supplemental Table 3 lists the artifacts of all modalities). At a new diagnosis, static ^{18}F-FET PET and contrast enhancement yielded the highest accuracies as single modalities (83% and 79%). They also contributed most to an optimal disease prediction (p=0.002, and p=0.001). At detection of progression, contrast enhancement and static ^{18}F-FET PET yielded the highest accuracies (80% and 79%). ^{18}F-FET kinetics and static ^{18}F-FET PET contributed most to an optimal disease prediction (p=0.006, and p=0.009; see Supplemental Table 4 and Table 3 for further details). Multiparametric ^{18}F-FET PET/MR using standardized criteria yielded an accuracy of 87% at new diagnosis and 89% at detection of progression.

DISCUSSION

The accuracy of ^{18}F-FET PET/MR to identify malignancy at a new diagnosis was 85%. The slightly lower sensitivity (78%) and slightly superior specificity (89%) than in a prior ^{18}F-FET PET meta-analysis might be due to a more conservative interpretation of imaging findings in our study (*1*). The high specificity and negative predictive value of ^{18}F-FET PET/MR at new diagnosis might help rule out malignancy in untreated lesions. In accordance, 20% of the examined patients were prevented from further invasive diagnostic procedures. Therefore, ^{18}F-FET PET/MR at new diagnosis may particularly benefit the significant proportion of patients with non-malignant brain tumors, for whom a watch-and-wait strategy is sufficient. MR contrast enhancement and static ^{18}F-FET PET contributed most to the ^{18}F-FET PET/MR outcome at new diagnosis. Surprisingly, the diagnostic performance of static ^{18}F-FET PET was almost as high as of ^{18}F-FET PET/MR. Also, the proportion of clinical management changes in 33% of the patients by ^{18}F-FET PET/MR was in the range of prior reports for ^{11}C-Methionine PET alone with clinical management changes in 30-63% of the patients (*11,14*). Therefore, adding a static amino acid PET to an existing MR examination might be a cost-effective alternative to the multiparametric examination. Still, different studies revealed the additional value of dynamic ^{18}F-FET-PET for initial glioma staging and this topic needs further evaluation (*26-28*).

At detection of progression, ^{18}F-FET PET/MR reached an accuracy of 93%. The prevalence of true progression with 80% was high per se in our cohort. Nevertheless, ^{18}F-FET PET/MR still improved diagnostic validity. The positive predictive value reached nearly 100%, and the sensitivity (93%) and specificity (95%) were in the range of prior reports with amino acid PET/MR (*29,30*). Dynamic ^{18}F-FET PET was the crucial component of the multiparametric

examination at detection of progression. Nevertheless, the diagnostic performance of multiparametric ^{18}F-FET PET/MR surpassed every single modality, and consensus reading with an individual interpretation of the results further improved the diagnostic security. ^{18}F-FET PET/MR may save time by identifying true progression in lesions with first-time imaging progression during adjuvant therapy, whereas the RANO criteria require confirmation by follow-up MR imaging. This condition applied to more than half of our patients at detection of progression. The prompt diagnosis accelerates effective therapy decisions, benefiting patients with a severely reduced life expectancy. Additionally, ^{18}F-FET PET/MR can clear the nature of equivocal disease courses under therapy, another common condition in our cohort. ^{18}F-FET PET/MR changed the clinical management in 53% of the cases at detection of progression, primarily resulting in an altered therapy stratification. This proportion was slightly higher than in a previous study with ^{11}C-Methionine PET (*11*). Based on our results, the particular benefit of multiparametric ^{18}F-FET PET/MR may be the confirmation of true progression since false-positive outcomes are scarce.

The full potential of advanced MR techniques as components of ^{18}F-FET PET/MR might not have unfolded in this study as specialized studies reported higher accuracies (*31,32*). DSC-MRI and MRS were hindered by acquisition failures and a lack of standardized quantification and might be of minor importance than amino acid PET according to our results. Future multicenter studies might explore the most efficient modality combination of ^{18}F-FET PET/MR in glioma and if the clinical impact is higher than with a separate acquisition of the modalities (*11,33*). Furthermore, we did not investigate the patient outcome and cost-effectiveness directly in our study. However, it seems reasonable that waiving unnecessary invasive procedures and fast-

tracking clinical management decisions are beneficial (*11,34*). Adding ^{18}F-FET PET to MR, for example, in a hybrid scanner, has been reported to be reasonable in terms of cost-effectiveness in selected patients (*35-37*). Further studies considering these aspects might evaluate finally if ^{18}F-FET PET/MR as a hybrid modality qualifies for evidence-based use in clinical routine.

Our study has several limitations. The results when performing ^{18}F-FET PET/MR examinations on clinical demand may differ from a randomized controlled trial. Our patient cohort was heterogeneous, and we did not evaluate specific histological entities separately. The used AC for PET might have a minor impact on TBRmax and tracer kinetics, especially in patients with borderline findings. However, it can be minimized by a careful assessment of the multimodal data sets (*23*). Partially missing recommendations and clinical applications for standardized acquisition, image post-processing, assessment, or quantification might lead to over- or underestimating the diagnostic performance of single modalities (*38*). A stepwise assessment of the single parameters' incremental value might better identify the most efficient composition of multiparametric ^{18}F-FET PET/MR. Therefore, the exact data of this study are not generally transferable. However, it provides an exemplary insight into the actual impact of ^{18}F-FET PET/MR on clinical management of brain tumor patients outside clinical trials.

CONCLUSION

In conclusion, ^{18}F-FET PET/MR has high accuracy in clarifying equivocal conditions of brain tumor patients, particularly at detection of progression. The clinical value of a simultaneous examination and the optimal modality combination need further exploration. At a new diagnosis, ^{18}F-FET PET/MR appears to help rule out malignancy, with separate static ^{18}F-FET PET having a comparable accuracy. During the disease course, ^{18}F-FET PET/MR facilitates clinical management by distinguishing between true tumor progression and therapy-related alterations.

FINANCIAL DISCLOSURE

GT has served on advisory boards of AbbVie, Bayer and BMS; received consulting fees from AbbVie, Bayer; received speaker fees from Medac and Novocure; received travel grants from Novocure, Medac and BMS; received research grants from Roche Diagnostics and Medac, all not related to this work. ClF has served on advisory boards of AAA, Bayer, ImaginAB, and SIRTEX; received consulting fees from Astellas and IPSEN; received research grants from GE Healthcare, Siemens Healthineers, and Oncovision, all not related to this work. The other authors declare no conflict of interest.

ACKNOWLEDGEMENTS

The work was funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy -EXC 2180–390900677.

KEY POINTS

Question: Does ^{18}F-FET PET/MR improve the clinical management of brain tumor patients with equivocal findings?

Pertinent Findings: We retrospectively evaluated the diagnostic performance of ^{18}F-FET PET/MR and its impact on clinical management at a new diagnosis of brain tumors and detection of progression. ^{18}F-FET PET/MR identified malignancy or true progression with an accuracy of 91% and changed the clinical management in 47% of the cases.

Implications for Patient Care: ^{18}F-FET PET/MR as add-on diagnostics for equivocal findings in brain tumors might improve patients' outcome by increasing the diagnostic certainty and leading to prompt changes in the clinical management at different disease stages.

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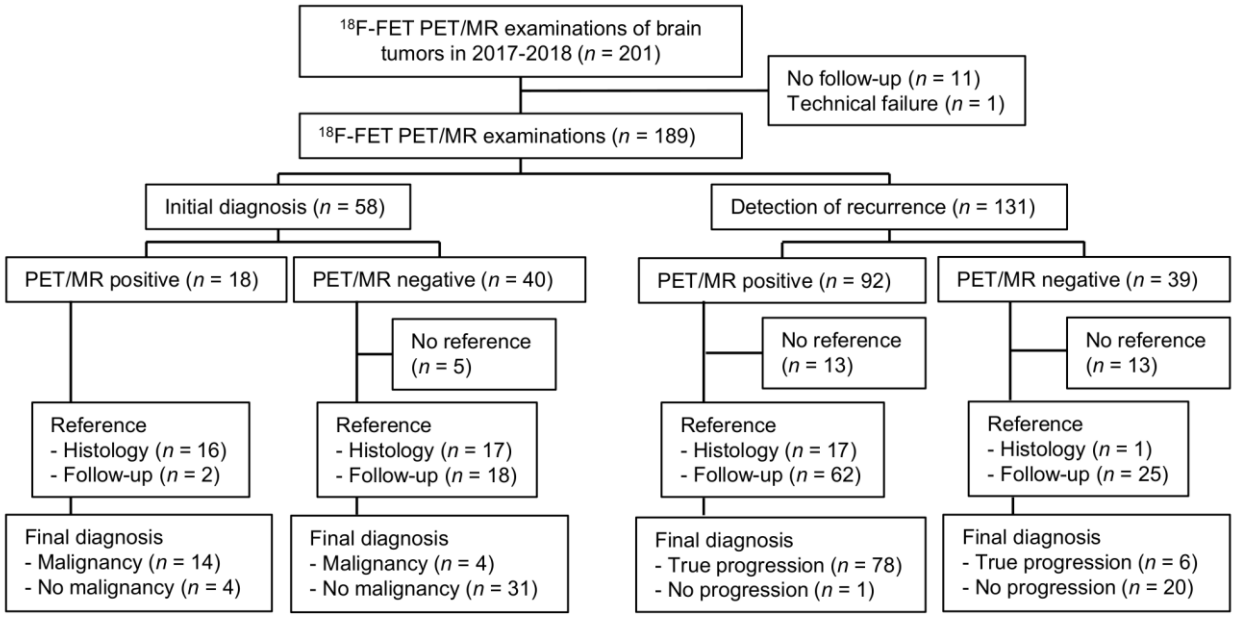


FIGURE 1: Flowchart presenting the inclusion process of patients.

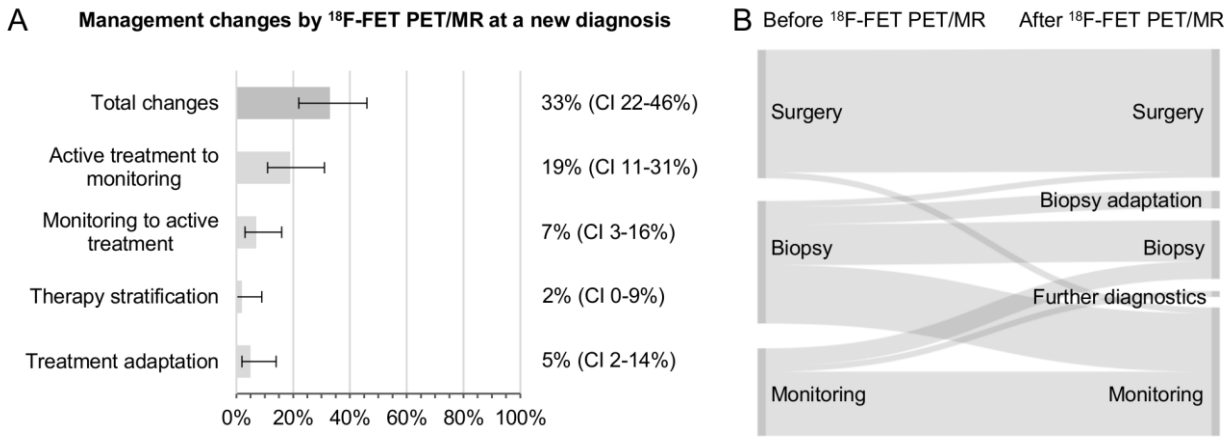


FIGURE 2: A) Frequency (percentage with 95% confidence intervals (CI)) of clinical management changes based on ^{18}F-FET PET/MR outcome at a new tumor diagnosis, categories as explained in Table 1, B) Sankey diagram showing the therapies recommended before and applied after ^{18}F-FET PET/MR at new diagnosis.

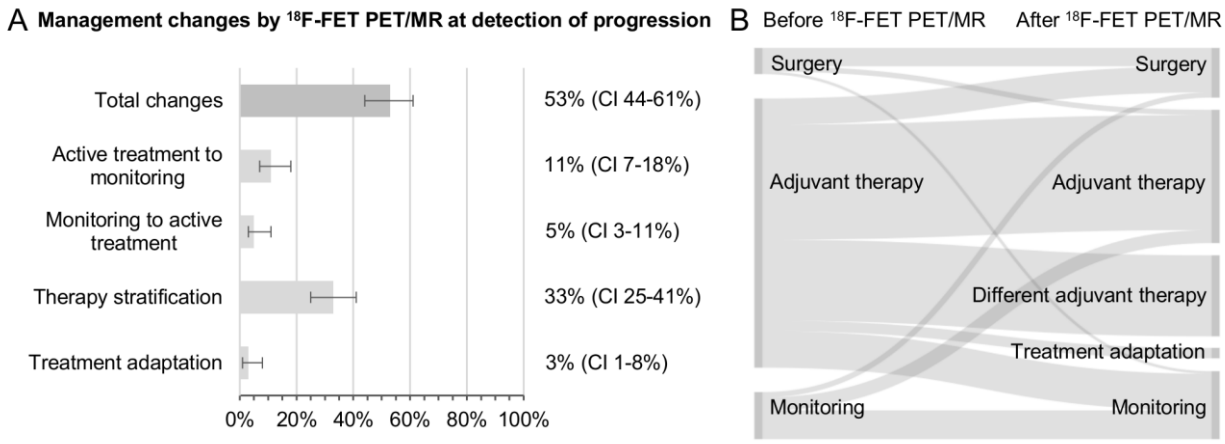


FIGURE 3: A) Frequency (percentage with 95% confidence intervals (CI)) of clinical management changes based on ^{18}F-FET PET/MR outcome at detection of brain tumor progression, categories as explained in Table 1, B) Sankey diagram showing the therapies recommended before and applied after ^{18}F-FET PET/MR at detection of progression.

TABLES

TABLE 1: Categories of clinical management changes based on ^{18}F-FET PET/MR

Management change	Criteria
Active treatment to monitoring	- Waiving of invasive diagnostics for tumor characterization - Waiving of surgery or adjuvant therapy during the disease course
Monitoring to active treatment	- Subsequent invasive diagnostics - Treatment start
Therapy stratification	- Shift from adjuvant therapy to surgery or reversely, or change of the adjuvant treatment - Begin of or waiving an additional adjuvant treatment - Waiving a planned change and continuing the present treatment
Treatment adaptation	- Change of the location or extent of biopsy or resection - Adjustment of the irradiation volume or the chemotherapy dose

TABLE 2: Diagnostic performance of ^{18}F-FET PET/MR in the clinical setting

Parameter	New diagnosis	Detection of progression
Total case number	53	105
Disease prevalence	34%	80%
True-positive/true-negatives	14/31	78/20
False-positives/false-negatives	4/4	1/6
Sensitivity*	78% (CI 52-94%)	93% (CI 85-97%)
Positive predictive value*	78% (CI 57-90%)	99% (CI 92-100%)
Specificity*	89% (CI 73-97%)	95% (CI 76-100%)
Negative predictive value*	89% (CI 76-95%)	77% (CI 61-88%)
Accuracy*	85% (CI 72-93%)	93% (CI 87-97%)

* With 95% confidence intervals (CI)

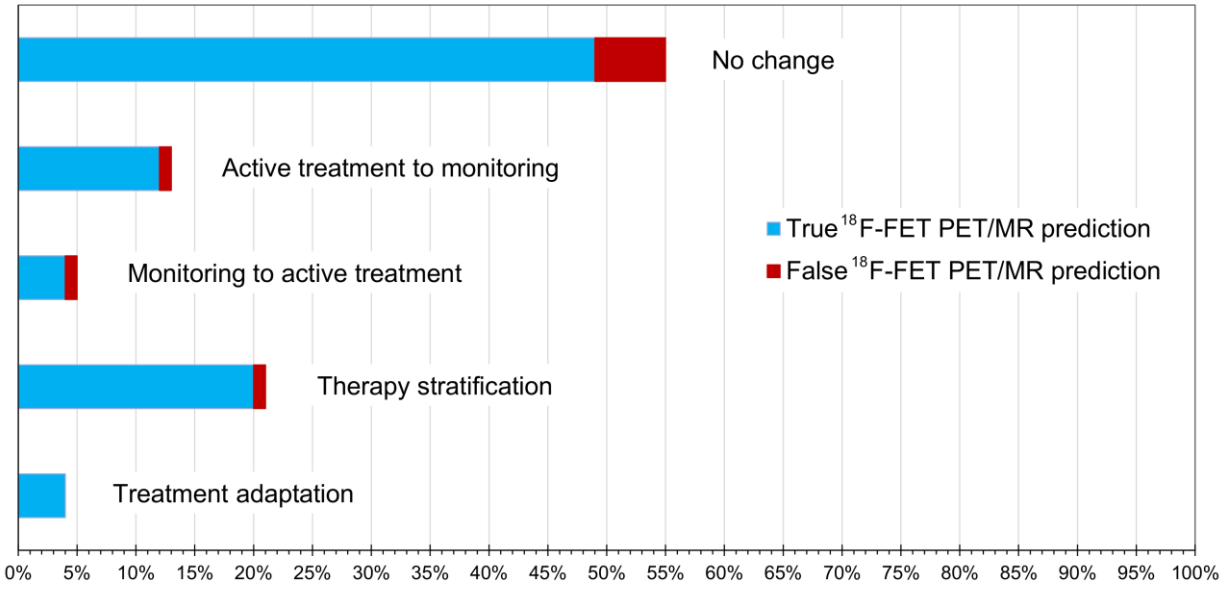
TABLE 3: Contribution of single modalities in multiparametric ^{18}F-FET PET/MR to predict the outcome

Parameter	New diagnosis (p-value)	Detection of progression (p-value)
MR contrast enhancement	0.001*	0.735
DSC-MRI	0.480	0.411
MRS	0.229	0.814
Static ^{18}F-FET PET	0.002*	0.009*
^{18}F-FET tracer kinetics	0.939	0.006*

* Significant p-values in multiple logistic regression

DSC-MRI, dynamic susceptibility perfusion MRI; MRS, ^{1}H-MR spectroscopy.

Graphical Abstract



SUPPLEMENTAL TABLE 1: Frequency of the different pathologic tumor entities

Pathologic tumor entity*	New diagnosis	Detection of progression
Astrocytoma, NOS	1	
Diffuse astrocytoma, IDH-mutant	3	11
Diffuse astrocytoma, IDH-wildtype	3	2
Anaplastic astrocytoma, IDH-mutant	2	7
Anaplastic astrocytoma, IDH-wildtype	5	16
Anaplastic astrocytoma, NOS		1
Glioblastoma, IDH-wildtype	8	46
Glioblastoma, IDH-mutant	2	10
Glioblastoma, NOS		2
Diffuse midline glioma, H3 K27M-mutant	1	
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	6	17
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted		8
Pilocytic astrocytoma	1	1
Anaplastic ependymoma		1
Ganglioglioma		1
Chondrosarcoma		1
Carcinosarcoma		1
B-cell lymphoma	1	
Metastases		4
Focal cortical dysplasia	1	
Gliosis, no tumor		1
Inconclusive pathology	1	
No pathologic diagnosis available	23	1

* Specification according to the WHO 2016 classification of central nervous system tumors where applicable

Abbreviations: NOS, not otherwise specified; IDH, isocitrate dehydrogenase.

SUPPLEMENTAL TABLE 2: Tumor characteristics in the single modalities

Modality	**New diagnosis (malignancy)**		**Detection of progression**	
Reference standard	Positive	Negative	Positive	Negative
Total number	18	35	84	21
LA x SA FLAIR (cm^2, median [range])	11.5 [3.5-19.8]	4.0 [0.7-35.2]	11.5 [0.5-70]	5.1 [1.6-28.1]
MR contrast enhancement (n)*	14/18	6/35	72/84	9/21
LA x SA MR-CE (cm^2, median [range])	0.7 [0.2-6.1]	0.3 [0.1-0.7]	5.0 [0.1-46.7]	0.6 [0.3-1.4]
Hyperperfusion (DSC-MRI; n)*	12/18	6/35	52/79	2/19
Increased Cho/NAA (MRS; n)*	10/17	10/31	44/66	6/18
TBRmax (static ^{18}F-FET PET; median [range])	3.4 [1.5-4.9]	1.6 [1.0-6.5]	3.0 [1.0-6.2]	1.2 [0.9-3.0]
^{18}F-FET washout kinetics (n)*	10/18	5/35	62/83	2/20

* Measurements were not assessable in all patients because of artifacts (see Supplemental Table 3)

Abbreviations: FLAIR, fluid-attenuated inversion recovery; LA, longitudinal axis; SA, short axis; n, number; MR-CE, MR contrast enhancement; DSC-MRI, dynamic susceptibility perfusion; Cho/NAA, Choline/N-acetyl-aspartate ratio; MRS, ^{1}H-MR spectroscopy; TBRmax, maximum tumor-to-background ratio; ^{18}F-FET, ^{18}F-fluor ethyl tyrosine.

SUPPLEMENTAL TABLE 3: Imaging artifacts in the single modalities

Modality	Number*	Characteristics
Standard MRI	0	
DSC-MRI	8	Limited validity, n=5 Small lesions, n=2
	9	Technical failure, n=3 Not measured (unknown reason), n=2 Patient motion, n=1 Examination disruption by patient, n=1
MRS	15	Limited validity, n=15
	26	Not measurable tumor localization, n=11 Measurement of divergent tumor area, n=9 Not measured (unknown reason), n=4 Patient motion, n=1 Small lesion, n=1
MR-based AC of ^{18}F-FET PET (within tumor area)	8†	Tissue class bone, n=4 Tissue class fat, n=3 Tissue classes bone and fat, n=1
^{18}F-FET kinetics evaluation	2	Limited validity, n=2
	2	Patient motion, n=2

* Differentiation of artifacts where we could evaluate the measurement and lacking measurements

† We could not evaluate retrospectively the AC artifacts in 37 cases

Abbreviations: DSC-MRI, dynamic susceptibility perfusion; MRS, ^{1}H-MR spectroscopy; AC, attenuation correction; ^{18}F-FET, ^{18}F-fluor ethyl tyrosine.

SUPPLEMENTAL TABLE 4: Performance of metrics the single modalities and the multiparametric ^{18}F-FET PET/MR using standardized criteria

	Sensitivity*	Specificity*	PPV*	NPV*	Accuracy*
New diagnosis					
MR contrast enhancement	0.78 (0.52-0.94)	0.80 (0.63-0.92)	0.67 (0.50-0.80)	0.88 (0.74-0.94)	0.79 (0.66-0.89)
DSC-MRI	0.61 (0.36-0.83)	0.83 (0.66-0.93)	0.65 (0.45-0.81)	0.81 (0.69-0.88)	0.75 (0.62-0.86)
MRS	0.56 (0.31-0.78)	0.60 (0.42-0.76)	0.42 (0.29-0.56)	0.72 (0.59-0.82)	0.58 (0.44-0.72)
TBRmax (static ^{18}F-FET PET)	0.67 (0.41-0.87)	0.91 (0.77-0.98)	0.80 (0.56-0.93)	0.84 (0.73-0.91)	0.83 (0.70-0.92)
^{18}F-FET kinetics	0.56 (0.31-0.78)	0.86 (0.70-0.95)	0.67 (0.45-0.83)	0.79 (0.69-0.86)	0.75 (0.62-0.86)
Multiparametric ^{18}F-FET PET/MR†	0.67 (0.41-0.87)	0.97 (0.85-1.0)	0.92 (0.63-0.99)	0.85 (0.75-0.92)	0.87 (0.75-0.95)
Detection of progression					
MR contrast enhancement	0.86 (0.76-0.92)	0.57 (0.34-0.78)	0.89 (0.83-0.93)	0.50 (0.35-0.66)	0.80 (0.71-0.87)
DSC-MRI	0.60 (0.48-0.70)	0.81 (0.58-0.95)	0.93 (0.84-0.97)	0.33 (0.26-0.41)	0.64 (0.54-0.73)
MRS	0.52 (0.41-0.63)	0.57 (0.34-0.78)	0.83 (0.74-0.89)	0.23 (0.16-0.32)	0.53 (0.43-0.63)
TBRmax (static ^{18}F-FET PET)‡	0.79 (0.68-0.87)	0.81 (0.58-0.95)	0.94 (0.87-0.98)	0.49 (0.37-0.60)	0.79 (0.70-0.86)
^{18}F-FET kinetics	0.71 (0.61-0.81)	0.86 (0.64-0.97)	0.95 (0.87-0.98)	0.43 (0.34-0.52)	0.74 (0.65-0.82)
Multiparametric ^{18}F-FET PET/MR†	0.92 (0.84-0.97)	0.76 (0.53-0.92)	0.94 (0.88-0.97)	0.70 (0.52-0.83)	0.89 (0.81-0.94)

* with 95% confidence intervals

† based on a multiple logistic regression model

‡ using a cut-off value of TBRmax=2.2 as derived from receiver operating characteristic analysis

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; DSC-MRI, dynamic susceptibility perfusion; MRS, ^{1}H-MR spectroscopy; TBRmax, maximum tumor-to-background ratio; ^{18}F-FET, ^{18}F-fluor ethyl tyrosine.