Diagnostic Accuracy of MR Spectroscopic Imaging and 18F-FET PET for Identifying Glioma: A Biopsy-Controlled Hybrid PET/MRI Study

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Contrast-enhanced MRI is the method of choice for brain tumor diagnostics, despite its low specificity for tumor tissue. This study compared the contribution of MR spectroscopic imaging (MRSI) and amino acid PET to improve the detection of tumor tissue. **Methods:** In 30 untreated patients with suspected glioma, O-(2-[18F]fluoroethyl)-L-tyrosine (18F-FET) PET; 3-T MRSI with a short echo time; and fluid-attenuated inversion recovery, T2-weighted, and contrast-enhanced T1-weighted MRI were performed for stereotactic biopsy planning. Serial samples were taken along the needle trajectory, and their masks were projected to the preoperative imaging data. Each sample was individually evaluated neuropathologically. 18F-FET uptake and the MRSI signals choline (Cho), N-acetyl-aspartate (NAA), creatine, myoinositol, and derived ratios were evaluated for each sample and classified using logistic regression. The diagnostic accuracy was evaluated by receiver operating characteristic analysis. **Results:** On the basis of the neuropathologic evaluation of tissue from 88 stereotactic biopsies, supplemented with 18F-FET PET and MRSI metrics from 20 areas on the healthy-appearing contralateral hemisphere to balance the glioma/nonglioma groups, 18F-FET PET identified glioma with the highest accuracy (area under the receiver operating characteristic curve, 0.89; 95% CI, 0.81–0.93; threshold, 1.4 × background uptake). Among the MR spectroscopic metabolites, Cho/NAA normalized to normal brain tissue showed the highest diagnostic accuracy (area under the receiver operating characteristic curve, 0.81; 95% CI, 0.71–0.88; threshold, 2.2). The combination of 18F-FET PET and normalized Cho/NAA did not improve the diagnostic performance. **Conclusion:** MRSI-based delineation of gliomas should preferably be supplemented by 18F-FET PET.

**Key Words:** MR spectroscopic imaging; 18F-FET PET; brain tumors; multimodal imaging; stereotactic biopsy

Currently, contrast-enhanced MRI is the method of choice for diagnosis and treatment monitoring in patients with brain tumors (1), but differentiation between the tumor center, infiltration zone, and peritumoral tissue changes, such as edema, may be challenging, particularly in patients with nonenhancing gliomas (2). Consequently, accurate delineation of glioma extent based on conventional MRI alone may be challenging. Accurate imaging-based tumor localization is essential for treatment planning and for identifying the most metabolically active parts for biopsy planning (3,4), especially when biopsy sampling is difficult, such as in the brain stem (5).

Advanced MRI methods and amino acid PET are of value to obtain additional diagnostic information in clinically challenging situations (6). In brain tumor diagnostics, amino acid PET has been recommended by the Response Assessment in Neuro-Oncology Working Group as a supplement to structural MRI (7). In contrast to 18F-FDG, uptake of radiolabeled amino acids is low in normal brain tissue, and brain tumors can be depicted with high tumor-to-background contrast. A key feature of common amino acid tracers such as O-(2-[18F]fluoroethyl)-L-tyrosine (18F-FET) is their ability to pass through the intact blood–brain barrier, which enables depiction of the tumor mass beyond contrast enhancement on MRI and of nonenhancing gliomas (6,8). Local maxima of 18F-FET uptake in heterogeneous gliomas usually colocalize with the highest 18F-FDG uptake, but 18F-FET PET is considerably more sensitive than 18F-FDG PET for biopsy guidance (6).

Another approach for detecting neoplastic tissue with high accuracy is the use of metabolic markers derived from MR spectroscopic imaging (MRSI) (9). Most commonly, the MR signal of increased total choline (Cho), which reflects the abnormal Cho
metabolism in cancers (10), is used as a marker of malignant transformation. However, the congruency between the tumor borders delineated by the increased Cho-to-N-acetyl-aspartate (NAA) ratio measured using MRSI, compared with 18F-FET uptake, has been investigated in only a few studies. The comparison of 2-dimensional spatially resolved MRSI and 18F-FET uptake showed a congruency greater than 75% in 15 patients with gliomas (11). In contrast to that finding, a study using 3-dimensional volumetric brain MRSI found a low level of overlap, 40%, and an average distance of 0.9 cm between the centers of mass of both modalities (12).

Recently, the combination of conventional and advanced MRI methods, as well as 18F-FET PET, was investigated in a biopsy-controlled study, but the added value of MRSI could not be assessed because of missing spectroscopic data from the tumor area (13).

The aim of this study was to investigate the diagnostic accuracy of 18F-FET PET and MRSI and their combined use to identify neoplastic tissue in patients with newly diagnosed lesions indicative of glioma, with histopathology as the gold standard. The imaging findings were validated by tissue obtained from spatially correlated stereotactic biopsies, which were mapped into the preoperative imaging data on the basis of coordinates from the stereotactic surgery.

**MATERIALS AND METHODS**

**Patients**

The study was based on a series of 35 consecutive patients with structural MRI findings indicating glioma and in whom a stereotactic biopsy was planned for clinical reasons such as nonenhancing tumors or an unclear differential diagnosis. The patients were scheduled for 18F-FET PET–guided stereotactic biopsy as part of clinical management and underwent hybrid 18F-FET PET/MRSI before biopsy. Patients with incomplete sets of multimodal data or with data of low spectral quality were withdrawn from the study. The study adhered to the standards established in the Declaration of Helsinki and was approved by the ethical committee of the medical faculty of the RWTH Aachen University (EK 096/18). All patients gave written informed consent before the measurement.

**MRI**

All studies were performed on a Siemens 3-T TIM Trio MRI scanner with a Siemens 8-channel head coil. At the time of the 18F-FET PET measurement, T1-weighted MR images were acquired before and after the administration of a gadolinium-based contrast agent (Dotarem; Guerbet) in addition to T2-weighted and fluid-attenuated inversion recovery images. The supplemental materials (available at http://jnm.snmjournals.org) provide further details.

A second contrast-enhanced T1-weighted MRI scan was acquired just before the stereotactic surgery, and a cranial CT scan was conducted with the attached stereotactic frame for biopsy planning.

**MRSI**

The high-resolution 3-dimensional volumetric MRSI acquisition covered the cerebrum and used a spin-echo excitation with echo-planar readout (14), an echo time of 17.6 ms, an acquisition time of 16 min, and integrated lipid and water suppression. The metabolite signals were scaled with an unsuppressed water reference signal from interleaved measurements. The supplemental materials provide further details.

**PET Imaging**

The amino acid 18F-FET was produced and applied as described previously (15). All patients fasted for at least 12 h before the PET measurement and were injected intravenously with 3 MBq of 18F-FET per kilogram of body weight. The dynamic 18F-FET PET acquisition over 50 min was performed using a Siemens BrainPET insert (16). The supplemental materials provide further details. All reconstructed frames (isotropic resolution, 1.25 mm) were smoothed with a 2.5-mm gaussian kernel, and motion was corrected using PMOD (version 3.5; PMOD Technologies LLC). The summed images from 20 to 40 min after injection were used for the analysis.

**Stereotactic Biopsies**

Before stereotactic biopsy, contrast-enhanced MRI and 18F-FET PET were spatially registered on an intraoperatively obtained cranial CT scan as a basic image for planning the biopsy trajectory. The trajectory targeted the area with the highest 18F-FET uptake while avoiding vessels and eloquent brain areas. The samples were classified or reclassified according to the 2021 World Health Organization (WHO) classification of tumors of the central nervous system taxonomy (supplemental materials) (17). The biopsies were taken an average of 11 d after the PET measurements (SD, 11 d; minimum, 3 d; maximum, 56 d).

For ethical reasons, samples could not be taken from healthy brain tissue; thus, the number of control samples was underrepresented. To balance the groups of samples for statistical analysis, virtual negative biopsies (i.e., the noninvasive examination of healthy-appearing contralateral brain regions using 18F-FET PET and MRSI) were performed on the contralateral side. The supplemental materials provide further details.

**Data Analysis**

The spectroscopic data were reconstructed using the Metabolite Imaging and Data Analysis System software package (18). After the interpolation of the raw data to 64 × 64 × 32 voxels (4.375 × 4.375 × 5.625 mm³), a final spatial resolution of 108 mm² was gained. The data were transformed into volumetric metabolite maps using automatic spectral analysis and after signal normalization to the simultaneously acquired water reference signal (19). The maps comprised the metabolite distributions of Cho, creatine (Cr), NAA, and myo-inositol (mI). For the final analysis, ratio maps of Cho/NAA, NAA/Cr, Cho/Cr, and mI/Cr were calculated.

The 18F-FET PET data, the MRSI data, all other MRI data, and the biopsy track masks were registered to the T1-weighted data. Masks of the tumor and the surrounding edema were manually delineated on the basis of the fluid-attenuated inversion recovery and T2-weighted data (22) and used to keep the normalization to the water signal devoid of distortions caused by the edema of the tumor tissue.

The 18F-FET uptake and MRSI metabolite data were normalized to the respective background signals, which were given by the mean signal outside the area delineated by the previously described tumor masks. This procedure is referred to below as normalization to normal-appearing tissue. The normalized 18F-FET images, 18F-FETn, (in this paper, signals normalized to normal-appearing tissue signal levels are denoted by subscript “n”), were resampled to the resolution of the metabolite maps. In addition to the normalized metabolite values, the nonnormalized values were analyzed to enable comparison with literature values.

The biopsy masks were down-sampled to match the spatial resolution of the spectroscopic data. Voxels with a biopsy partial volume of less than 50% or an underlying spectral line width outside the interval from 3 to 12 Hz were excluded from further analysis.

The histologic findings “glial tumor” and “infiltration zone” were labeled as tumor tissue in terms of PET/MRSI. Benign results and findings that were positive only on the microscopic scale, such as “proliferated brain tissue with tumor cells,” were considered negative.

The threshold for neoplastic tissue based on different metabolite combinations or 18F-FET uptake was determined by logistic regression as described in the supplemental materials.
RESULTS

From July 2018 to September 2020, a series of 35 patients with suspected brain tumors was recruited for the study. After the exclusion of 4 patients because of low spectral quality and 1 patient because of missing biopsy coordinates, the analyzed group included 30 patients (14 women and 16 men) with an average age (±SD) of 48 ± 13 y (range, 27–82 y).

Supplemental Table 1 shows the individual characteristics and neuropathologic diagnoses according to the 2021 WHO classification of tumors of the central nervous system, and Supplemental Table 2 shows patients excluded because of insufficient spectral quality. In total, 9 patients with enhancing gliomas, 15 patients with nonenhancing gliomas, 2 patients with enhancing lesions other than gliomas, and 4 patients with nonglioma lesions without contrast enhancement were included.

Patient 4 had the contradicting findings of vasculitis, contrast enhancement, and high 18F-FET uptake (2.6). Because the follow-up biopsy 18 mo later showed a glioblastoma (IDH wild-type; central nervous system WHO grade 4), the first biopsy was considered a sampling error, and the later diagnosis was used.

Per patient, 2.9 ± 1.2 (range, 2–7) cylindric specimens with a diameter of 2.8 mm and a length of 5–10 mm were obtained along 1–2 biopsy trajectories. Eighteen biopsies were excluded because of the low spectral quality of the corresponding MR spectrum. The 18F-FET PET and MRSI data were acquired 13 ± 12 d before the biopsies, and the T1-weighted series for biopsy planning was measured 3 ± 5 d before surgery. In total, 108 multimodal data-sets, comprising 88 real biopsies supplemented with 20 virtual negative biopsies, were included in the analysis. Fifty-four biopsies were neuropathologically evaluated as glioma tissue.

The combined analysis of the markers with the highest accuracy, 18F-FET uptake and Cho/NAA, did not pass the significance threshold of a P value of 0.05 or less. The results may indicate the tendency toward slightly improved accuracy (AUC, 0.90; Cho/NAA shows an example of a multimodal MRSI and 18F-FET PET dataset at spectroscopic imaging resolution and registered to the anatomic T1-weighted data. Because the planning of the biopsy trajectories was based on the 18F-FET uptake and the MRI results but did not take into account the MRSI results, the biopsy sites did not necessarily coincide with the sites of maximum spectroscopic signal (Fig. 2).

Among the analyses of the single-modality data, uptake of 18F-FET resulted in the highest diagnostic accuracy, with an averaged area under the receiver operating characteristic curve (AUC) of 0.89 after cross-validation (SD, 0.003; 95% CI, 0.81–0.93), which is linked to an uptake threshold of 1.4 times the background uptake (Tables 1 and 2).

Generally, the accuracy of the metabolite results generated from MRSI increased by up to 0.06 if the signals were normalized to normal-appearing tissue and additionally to another metabolite signal (such as Cho/NAA). When the diagnostic distinction between glial tumor and normal tissue was based on the spectroscopic marker Cho/NAA, the accuracy decreased to an average AUC of 0.81 (SD, 0.004; 95% CI, 0.71–0.88), based on a Cho/NAA threshold of 2.2. All other analyzed spectroscopic signals, NAA/Cr, Cho/Cr, NAA/Cr (AUC, 0.72), mIno/Cr (AUC, 0.70), and mln/cr (AUC, 0.70), showed lower accuracies. The result of Cr did not pass the significance threshold. The receiver operating characteristic curves of the 5 highest accuracy values are compared in Figure 3.

The combined analysis of the markers with the highest accuracy, 18F-FET uptake and Cho/NAA, did not pass the significance threshold of a P value of 0.05 or less. The results may indicate the tendency toward slightly improved accuracy (AUC, 0.90; Cho/NAA.
term, \( P = 0.3 \) compared with the \(^{18}\text{F}-\text{FET}_n\) uptake (AUC, 0.89) and Cho/NAA\(_n\) (AUC, 0.81) alone. The results obtained after introducing an interaction term between \(^{18}\text{F}-\text{FET}_n\) and Cho/NAA\(_n\) are shown in Supplemental Table 3.

The subgroup analysis of gliomas without contrast enhancement showed a slightly decreased AUC of 0.88 (95% CI, 0.75–0.94) when the diagnosis was based on \(^{18}\text{F}-\text{FET}_n\) uptake and an increased AUC of 0.85 (95% CI, 0.72–0.93) for Cho/NAA\(_n\). Compared with the values from all patients, the threshold values dropped to 1.3 for \(^{18}\text{F}-\text{FET}_n\) and increased to 2.3 for Cho/NAA\(_n\).

Accordingly, compared with the evaluation of the entire group of patients, the restriction to gliomas with contrast enhancement showed a higher diagnostic accuracy for \(^{18}\text{F}-\text{FET}_n\) and a lower accuracy for Cho/NAA\(_n\). \(^{18}\text{F}-\text{FET}_n\)-based diagnosis resulted in an AUC of 0.91 (95% CI, 0.80–0.96; threshold, 1.5). Using Cho/NAA\(_n\) for diagnosis resulted in an AUC of 0.77 (95% CI, 0.61–0.88; threshold, 2.0).

The \(^{18}\text{F}-\text{FET}_n\)-based diagnostics showed more accurate results, with 78% correctly classified samples compared with 71% correct classifications in the leave-one-out cross-validation for Cho/NAA\(_n\) (Table 2). \(^{18}\text{F}-\text{FET}\) had superior sensitivity, 76%, whereas Cho/NAA showed better specificity, 83%. The positive predictive value of

TABLE 1

Results Depending on Different Model Terms in Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Marker</th>
<th>AUC</th>
<th>95% CI</th>
<th>Threshold</th>
<th>( P ) intercept</th>
<th>( P ) slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^{18}\text{F}-\text{FET}_n^*)</td>
<td>0.89</td>
<td>0.81–0.93</td>
<td>1.4</td>
<td>3.7 ( \times ) 10^{-6}</td>
<td>3.4 ( \times ) 10^{-6}</td>
</tr>
<tr>
<td>Cho/NAA(_n^*)</td>
<td>0.81</td>
<td>0.71–0.88</td>
<td>2.16</td>
<td>5 ( \times ) 10^{-4}</td>
<td>2 ( \times ) 10^{-4}</td>
</tr>
<tr>
<td>Cho/NAA(_n^*)</td>
<td>0.79</td>
<td>0.68–0.86</td>
<td>0.65</td>
<td>0.0014</td>
<td>4.8 ( \times ) 10^{-4}</td>
</tr>
<tr>
<td>Cho/Cr(_n^*)</td>
<td>0.72</td>
<td>0.61–0.80</td>
<td>1.65</td>
<td>7.5 ( \times ) 10^{-4}</td>
<td>6.9 ( \times ) 10^{-4}</td>
</tr>
<tr>
<td>Cho/NAA(_n^*)</td>
<td>0.71</td>
<td>0.60–0.80</td>
<td>0.39</td>
<td>8.6 ( \times ) 10^{-4}</td>
<td>8 ( \times ) 10^{-4}</td>
</tr>
<tr>
<td>NAA/Cr(_n^*)</td>
<td>0.78</td>
<td>0.68–0.86</td>
<td>0.76</td>
<td>4.8 ( \times ) 10^{-5}</td>
<td>1.8 ( \times ) 10^{-5}</td>
</tr>
<tr>
<td>NAA/Cr(_n^*)</td>
<td>0.75</td>
<td>0.65–0.84</td>
<td>0.86</td>
<td>1.1 ( \times ) 10^{-4}</td>
<td>2.9 ( \times ) 10^{-5}</td>
</tr>
<tr>
<td>Cho/( \text{mIno} )(_n^*)</td>
<td>0.70</td>
<td>0.59–0.79</td>
<td>0.99</td>
<td>0.006</td>
<td>0.004</td>
</tr>
<tr>
<td>Cho(_n^*)</td>
<td>0.77</td>
<td>0.67–0.85</td>
<td>1.37</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Cho(_n^*)</td>
<td>0.71</td>
<td>0.60–0.80</td>
<td>10,594</td>
<td>0.037</td>
<td>0.024</td>
</tr>
<tr>
<td>NAA(_n^*)</td>
<td>0.74</td>
<td>0.64–0.83</td>
<td>0.66</td>
<td>2.4 ( \times ) 10^{-4}</td>
<td>9 ( \times ) 10^{-5}</td>
</tr>
<tr>
<td>NAA(_n^*)</td>
<td>0.72</td>
<td>0.61–0.81</td>
<td>22,129</td>
<td>0.003</td>
<td>0.001</td>
</tr>
<tr>
<td>( \text{mIno} )(_n^*)</td>
<td>0.70</td>
<td>0.59–0.79</td>
<td>0.87</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>(^{18}\text{F}-\text{FET}_n), Cho/NAA(_n)</td>
<td>0.90</td>
<td>0.82–0.94</td>
<td>NA</td>
<td>2.6 ( \times ) 10^{-6}</td>
<td>6.2 ( \times ) 10^{-5}; 0.305</td>
</tr>
<tr>
<td>(^{18}\text{F}-\text{FET}_n), Cho/NAAn</td>
<td>0.89</td>
<td>0.81–0.94</td>
<td>NA</td>
<td>2.4 ( \times ) 10^{-6}</td>
<td>3.5 ( \times ) 10^{-5}; 0.563</td>
</tr>
</tbody>
</table>

\* \( P < 0.05 \) in all terms of model.
NA = not applicable.
All models contain constant and 1 or 2 linear terms, which represent level of markers \(^{18}\text{F}-\text{FET}, \text{Cho}, \text{NAA}, \text{Cr}, \text{mIno}, \text{and ratios thereof.}
Table is limited to results in which normalized metabolite signal reached AUC of 0.70 or more.

The subgroup analysis of gliomas without contrast enhancement showed a slightly decreased AUC of 0.88 (95% CI, 0.75–0.94) when the diagnosis was based on \(^{18}\text{F}-\text{FET}_n\) uptake and an increased AUC of 0.85 (95% CI, 0.72–0.93) for Cho/NAA\(_n\). Compared with the values from all patients, the threshold values dropped to 1.3 for \(^{18}\text{F}-\text{FET}_n\) and increased to 2.3 for Cho/NAA\(_n\).

Accordingly, compared with the evaluation of the entire group of patients, the restriction to gliomas with contrast enhancement showed a higher diagnostic accuracy for \(^{18}\text{F}-\text{FET}_n\) and a lower accuracy for Cho/NAA\(_n\). \(^{18}\text{F}-\text{FET}_n\)-based diagnosis resulted in an AUC of 0.91 (95% CI, 0.80–0.96; threshold, 1.5). Using Cho/NAA\(_n\) for diagnosis resulted in an AUC of 0.77 (95% CI, 0.61–0.88; threshold, 2.0).

TABLE 2

Results of Leave-One-Out Cross-Validation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>18F-FET</th>
<th>Cho/NAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean AUC ± SD</td>
<td>0.89 ± 0.003</td>
<td>0.81 ± 0.004</td>
</tr>
<tr>
<td>Mean threshold ± SD</td>
<td>1.4 ± 0.001</td>
<td>2.16 ± 0.004</td>
</tr>
<tr>
<td>Accuracy</td>
<td>0.78</td>
<td>0.71</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.76</td>
<td>0.59</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.80</td>
<td>0.83</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>0.79</td>
<td>0.78</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>0.77</td>
<td>0.67</td>
</tr>
</tbody>
</table>

FIGURE 3. Receiver operating characteristic curves of \(^{18}\text{F}-\text{FET}_n\) PET and MRSI metabolic markers Cho/NAA\(_n\), NAA/Cr\(_n\), Cho\(_n\), and NAA\(_n\) based on analysis of 88 biopsies and 20 imaging data points from normal-appearing brain tissue.
18F-FET uptake was similar to that of Cho/NAAn (79% vs. 78%), and its negative predictive value was higher than that of Cho/NAAn (77% vs. 67%).

**DISCUSSION**

The major finding of this study is the higher accuracy of 18F-FET uptake than of Cho/NAAn for the imaging-based diagnosis of tumor tissue in enhancing and nonenhancing gliomas. Glioma delineation was optimal with the 18F-FETn-based tumor-to-background ratio of 1.4 and a Cho/NAAn of at least 2.2.

When 18F-FET uptake was considered, the trend toward the highest diagnostic accuracy was found in enhancing gliomas. Cho/NAAn showed a trend toward higher accuracy in nonenhancing gliomas but still had a lower value than 18F-FETn. Given the relatively low number of patients, the corresponding overlapping 95% CIs do not allow a clear statement and may be responsible for the observed counterintuitive tendency toward lower accuracy for Cho/NAAn in enhancing gliomas. However, the trend toward the higher diagnostic accuracy of 18F-FETn is consistent with previously reported results (13).

Regardess of contrast enhancement, 18F-FET PET–based diagnosis generally showed higher diagnostic accuracy than Cho/NAAn. Hence, 18F-FET PET is significantly more sensitive for identifying glioma tissue, albeit at the cost of a somewhat decreased specificity compared with Cho/NAAn.

The selection of metabolites and derived ratios includes those that can be determined with high accuracy at 3 T (20). The individual signals from Cho and NAA showed lower accuracy than their ratio. This finding is consistent with the finding that although Cho is variably elevated in different glioma types, NAA is reduced nonuniformly as a broad marker of neuronal loss (2/). Compared with Cho/NAAn, the other investigated metabolite signals, Cho, NAA, NAA/Cr, Cho/Cr, mlno, and mlno/Cr, generally showed lower accuracy in diagnosing glioma. Frequently, study results are reported as metabolite ratios, such as Cho/NAAn, without further normalization. This study showed higher accuracies if signal ratios were additionally normalized to normal-appearing tissue.

Four of 35 patients (11%) were excluded from the analysis because of insufficient spectral quality. In addition, 18 samples had to be excluded from the remaining group of 106 samples (17%) for the same reason, which reduces the clinical utility of MRSI.

Within the limitations given by a different patient group, the observed 18F-FET tumor threshold of 1.4 times the background uptake confirms the previously reported value and the widely used threshold of 1.6 (22,23). Besides the fact that the threshold values were determined with different PET scanners and influenced by different point spread functions, the current study included fewer subjects and more patients with gliomas showing equivocal findings on MRI. Therefore, the slightly decreased threshold in our study should be considered with caution and requires further biopsy-controlled studies in larger patient groups.

Relatively few studies have calibrated glioma–to-normal-tissue thresholds using coordinate-controlled biopsies. The found threshold of 0.65 for the absolute Cho/NAAn ratio corresponds to the previously published integral Cho/NAAn ratio (not corrected for proton number) of at least 2, which, however, was determined for a longer echo time (135 ms instead of 17 ms) using spatial 2-dimensional MRSI and approximately the 3-fold measured voxel size from a smaller group of patients (24). Data acquired with an even larger voxel size and long echo time resulted in a minimum ratio of 1.3 (25). This value was obtained from predominantly high-grade gliomas and fits as a lower limit to our threshold value.

The accuracy of the results depends on the decision as to which neuropathologic findings are considered positive for tumor tissue. In the presented analysis, the presence of single tumor cells in the tissue samples was not rated as tumor tissue because such findings are not accessible with either imaging method in view of the limited spatial resolution.

A limitation of this study was the small number of patients and the large proportion of equivocal MRI findings, often due to lack of contrast enhancement. Nevertheless, because diagnosis is particularly difficult in these patients, the importance and value of amino acid PET for this group of patients is further emphasized. A further limitation was the study design, which favored 18F-FET over MRSI; planning of biopsy tracks to target the most metabolically active part of the tumor was based on 18F-FET PET, because MRSI data were not yet available at the time of biopsy. Therefore, the use of MR spectroscopic data for biopsy planning (26,27) could not be properly compared with the use of 18F-FET PET data. A further consequence of the study design was a lack of Cho/NAAn-positive but 18F-FET-negative samples. Therefore, the relevance of a high Cho/NAAn ratio with low 18F-FET uptake—which may indicate gliosis, inflammation, or demyelination (3,28,29) or a later recurrence and reduced progression-free survival (26,30)—remains to be addressed in future studies. Generally, in this study, histology was considered the gold standard for defining the diagnosis since the biopsies were analyzed by 2 experienced neuropathologists according to the 2021 WHO classification of tumors of the central nervous system.

The multimodal approach using MRSI, 18F-FET PET, and neuropathology necessitates the combination of data from the millimeter scale down to the submillimeter scale. Only the 18F-FET PET data can be down-sampled to a spectroscopic imaging resolution, whereas the neuropathologic results are bound to the dimensions of the biopsy cylinders. Accordingly, possible location errors are on this order of magnitude. Since the 18F-FET concentration in the blood compartment is high in the first hour after administration, special attention during the evaluation was placed on ensuring that the 18F-FET signal was not partially confused with an increased signal contribution from blood vessels (15). In rare cases, however, after the resampling of the 18F-FET data to the resolution of the metabolite maps, contamination of the larger voxels cannot be completely ruled out. Moreover, the MRSI data bear the MR spectroscopy inherent chemical shift displacement error. With the given readout gradient of 13.72 mT/m, this error is a fraction of the nominal voxel size in the anterior–posterior direction and, therefore, negligible for the analysis in spectroscopic imaging resolution.

**CONCLUSION**

Amino acid PET using the tracer 18F-FET allows the diagnosis and identification of viable glioma tissue with a high diagnostic accuracy. For a mixed group of enhancing and nonenhancing gliomas, tumor delineation was most accurate with an 18F-FET uptake threshold of 1.4 times the background signal. MRSI provides the highest diagnostic accuracy, with a Cho/NAAn threshold of 2.2. Further data are required to assess the possible diagnostic benefit of the combined analysis of 18F-FET uptake and MR spectroscopic metabolites, such as Cho/NAAn, and to assess the diagnostic meaning of Cho/NAAn-positive but 18F-FET-negative findings.
DISCLOSURE

Norbert Galldiks and Philipp Lohmann received honoraria from Blue Earth Diagnostics for lectures. Norbert Galldiks received honoraria from Telix Pharmaceuticals for advisory board participation. Karl-Josef Langen and Felix Mottaghy received honoraria from Telix Pharmaceuticals for consultancy services. No other potential conflict of interest relevant to this article was reported.

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KEY POINTS

QUESTION: What is the diagnostic accuracy of 18F-FET PET and MRSI for the detection of glioma?
PERTINENT FINDINGS: Validated using tissue samples from stereotactic biopsies, 18F-FET PET identified glioma with an accuracy of 0.89. The MRSI marker Cho/NAA showed a diagnostic accuracy of 0.81.

IMPLICATIONS FOR PATIENT CARE: MRI-based delineation of gliomas should preferably be supplemented by 18F-FET PET.

REFERENCES