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Title:

Diagnosis of glioma recurrence using multiparametric dynamic 18F-Fluoroethyl-Tyrosine PET-MRI

Authors:

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Highlights

- The study introduces combined dynamic 18F-FET-PET/MRI for the diagnosis of recurrence in gliomas
- We demonstrate the feasibility of the approach and evaluate the accuracy of the different modalities in the hybrid imaging protocol
- Multiparametric analysis is shown to be particularly useful at confirming foci of recurrence

Abstract

OBJECTIVES: To investigate the value of combined 18F-fluorethyltyrosine-(FET)-PET/MRI for differentiation between recurrence and treatment-related changes in glioma patients.

METHODS: 63 lesions suggestive of recurrence in 47 glioma patients were retrospectively identified. All patients had a dynamic FET scan, as well as morphologic MRI, PWI and DWI on a hybrid PET/MRI scanner. Lesions suggestive of recurrence were marked. ROC analysis was performed univariately and on parameter combination.

RESULTS: 50 lesions were classified as recurrence, 13 as radiation necrosis. Diagnosis was based on histology in 23 and follow-up imaging in 40 cases. Sensitivities and specificities for static PET were 80 and 85 %, 66 % and 77% for PWI, 62 and 77% for DWI and 64 and 79 % for PET time-to-peak. AUC was 0.86 (p<0.001) for static PET, 0.73 (p=0.013) for PWI, 0.70 (p=0.030) for DWI and 0.73 (p<0.001) for dynamic PET. Multiparametric analysis resulted in an AUC of 0.89, notably yielding sensitivity of 76 % vs. 56 % for PET alone at 100 % specificity.
CONCLUSION: Simultaneous dynamic FET-PET/MRI was reliably feasible for imaging of recurrent glioma. While all modalities were able to discriminate between recurrence and treatment-related changes, multiparametric analysis added value especially when high specificity was demanded.

**Keywords**

Magnetic resonance imaging; Positron emission tomography; Glioma; MRI, perfusion weighted; Hybrid Imaging

**Introduction**

Maximum safe resection followed by external beam radiation combined with concomitant and adjuvant radiochemotherapy is considered the first-line therapy for high-grade gliomas [1]. According to the RANO response criteria, follow-up MRI is scheduled 4 to 6 weeks after irradiation is completed [2]. Many patients show signs of progression (contrast enhancement and/or T2 hyperintensities) at this early point in time, and the number increases during the following months [3]. However, these imaging findings do not prove tumour progression, as therapy-related changes such as necrosis and inflammation may be indistinguishable on standard MRI, a phenomenon called pseudoprogression. While these early reactive changes normally subside spontaneously, a more severe form which usually occurs at a later time point, namely radiation necrosis, is more reluctant to regress and more likely to evoke neurological symptoms. Since pseudoprogression and radiation necrosis show considerable overlap and share common pathophysiological features, we will refer to both phenomena as therapy- or treatment-related changes. Differentiation between therapy-related changes and true progression is of high clinical importance. Early recognition of progression offers the possibility for therapeutic
intervention, such as re-resection or re-irradiation. Consequently, several imaging methods have been investigated for this purpose, and are now finding their way into clinical practice. Different techniques aim at the determination of tissue perfusion, i.e. perfusion-weighted MRI (PWI). Commonly used, dynamic susceptibility contrast (DSC) determines blood supply and vascularization by contrast-induced T2/T2* signal loss, and several studies have shown that vital tumour tissue exhibits increased perfusion in DSC compared to treatment-related changes [4]. Dynamic contrast-enhanced T1-weighted imaging is another possibility of obtaining perfusion-related measures, but is more difficult to quantify and, according to current guidelines, is regarded more as a supplement to DSC [5].

Diffusion-weighted imaging (DWI) is a modality used for estimating water mobility, with higher values of the apparent diffusion coefficient (ADC) favouring post-treatment changes [6, 7]. When multiple diffusion gradients are acquired, measures such as fractional anisotropy (FA) might be able to detect alterations of the fibre structure caused by tumour infiltration [8]. MR spectroscopy has been employed to detect abnormal concentrations of certain metabolites in the case of recurrence, although reliable clinical implementation is challenging [9, 10]. On the other hand, amino acid PET with 11C-methionine and 18F-fluroethyltyrosine (FET) has gained wide acceptance especially in Europe and several Asian countries as an add-on technique for cases that cannot be adequately solved by MR imaging alone [11, 12]. Additional information can be obtained by dynamic FET-PET imaging, with active tumour showing ‘faster’ tracer uptake with subsequent wash-out, further improving the already remarkable diagnostic accuracy of static PET [13, 14].

With the advent of hybrid PET/MR imaging, both morphological and functional imaging can be performed in one examination, increasing comfort for the often severely ill patients, and optimizing spatial and temporal co-registration of the different modalities.
Although there is an increasing number of studies on multimodal advanced MR imaging [16], little is known about the possible benefit from combining PET and MRI in terms of increased sensitivity and specificity. Sogani et al. have examined a cohort of 32 low and high grade glioma patients with a hybrid PET/MRI protocol and demonstrated added value of the modalities, but did not use dynamic FET imaging [17]. In contrast, Jena et al. combined FDG and PET/MRI and could likewise show a benefit from multimodal analysis [18].

In this work, we investigate a cohort of glioma patients who had received a state-of-the-art combined dynamic FET-PET/MRI protocol and seek to determine the benefit of static and dynamic FET imaging, diffusion (DWI) and perfusion weighted MRI (PWI) and their multiparametric combination in gliomas.

Material and methods

Participants and Lesions

All patients gave their consent on anonymous evaluation of their data, and the institutional review board waived informed consent for the current study. We retrospectively analysed pre-treated glioma patients who had received a standardized simultaneous dynamic FET-PET/MRI protocol for brain tumour imaging and showed contrast-enhancing lesions suggestive of glioma recurrence. PET/MRI examinations took place between March 2015 and April 2017. All patients had undergone maximum safe resection followed by adjuvant therapy according to current guidelines.

PET/MRI protocol

Simultaneous MRI and dynamic PET examinations were performed on a clinical 3T Biograph mMR scanner (Siemens Healthcare, Malvern, PA). To achieve standardized
metabolic conditions, patients had to fast for a minimum of 6 hours. After i.v. injection of a target dose of 190 MBq O-(2-\(^{18}\)F-fluoroethyl)-L-tyrosine, dynamic FET-PET acquisitions were performed for 40 min. From the list-mode PET data, static images at 10 – 20 min and 30 – 40 min p.i. and dynamic images with 20x3, 2x5, 10, 20, 2x30, 2x60, 120, 180 and 6x300 seconds were reconstructed using 3D OSEM into 192 x 192 matrices, resulting in an isotropic voxel size of 1.16 mm\(^3\). Attenuation correction was performed using a dual-echo ultrashort-echo-time-based attenuation map implemented by the manufacturer.

30 min after the begin of the PET acquisition, a pre-bolus of 7.5 ml Gd-DTPA was administered to reduce leakage effects. At least 3 minutes later, DSC imaging (single-shot spin-echo echo-planar imaging TR=1500ms, TE=30ms, α=90°, 60-80 dynamics) was performed during the injection of 15 ml Gd-DTPA at a rate of 4 ml/s.

For morphologic correlation, 3D T2-weighted FLAIR and T1-weighted MPRAGE sequences were performed before and after the Gd-DTPA injection, respectively. Diffusion-weighted imaging was acquired by means of single-shot, spin-echo echo-planar imaging with b-values of 0 and 800 s/mm\(^2\) in 12 directions.

**Image analysis and VOI definition**

All image processing was done using MATLAB R2016b (MathWorks, Natick, MA); for image co-registration by a mutual information approach, SPM (Wellcome Department of Cognitive Neurology, London, UK) was used. VOI definition was performed using VINCI (Max-Planck-Institute for Metabolism Research, Cologne, Germany).

All images were resampled and co-registered to the late static FET images (30 – 40 minutes p.i.), to correct for motion during the examination, and to account for differences in resolution. Independent lesions suggestive of tumour progression were identified by a board-certified nuclear medicine physician and a neuroradiologist,
including MR time series and clinical information on the cases. In order to define independent lesions, these had to be clearly distinct from each other, with no visible connection in contrast-enhanced MR or PET imaging, and occurring at different margins of the resected/irradiated area. Subsequently, in the resampled T1+ images, spherical 3D VOIs with 2 cm diameter were drawn to include the contrast enhancement. The resection cavity, artefacts and the liquor spaces were excluded from the lesions manually. If lesions were larger than the spherical VOI, further positioning aimed at including highest static PET intensity and highest perfusion. We determined mean values within a 90% isocontour volume around the maximum value for static PET and perfusion, and around the minimum value for ADC inside the spherical VOI. The 90% isocontour VOI of early FET uptake (10 – 20 minutes p.i.) was also used for dynamic FET analysis in order to identify early-enhancing hot spots. Static FET images at 10–20 and 30–40 minutes post-injection were normalized to the mean tracer uptake in a 1.5 cm circular region in grey matter of the non-tumour-bearing hemisphere, resulting in tumour-to-background ratios (TBRs). On the time-activity curves of the dynamic FET data, we determined the time-to-peak of the FET activity. CBV maps were calculated using an established protocol [19] and normalized to normal-appearing white matter of the contra-lesional hemisphere, which was defined as a rCBV value of 1%. Optionally, a mathematic leakage correction as proposed by Boxerman et al [20] was applied. ADC and FA maps were generated using software provided by the manufacturer (Siemens Healthcare).

**Multimodal analysis**

For further data analysis, SPSS 24 (IBM Inc., Armonk, NY) was used. The single modalities were analysed for their ability to determine progression using ROC analysis, and the area under the curve (AUC), specificities and sensitivities at optimal cut-offs were calculated. Optimal cut-offs were defined by minimal Euclidean distances from
the upper left corner of the ROC graph. For further analysis, missing values were replaced by the means of the respective parameter. Discriminant function analysis was employed to determine an optimal linear combination of the different modalities. In order to include the discrete TTP data from dynamic PET imaging (TTP values were in 5 minute steps due to reconstructed time frames), we dichotomized the TTP according to its optimal threshold in single-modality analysis.

**Standard of reference**

When available, histology from re-resection or biopsy was used as a standard of reference. For the remaining cases, a final diagnosis was established based on follow-up MRI scans. Due to the difficulties in differentiating treatment-related changes from recurrence, which were the motivation for this study, we demanded an increase in contrast enhancement in two subsequent scans, or an increase in contrast enhancing volume of >25 % without treatment change in order to prove tumour progression.

**Results**

63 independent lesions suggestive of progression in 47 patients (median age 54±11 years, 22 men) with pre-treated gliomas (27 glioblastoma, 13 anaplastic astrocytoma, 2 diffuse astrocytoma, 1 oligodendroglioma and 3 anaplastic oligodendroglioma, see Table 1) were identified. Of these, 4 had two examinations for their first and second recurrence, respectively, one patient had 3 examinations, with a mean of 7 months between the scans. In patients with multiple clearly distinguishable lesions, occurring at different tumour margins, the median distance between the borders of the lesions was 25.6 mm (range 13.5 to 57.4 mm). Out of the 63 differentiable lesions, 50 were classified as tumour progression, while 13 were classified as treatment-related changes. This diagnosis was based on histology in 23 and on follow-up imaging in 40...
lesions. Median delay between primary diagnosis and occurrence of the lesions was 15 months, and the median follow up time was 6 months. Multimodal image acquisition was reliably feasible: PET data were available for all lesions, DSC perfusion could be analysed in 62 and DWI in 61 out of 63 identified lesions. Failure of acquisition in the cases with missing data was due to patient motion and susceptibility artefacts.

**Single-modality analysis**

Static PET imaging with measurements from 30 to 40 minutes after injection demonstrated a sensitivity and specificity of 80.0 % and 84.6 % at an optimal cut-off of TBR 2.07 (AUC 0.86±0.10, p<0.001, see Fig. 3). Early static PET images, measured from 10 to 20 minutes p.i. yielded a slightly lower sensitivity of 76.0 % at the same specificity (AUC 0.85±0.11, p<0.001). Analysis of dynamic PET time-to-peak alone, not including static imaging, showed sensitivities and specificities of 64.4 % and 78.6 % at an optimal-cut off between 20 and 25 minutes (AUC 0.73±0.14, p=0.012).

Perfusion MR imaging with dynamic susceptibility contrast resulted in an AUC of 0.73±0.15 (p=0.013) for uncorrected rCBV and 0.71±0.14 (p=0.022) for rCBV with additional mathematic leakage correction. Optimal cut-offs for the detection of tumour progression were 4.32 for uncorrected and 3.35 for corrected rCBV (a value of 1% representing white matter perfusion), resulting in sensitivities and specificities of 62.0 % and 76.9 % for uncorrected and 66.0 % and 76.9 % for corrected rCBV.

Diffusion-weighted imaging in the form of ADC and nADC maps, showed only moderate value in detecting tumour progression: the AUC in ROC analysis was 0.69 ±0.16 and 0.70±0.15, optimal cut-off for discrimination were 1610*10^6 mm²/s and 1.22, and sensitivities and specificities were 50.0 % and 76.9 % and 62.0 % and 76.9 %, respectively. FA performed worse than ADC in our setting, with a sensitivity of 64.6%, specificity of 61.5% and an AUC of 0.59±0.19 at an optimal cut-off of 98.9.
**Multimodal analysis**

In order to determine a linear combination of the modalities, which optimizes differentiation between tumour recurrence and treatment-related changes, we performed discriminant function analysis. We included late static PET, rCBV and nADC as the best diffusion parameter in the analysis. The resulting weights were 0.536 for late PET uptake, -1.848 for nADC, 0.042 for rCBV and 0.903 for the dichotomized FET TTP (<>20 min). ROC analysis revealed an AUC of 0.89±0.08 (p<0.001); At a specificity of 100 %, the multiparametric approach resulted in a sensitivity of 76.0 %, compared with 56.0 % when using static FET PET information alone (threshold for 100 % specificity with PET only: TBR 2.65).

**Discussion**

The aim of this study was to demonstrate the feasibility of combined dynamic FET-PET/MRI for the diagnosis of recurrence in gliomas, to compare the accuracy of the different modalities and to estimate the benefit of multiparametric imaging. Previous studies investigating hybrid PET/MRI for glioma recurrence imaging had either used different – older – tracers (^{18}F-FDG, ^{11}C-methionine), or did not take advantage of dynamic PET protocols in order to determine ^{18}F-FET uptake kinetics. Although the protocol included several modalities, each with its possible sources of errors, the acquisition was remarkably stable, and in 60 of 63 lesions (95 %), all modalities were evaluable for analysis. Failure of acquisition in the remaining cases was due to patient motion and MRI artefacts.

As expected, all single modalities were able to predict tumour progression on a significant level, showing a tendency towards higher specificities than sensitivities. The highest accuracy was provided by static FET imaging, with an optimal TBR mean
threshold of around 2.1, which is in line with earlier published results [13]. Late FET images (30 – 40 min. p.i.) provided slightly better discrimination than early images (10 – 20 min. p.i.), approving the established FET imaging protocols, though not supporting reports about higher performance of early FET imaging for the primary diagnosis of glioma [21]. Perfusion-weighted imaging exhibited considerably lower specificities and, particularly, sensitivities. Interestingly, mathematic leakage correction for rCBV provided no benefit compared to the simpler, uncorrected rCBV values. A possible explanation for this finding is, that contrast agent extravasation related to a disturbed blood-brain-barrier may be a predictive marker on its own, and therefore leakage correction does not necessarily improve the diagnostic value of the method. In our study, DSC was chosen for perfusion imaging, as it is the most widely-used method in brain tumours, with rCBV being a robust parameter in most studies [5]. However, DCE is increasingly proposed as an add-on, particularly to obtain parameters relating to blood-brain-barrier intactness. While DCE glioma protocols did not show stable results in our environment, improvements in scanner hardware and reconstruction software might lead to the introduction of DCE as a clinical standard in hybrid imaging in the future.

Diffusion-weighted imaging performed worse in our cohort than it had been published previously [7]. Our observation that normalized ADC values showed better results than quantitative ADC might point to issues with absolute quantification. Optimizations might therefore be possible by using proprietary software for DWI analysis instead of the solution provided by the manufacturer of the scanner.

While static FET uptake shows a certain specificity for tumour tissue, unspecific enhancement may occur e. g. due to inflammatory processes. Dynamic FET PET offers additional information on tracer kinetics, and recurrent tumour is expected to
exhibit both faster uptake and wash-out than unspecific therapy-related changes [13].

In our study, the established dynamic parameter TTP provided a moderate diagnostic accuracy, but was more useful when added in the multiparametric analysis, which is in agreement with results published by Galldiks et al. However, that study included a dynamic PET scan over 50 minutes, compared with 40 minutes in our protocol which might have contributed to a slightly better diagnostic performance.

Finally, multiparametric analysis of late static FET, FET TTP, rPH and nADC provided improved accuracy particularly when high specificity for the diagnosis of recurrence was demanded. In this work, we only performed a basic analysis of the multiparametric data by determining a linear combination of the parameters optimally correlated to the final diagnosis. This approach has been chosen, because our primary aim was to demonstrate the feasibility of the protocol and to estimate the possible added value of hybrid PET/MR imaging. We are aware of more sophisticated methods for multiparametric analysis; particularly, machine learning [22] or deep learning techniques [23] have been proposed for this purpose and could be translated to clinical tools assisting the diagnostic radiologist. However, larger patient groups are needed to train the algorithms in order to achieve reliable results.

$^1$H-spectroscopy was not part of our study because of the considerable scanning time needed to perform the sequences. The scanning time limitation not only affects hybrid PET/MRI but also stand-alone MRI protocols, which must often be divided into several sessions to include high-resolution morphological imaging, PWI, DWI and spectroscopy. While one group reported promising results regarding the inclusion of $^1$H-MR spectroscopy in a combined PET/MRI protocol [17, 18], other studies showed only moderate accuracy of the method for the detection of glioma recurrence [10, 24].
The combination of PET and MR spectroscopy for glioma imaging is still a highly interesting topic [25] which deserves further exploration.

Besides the relatively low number of patients included and the heterogeneity of the cohort in terms of tumour grade, one major limitation of our study is the lack of a consistent histologic gold standard. Only about one third of our lesions had a final diagnosis proven by histology. Consequently, our results might be driven mainly by follow-up imaging. Nevertheless, even histologic evaluation is sometimes problematic, and often a mixture of tumour-related and radiation-induced necrosis and vital tumour tissue is present. Furthermore, follow-up imaging may correlate just as well with the clinical outcome of patients. Future prospective studies aimed at confirming the value of multiparametric FET-PET/MRI should however seek additional histologic confirmation whenever possible.

**Conclusion**

Simultaneous dynamic FET-PET/MRI was reliably feasible for imaging of recurrent glioma. While all modalities were to some extent able to discriminate between recurrence and treatment-related changes, FET-PET showed the highest diagnostic accuracy. Multiparametric analysis with advanced MRI added value especially at high specificity, which might be useful when discussing early re-resection or re-irradiation.

**Conflict of Interest**

The authors declare no conflict of interest. JG reports personal fees from Brain Lab AG, outside the submitted work.
The study was supported by funding from the German Research Foundation DFG (grant to CP and TP: FO 886/1-1; PR 1039/4-1). The research leading to these results has received funding from the European Union Seventh Framework Program (FP7) under Grant Agreement No. 294582 ERC Grant MUMI.
References


Figure Legends

Figure 1 – PET/MRI protocol
Hybrid PET/MRI protocol showing the MR sequences used in this study; DTI – diffusion tensor imaging in 12 directions; UTE – dual-echo ultrashort-echo-time sequence used for attenuation correction.

Figure 2 – Multimodal imaging of tumour progression and treatment-related changes
A to E: New contrast-enhancing lesion (A) (indicated by a red circle) in a 37-year old patient with anaplastic astrocytoma (WHO °III) 10 months after resection and radiation therapy. FET-PET shows increased high FET uptake 30-40 min. p.i. (B, colorbar indicating SUV), increased perfusion (C), normal to low ADC values (D) and early FET TTP (E), suggesting vital tumour tissue. Re-resection was scheduled, with histology proving tumour progression. F to K: Contrast-enhancing lesion (F) in a 63-year old patient with glioblastoma 6 months after combined radiochemotherapy. FET-PET 30-40 min. p.i. shows weak uptake (G), moderate perfusion (H) and mildly elevated ADC values (I) as well as indeterminate to late FET TTP (K), suggestive of mostly therapy-related changes. Follow up for 9 months did not show further signs of progression. Units for PET are SUV, for ADC $10^{-6}$ mm$^2$/s. Note that the VOI in D has been edited manually as explained in the methods to exclude the resection cavity.

Figure 3 – ROC analysis of single imaging modalities and multimodal combined imaging
ROC plot for static FET PET, diffusion weighted (nADC) and perfusion-weighted MRI (rCBV) as well as dynamic FET PET (FET TTP). Discrimination is improved by multiparametric imaging, demonstrating advantages over single modality FET-PET, especially with respect to a higher specificity.
# Table 1 – Patient data

<table>
<thead>
<tr>
<th>Description</th>
<th>Count</th>
<th>Percentage</th>
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<tr>
<td>Patients , N</td>
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<tr>
<td><strong>Mean age, y</strong></td>
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<td></td>
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<tr>
<td><strong>Sex, n (%)</strong></td>
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</tr>
<tr>
<td>Female</td>
<td>22</td>
<td>(47)</td>
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<tr>
<td>Male</td>
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<td>(53)</td>
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<td><strong>Histology, n (%)</strong></td>
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<tr>
<td>Diffuse astrocytoma</td>
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<tr>
<td>Oligodendroglioma</td>
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<td>(2)</td>
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<td>WHO *II</td>
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<tr>
<td>Anaplastic astrocytoma</td>
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<td>(28)</td>
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<tr>
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<tr>
<td>Anaplastic oligodendroglioma</td>
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<td>(6)</td>
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<td></td>
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<tr>
<td>Glioblastoma</td>
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<td>(57)</td>
</tr>
<tr>
<td>WHO *IV</td>
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<td></td>
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<tr>
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<tr>
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</tr>
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Table 2 – Comparison of single imaging modalities and multimodal combined imaging

<table>
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<tr>
<th></th>
<th>AUC</th>
<th>cut-off</th>
<th>p</th>
<th>Sensit.</th>
<th>Specif.</th>
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<td>&lt;0.001</td>
<td>80.0%</td>
<td>84.6%</td>
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<td>(0.766 - 0.961)</td>
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<td>FET 10-20</td>
<td>0.848</td>
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<td>&lt;0.001</td>
<td>76.0%</td>
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<td>(0.743 - 0.952)</td>
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<td>FET TTP</td>
<td>0.728</td>
<td>20 min.</td>
<td>0.012</td>
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<td>78.6%</td>
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<tr>
<td>rCBV uncor.</td>
<td>0.726</td>
<td>4.32</td>
<td>0.013</td>
<td>62.0%</td>
<td>76.9%</td>
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<td>(0.576 - 0.876)</td>
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<tr>
<td>rCBV corr</td>
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<td>3.35</td>
<td>0.022</td>
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<td>76.9%</td>
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<td>(0.550 - 0.844)</td>
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<td>ADC</td>
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<tr>
<td>nADC</td>
<td>0.697</td>
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<td>76.9%</td>
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<td>(0.550 - 0.844)</td>
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<td>FA</td>
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<td>0.307</td>
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<td>61.5%</td>
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<td>Multi-parametric</td>
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<td>92.3%</td>
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<td>(0.812 - 0.970)</td>
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AUC – area under the curve; 95% CI are given in parentheses