Diagnostic yield of simultaneous dynamic contrast-enhanced magnetic resonance perfusion measurements and \([^{18}\text{F}]\text{FET PET}\) in patients with suspected recurrent anaplastic astrocytoma and glioblastoma

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Abstract

Purpose Both amino acid positron emission tomography (PET) and magnetic resonance imaging (MRI) blood volume (BV) measurements are used in suspected recurrent high-grade gliomas. We compared the separate and combined diagnostic yield of simultaneously acquired dynamic contrast-enhanced (DCE) perfusion MRI and O-(2-[18F]-fluoroethyl)-L-tyrosine (\([^{18}\text{F}]\text{FET}\)PET) PET in patients with anaplastic astrocytoma and glioblastoma following standard therapy.

Methods A total of 76 lesions in 60 hybrid \([^{18}\text{F}]\text{FET PET/MRI}\) scans with DCE MRI from patients with suspected recurrence of anaplastic astrocytoma and glioblastoma were included retrospectively. BV was measured from DCE MRI employing a 2-compartment exchange model (2CXM). Diagnostic performances of maximal tumour-to-background \([^{18}\text{F}]\text{FET}\) uptake (TBR\(_{\text{max}}\)), maximal BV (BV\(_{\text{max}}\)) and normalised BV\(_{\text{max}}\) (nBV\(_{\text{max}}\)) were determined by ROC analysis using 6-month histopathological (\(n=28\)) or clinical/radiographical follow-up (\(n=48\)) as reference. Sensitivity and specificity at optimal cut-offs were determined separately for enhancing and non-enhancing lesions.

Results In progressive lesions, all BV and \([^{18}\text{F}]\text{FET}\) metrics were higher than in non-progressive lesions. ROC analyses showed higher overall ROC AUCs for TBR\(_{\text{max}}\) than both BV\(_{\text{max}}\) and nBV\(_{\text{max}}\) in both lesion-wise (all lesions, \(p=0.04\)) and in patient-wise analysis (\(p<0.01\)). Combining TBR\(_{\text{max}}\) with BV metrics did not increase ROC AUC. Lesion-wise positive fraction/sensitivity/specificity at optimal cut-offs were 55%/91%/84% for TBR\(_{\text{max}}\), 45%/77%/84% for BV\(_{\text{max}}\) and 59%/84%/72% for nBV\(_{\text{max}}\). Combining TBR\(_{\text{max}}\) and best-performing BV cut-offs yielded lesion-wise sensitivity/specificity of 75/97%. The fraction of progressive lesions was 11% in concordant negative lesions, 33% in lesions only BV positive, 64% in lesions only \([^{18}\text{F}]\text{FET positive and 97\% in concordant positive lesions.}\)

Conclusion The overall diagnostic accuracy of DCE BV imaging is good, but lower than that of \([^{18}\text{F}]\text{FET PET}\). Adding DCE BV imaging did not improve the overall diagnostic accuracy of \([^{18}\text{F}]\text{FET PET}\), but may improve specificity and allow better lesion-wise risk stratification than \([^{18}\text{F}]\text{FET PET alone.}\)

Keywords Glioma · Magnetic resonance imaging · Perfusion imaging · Blood volume · Positron emission tomography · Amino acid tracers
Introduction

The prognosis of high-grade gliomas is poor, and treatment options are limited [1]. Accurate diagnosis of tumour recurrence remains a challenge in patients with treated high-grade glioma, and magnetic resonance imaging (MRI) thus plays a pivotal role in the post-treatment management of brain tumour patients. However, the diagnostic accuracy of conventional MRI in the post-treatment setting is low due to the presence of treatment-induced changes mimicking disease progression. Post-treatment-related effects include both pseudo-progression, an acute inflammatory response to radio-chemotherapy, and late treatment damage (radiation necrosis). Surgical trauma may further complicate the evaluation of MRI up to 2–3 months after surgery [2]. The specificity of conventional MRI for biopsy-verified recurrent glioma has been reported to be as low as 50% [3]. Various additional functional imaging modalities may be applied in order to establish the nature of progressive MRI lesions, e.g. MRI perfusion measurements and positron emission tomography (PET) [4].

MRI perfusion measurements for estimation of tumour blood volume (BV), considered a measure of tumour angiogenesis, are most commonly performed using the dynamic susceptibility contrast (DSC) approach [5]. Although high diagnostic accuracy with sensitivity and specificity in the 85–90% range for detection of progressive disease has been reported [6], the DSC approach is limited by being non-quantitative and suffers from incomplete coverage of lesions in the presence of susceptibility artefacts often present in the post-treatment setting [7–9]. The alternative T1 weighted dynamic contrast-enhanced (DCE) approach allows conversion of the MRI signal to gadolinium (Gd) concentrations for kinetic modelling and is, in addition, less affected by susceptibility artefacts [9, 10]. A meta-analysis of studies of recurrent glioma found high pooled sensitivity (89%) and specificity (85%) of DCE to be similar to that of DSC when using the best-performing DCE parameter of the individual studies [6]. These previous studies were based on kinetic modelling using 2 or 3 parameter models (Tofts’ or the extended Tofts’ model) [11], or on model-independent area under signal curve-derived metrics [12]. Advances in DCE MRI allow sampling with higher temporal resolution and thus quantification of blood flow (F) which in turn permits the use of 4-parameter 2-compartment exchange models (2CXM), providing quantification of permeability (Ki) and blood volume (BV) [13–15]. To our knowledge, the diagnostic accuracy of 2CXM DCE in recurrent gliomas has not been investigated.

Amino acid PET tracers such as O-(2-[18F]-fluoroethyl)-L-tyrosine ([18F]FET) expressing L-amino-transferase on glioma cells are increasingly being used for discriminating tumour from post-treatment changes [16]. A meta-analysis of [18F]FET found pooled sensitivity and specificity of 90% and 85%, respectively [17], and a recent study of [18F]FET PET reported even higher diagnostic accuracy in late recurrent glioblastomas (> 6 months after radiotherapy) [18]. Still, increased tracer uptake may be observed in post-treatment changes [19]; thus, robust methods to improve specificity and evade false-positive findings are warranted.

Several studies have compared diagnostic the performance of amino acid PET with that of DSC perfusion MRI in suspected recurrent gliomas [20–28], but comparative studies applying DCE have to our knowledge not been published.

At our institution, [18F]FET PET/MRI with DCE BV imaging is applied to routine clinical imaging of glioma patients and is in particular used for high-grade gliomas in the post-treatment setting for patients with possible or suspected recurrent disease due to residual or progressive MRI lesions or clinical symptoms, and in patients scheduled for second-line treatment. These unique data allow us to compare the two modalities acquired simultaneously under similar physiological conditions in a large and clinically highly relevant patient population with suspected recurrence with correlation to clinical outcome. The aims of the study were primarily to compare the diagnostic value of simplified (semi-) quantitative cut-offs from DCE perfusion MRI and [18F]FET PET for detection of short-term disease progression, and secondly to investigate if bi-modal advanced imaging may be more accurate than single modalities.

Methods

Patient population

From the image archive system, we retrospectively identified all non-paediatric hybrid [18F]FET PET/MRI brain scans (n = 542) performed between January 2016 and September 2020. Eligibility according to the below criteria was initially assessed from the indication as stated in the imaging report and subsequently confirmed from patients’ records. Retrospective use of clinical data was approved by the Danish Patient Safety Authority (reference no. 3–3013-1957/1) and for data after January 2020 by the local hospital administration (Copenhagen University Hospital Rigs hospitalet). We also included baseline data from patients with RANO progression included in a study of combined nivolumab/bevacizumab undergoing surgery after a single dose of nivolumab. This prospective study was approved by the local ethics committee (The Capital Region of Denmark Committee on Health Research Ethics, ref. H-17040888) and conducted in accordance with the Helsinki Declaration, and participants gave informed written consent prior to the scan.
Inclusion criteria comprised

1) adult patients (> 18 years) with high-grade gliomas referred for [18F]FET PET/MRI due to findings suggestive of residual/progressive lesions on a previous MRI or progressive clinical symptoms,

2) histologically verified WHO grade III anaplastic astrocytoma (AIII) or grade IV glioblastoma (GBM) including secondary GBM according to the WHO 2016 classification [29], and

3) prior standard therapy, i.e. maximal safe resection and/or radiation/chemotherapy (please refer to Supplementary Table S1 in Online resource 1).

Exclusion criteria comprised.

1) tumours with oligodendroglial origin (1p/19q co-deletion) or atypical/mixed pathology (e.g. sarcomatous components) were not included in order to ensure a homogenous study sample,

2) previous or current exposure to antiangiogenic treatment, immune therapy or other non-standard therapy,

3) technical sub-optimal examination including a T1 measurement with less than 4 flip angles or DCE or PET imaging of poor quality (e.g. motion, poor DCE input function), and

4) non-evaluable outcome within 6 months follow-up (see below).

The flow chart of inclusion is provided in Fig. 1. We included a total of 76 unique lesions in 60 patients with the evaluable outcome within 6 months of follow-up as determined by histopathology in 28 lesions (27 progressive), MRI findings 45 (14 progressive) or by clinical decision in 3 (progressive) lesions. In patients with outcomes evaluated by histopathology, tissue sampling surgery/biopsy was obtained.
at a median of 13 days (range 7–92 days) after the scan. In
one additional patient, surgery was performed 290 days after
the scan due to progressive changes retrospectively visible
on MRI 5 months after the PET/MRI scan. In one patient, the
patient-wise outcome could not be determined. Details of
lesion characteristics and lesion-wise outcome are provided
in Online resource 2. In one patient with AIII, imaging was
performed 4 weeks after primary surgery to assess residual
tumour. All other patients had both surgery (or biopsy) and
radiotherapy at some point prior to imaging.

Pathology

Tumour classification including methylguanine-DNA meth-
yltransferase gene (MGMT) promoter methylation and isocitrate dehydrogenase-1 (IDH) mutation status was recorded
as stated in the pathology report established at the last sur-
gery or biopsy.

Follow-up and reference standard

Clinical records including pathology reports and subsequent
imaging were reviewed at the time of data analysis (April
2021). Diagnostic reference was based on both lesion and
patient-wise follow-up at 6 (± 2 weeks) months after PET/
MRI imaging.

In order to allow both lesion and patient-wise analysis,
the modified RANO criteria [30] were adapted to the pur-
pose of the analysis. Progressive disease was thus defined
by (1) histopathological verification on biopsy or resection,
(2) progression at a follow-up MRI at least 4 weeks later
(≥ 25% increase in the products of perpendicular diameters
of enhancing lesions, significant progression of non-enhanc-
ing lesions, or any new enhancing lesion, or (3) clinical diag-
nosis of progressive disease (e.g. clear clinical deterioration
not attributable to other causes apart from tumour or attrib-
utable to changes in steroid dose, or death of failure to attend
follow-up attributable to progressive disease).

Non-progression was defined as the absence of tumour
on histopathology, regression (> 50% reduction in the pro-
ducts of perpendicular diameters) or stable disease using the
modified RANO criteria [30] within a follow-up period of
6 months. As both recurrent tumour and treatment-related
changes respond to anti-angiogenetic second-line therapy,
e.g. bevacizumab, only patients with no other chemotherapy
than (continued) initial adjuvant temozolomide until the end-
point was met were included. Other reasons for exclusion
were lack of confirmation in case of, e.g., death from other
causes or termination of treatment without diagnostic con-
firmation as defined above.

In ambiguous cases, the outcome was determined by
consensus among two authors (OH and IL). When criteria
were conflicting, the clinical decision of progression vs non-
progression as stated in the patient record was used.

In patients with multiple lesions and only clinically
defined progression, only the dominant (if present) lesion
was classified as progressive and included only in the
lesion-wise analysis, whereas the maximal value from all
lesions (also without lesion-wise outcome) was used in
the patient-wise analysis. In lesions/patients with multiple
scans, only data from a single PET/MR scan was included
in the analysis; for lesions with histopathological confir-
mation, the last PET/MRI scan before biopsy/surgery was
included; otherwise, the first PET/MR scan with the long-
est follow-up was used.

Imaging protocol

Imaging was performed on a Siemens Biograph mMR 3 T
hybrid PET/MRI system equipped with a 16-channel head
coil (Siemens Biograph, Siemens, Erlangen, Germany). PET
imaging was performed according to recent guidelines [31].

The hybrid PET/MRI protocol included a single-bed
20-min simultaneous PET/MRI acquisition initiated 20 min
after i.v. injection of approximately 200 MBq [18F]FET. Details
of the imaging protocol, DCE acquisition and PET
reconstruction are provided in Online resource 1.

DCE data was analysed using in-house software for Mat-
lab as previously described [13, 14, 32] in which blood flow
is estimated by model-free deconvolution by Tikhonov’s
method, and subsequent fitting of BV, permeability (the
unidirectional clearance constant, Ki) and extra-vascular,
extra-cellular space (Ve) from a 2-compartment model.

Image analysis

Conventional pre- and post-contrast MRI were read as a
part of the clinical routine by an experienced neuroradiolo-
gist unless reporting was not deemed relevant due to a very
recent diagnostic MRI.

For the purpose of the study, [18F]FET PET and DCE BV
images were re-analysed by a single author (OH) blinded
to the disease course after imaging. Images were analysed
using Mirada RTx software (Mirada Medical, Oxford, UK).

Images were initially analysed lesion-wise. A lesion was
defined as a spatially distinct MRI T2/T2 FLAIR hyper-
intensity or post-contrast enhancement on T1 MRI, or as
focal uptake on [18F]FET PET. Initially, [18F]FET PET and
DCE parameter maps were registered and displayed fused
to post-contrast T1 MRI. In order to minimise the confound-
ing influence of [18F]FET PET on the reading of DCE BV
maps, the images were analysed in a fixed order (see below)
blinded to subsequently analysed modalities. In single cases,
DCE BV was re-evaluated if [18F]FET indicated tumour
components not recognised initially.
Post-contrast-enhanced T1 MRI

Lesions were classified as enhancing in the presence of any contrast enhancement irrespective of its suspected nature or a predominant larger non-enhancing component. Guided by the MRI report, the contrast enhancement was delineated in 3D by isocontouring and adjusted manually to obtain the contrast-enhancing volume (VOL_CE). Within VOL_CE, the median values of blood flow (Fmed), BV (BVm ed), Ki (Kimed) and of median \[^{18}F\]FET uptake to cortex ratio (TBRmed) within VOL_CE were recorded in order to obtain unbiased and representative quantitative values for all parameters of interest from anatomically defined lesion volumes.

DCE BV imaging

On BV maps co-registered to post-contrast 3D-T1 MRI, the volume of visually increased BV (VOL_BV) was delineated by isocontouring and adjusted manually avoiding signal from visible macrovascular structures. The voxel-wise maximal BV (BVmax) within VOL_BV was recorded, and the normalised maximal BVmax (nBVmax) was calculated as the ratio of BVmax to the mean BV value of an ellipsoid VOI (approx. 1 ml) drawn in the normal-appearing white matter of the contralateral hemisphere, usually in the centrum semiovale.

In visually BV negative lesion, BVmax was determined as the maximal value within VOL CE or for non-enhancing lesions either within VOL_FET or, if also \[^{18}F\]FET negative, in a spherical VOI in the centre of the FLAIR lesion.

\[^{18}F\]FET PET

The metabolically active \[^{18}F\]FET volume (VOL_FET) was delineated by isocontouring. VOL_FET was defined as tissue with \[^{18}F\]FET uptake exceeding 1.6 of the mean activity of a background region drawn in the normal-appearing cortex of the contralateral hemisphere [33].

Within VOL_FET, the maximal tumour-to-background \[^{18}F\]FET uptake ratio (TBRmax) was calculated as a measure of maximal metabolic activity. In \[^{18}F\]FET negative lesions (TBRmax < 1.6), maximal uptake was determined in an approach similar to BV imaging.

Statistics

For continuous parameters, median (range) is reported and group differences are tested using the Mann–Whitney test, while Wilcoxon signed rank test is used for paired observations. Categorical variables were analysed using Fischer’s exact test. A two-tailed significance level of 0.05 was applied.

Diagnostic accuracy was assessed and compared between \[^{18}F\]FET PET and DCE using the receiver operating characteristics (ROC) area under the curve (AUC) constructed from logistic regression models using single or multiple explanatory parameters. The equality of ROC AUCs was tested using the DeLong test [34]. Empirical optimal cut-offs of TBRmax, BVmax and nBVmax (and for median values within contrast-enhancing volumes) for separation of progressive and non-progressive lesions were derived from ROC analysis by maximisation of Youden’s index. As the exploratory analysis showed substantial differences between enhancing and non-enhancing lesions, optimal cut-off and associated sensitivity, specificity, and positive and negative predictive values were determined both for all lesions and separately for enhancing and non-enhancing lesions. To assess the diagnostic value of \[^{18}F\]FET PET and DCE combined, the combinations of best-performing parameters and cut-offs were used. Lesions above and below the optimal cut-off for each parameter were classified as positive and negative, respectively. In combined imaging, only lesions positive on both were classified as positive, while lesions negative on either or both were classified as negative.

Subgroup analysis was performed to assess the potential influence of recent radiotherapy (< 6 months), and of IDH and MGTM status. Due to the low number of non-enhancing lesions, subgroup analyses were only performed on enhancing lesions.

All statistical analyses were performed in STATA 15 (Stata Corp, College Station, TX).

Results

Summary statistics for evaluable lesions are shown in Table 1. Overall, in 60 patients, 76 unique lesions were included, of which 67 lesions were contrast-enhancing and 9 non-enhancing. All \[^{18}F\]FET PET, DCE and CE tumour metrics were significantly higher in progressive (n = 44) compared to non-progressive (n = 32) lesions. Scatter plots of correlations of median and maximal BV with \[^{18}F\]FET uptake in progressive and non-progressive lesions are shown in Fig. 2. Compared to lesions with clinical/radiological follow-up, lesions with histopathological verification were, in general, larger and were both metabolically more active and had higher BV values (Supplementary Table S2 in Online resource 1). Examples of \[^{18}F\]FET PET and DCE imaging are provided in Figs. 3 and 4.

ROC analyses (Fig. 5) showed higher ROC AUCs for TBRmax than both BVmax and nBVmax in both lesion-wise (all lesions, \(p = 0.04\)) and in patient-wise analysis (\(p < 0.01\)), although only borderline significant for BVmax in enhancing lesions (\(p = 0.06\)) and not different in non-enhancing lesions. Combining BVmax or nBVmax with TBRmax did not improve diagnostic performance assessed by ROC AUC. Accordingly, the diagnostic performance at optimal cut-offs (Table 2) was, in general, lower for BVmax and nBVmax.
than for TBR\textsubscript{max}. In non-enhancing lesions, optimal cut-off values were lower than in enhancing lesions, and nBV\textsubscript{max} had the highest specificity, but due to the small number of lesions (n = 9), confidence intervals are wide. Subgroup ROC analysis (Supplementary Table S3 in Online resource 1) of enhancing lesions showed similar cut-off and diagnostic performance for TBR\textsubscript{max} and BV\textsubscript{max} irrespective of recent RT, IDH and MGMT status, whereas optimal nBV\textsubscript{max} showed some variability.

According to the cut-offs determined by ROC analysis, 62 lesions (82%) were concordant positive (n = 34) or negative (n = 28) (Table 3). A total of 14 lesions were positive on only $[^{18}\text{F}]$FET PET (n = 11) or only DCE BV (n = 3). Among 15 patients with multiple lesions, four lesions were positive on $[^{18}\text{F}]$FET PET only and none on DCE BV only. The fraction of progressive lesions increased from 3/28 (11%) in lesions testing negative for both DCE BV and $[^{18}\text{F}]$FET PET to 97% in lesions testing positive on both. In

![Fig. 2](https://example.com/fig2)

**Fig. 2** Correlation of absolute and relative blood volume with $[^{18}\text{F}]$FET uptake according to progression. Scatterplots of absolute (left) and normalised (centre) maximal blood volume vs TBR\textsubscript{max} in progressive (open, n = 44) and non-progressive (solid, n = 32) lesions. Non-enhancing lesions are shown in red. Vertical and horizontal lines show optimal cut-offs for enhancing lesions (black) and non-enhancing lesion (red). Right: scatterplot of patient-wise maximal blood volume and TBR\textsubscript{max} with optimal cut-offs indicated with dashed lines in patients with progression (open, n = 43) and without progression (solid, n = 16). Note the logarithmic y-axis.

Table 1 Lesion summary statistics

| Lesion characteristics | All (n = 76) | Non-progressive (n = 32) | Progressive (n = 44) |
|------------------------|-------------|-------------------------|----------------------|
| Days from last surgery | 227 (15–2167) | 282 (25–1041) | 224 (15–2167) |
| Days from RT | 246 (56–4494) | 277 (67–966) | 226 (56–4494) |
| GBM, n (%) | 67 (88) | 28 (88) | 39 (89) |
| IDH wild-type, n (%) | 64 (84) | 26 (81) | 38 (86) |
| MGMT methylated, n (%) | 42 (55) | 24 (75) | 18 (41)‡ |
| RANO group | 9/32/32 | 5/22/5 | 4/10/30‡ |
| Maximum lesion values | | | |
| TBR\textsubscript{max} | 2.4 (0.3–5.0) | 1.7 (0.3–3.6) | 2.8 (0.9–5.0)‡ |
| BV\textsubscript{max} (mL/100 g) | 9.2 (0.2–106.3) | 3.4 (0.2–31.3) | 14.7 (1.2–106.3)‡ |
| nBV\textsubscript{max} | 11.0 (0.5–204.8) | 4.9 (0.5–42.6) | 20.5 (1.6–204.8)‡ |
| Lesion volumes | | | |
| VOL\textsubscript{FET} (ml) | 4.2 (0–46.4) | 0.06 (0–32.5) | 11.2 (0–46.4)‡ |
| VOL\textsubscript{BV} (ml) | 0.4 (0–33.8) | 0 (0–7.6) | 2.8 (0–33.8)‡ |
| VOL\textsubscript{CE} (ml) | 1.3 (0–32) | 0.3 (0–16.9) | 3.4 (0–32)‡ |
| Median values in contrast enhancing volumes | | | |
| TBR\textsubscript{med} | 1.8 (0.3–3.1) | 1.3 (0.3–2.2) | 2.0 (1.2–3.1)‡ |
| F\textsubscript{med} (mL/100 g/min) | 18.2 (3.1–73.4) | 13.1 (3.1–54.5) | 22.7 (11.2–73.4)‡ |
| BV\textsubscript{med} (mL/100 g) | 2.3 (0.14–14.7) | 1.3 (0.1–7.4) | 3.0 (0.4–14.7)‡ |
| K\textsubscript{med} (mL/100 g/min) | 6.2 (0–40) | 4.3 (0–40) | 6.7 (0.2–40)† |

$p < 0.05$ ‡$p < 0.01$ RT, radiotherapy; GBM, glioblastoma; IDH, isocitrate dehydrogenase; MGMT, methylguanine-DNA-methyltransferase; RANO, group (non-enhancing/non-measurable/measurable); TBR\textsubscript{max} maximal $[^{18}\text{F}]$FET tumour-to-background ratio; BV\textsubscript{max} maximal blood volume (BV); nBV\textsubscript{max} normalised maximal BV; VOL, lesion volume; TBR\textsubscript{med} median $[^{18}\text{F}]$FET tumour-to-background ratio; F\textsubscript{med}, BV\textsubscript{med} and K\textsubscript{med} median blood flow, blood volume and permeability in contrast-enhancing volume.
lesions testing positive only on $[^{18}F]$FET PET, the fraction with progression was intermediate (7/11 [64%], $p \leq 0.01$ vs both concordant negative and positive). The fraction of progressive lesion testing positive on only BV also tended to be lower, but the number of lesions (1 out of 3, all with $TBR_{\text{max}}$ in the range 1.9–2.1) was too low to assess differences. In the patient-wise analysis, the result of BV imaging did not appear to significantly influence risk as determined by $[^{18}F]$FET PET cut-offs alone. Outcomes in the lesion and patient-wise analysis stratified according to recent radiotherapy are provided in Supplementary Table S4 (see Online resource 1).

ROC analysis of median parameter values in contrast-enhancing lesion are provided in Table 4 and Supplementary Fig. 1 (see Online resource 1). Overall accuracies (ROC AUC) of $F_{\text{med}}$ and $BV_{\text{med}}$ were similar, and both were lower than that of $TBR_{\text{med}}$. Whereas $K_{i_{\text{med}}}$ yielded the lowest accuracy. Combing DCE metrics did not improve ROC AUC compared to $BV_{\text{max}}$ alone. No clear influences of recent radiotherapy, MGMT or IDH status were observed in subgroup analyses; see Supplementary Table S3 (Online resource 1).

At the 6-month follow-up, five patients had died, all of which were above the patient-wise cut-off for both BV and $TBR_{\text{max}}$.

In the present study, we have compared the diagnostic yield of quantitative DCE BV imaging using 2CXM analysis with that of simultaneously performed $[^{18}F]$FET PET imaging in patients with suspected progressive high-grade glioma after standard therapy. The results (Table 2 and Fig. 5) showed good diagnostic performance of maximal BV parameters both lesion-wise and patient-wise with overall accuracies (ROC AUC) of 0.80 and 0.83, respectively, but still lower than $[^{18}F]$FET PET, that showed very good-to-excellent diagnostic performance with ROC AUCs of 0.89 and 0.96, respectively. Combined imaging did not increase diagnostic accuracy compared to $[^{18}F]$FET PET, but the classification-based level of concordance (Table 3) appeared to allow better lesion-wise risk stratification than that of single modalities.

To our knowledge, this is both the first study to investigate the diagnostic performance of 2CXM analysis of DCE data and the first to compare DCE, in general, with amino acid PET, and also one of the largest studies of diagnostic accuracy of DCE imaging in the post-treatment setting. Additionally, attenuation correction in our study was performed.
with individually acquired low-dose CT making the amino acid PET measurements directly comparable to PET/CT. Previous PET/MRI DSC studies have been performed with either template-based or measured surrogate AC methods that either ignore the effects of surgical metal implants and cranial modifications or are susceptible to artefacts that may impact on measurements [35, 36]. Furthermore, our patient selection criteria are more restrictive than previous studies excluding patients with low-grade glioma, oligodendrogial tumours or non-standard treatment, as the underlying pathology of both tumour and treatment damage, and hence $^{[18F]}$FET PET characteristics, cannot be expected to be identical.

This may explain the higher patient-wise accuracy of static parameters in the present study of 0.96 compared to values in the vicinity of 0.70–0.81 in recent studies of unselected glioma populations [21, 25, 37, 38].

MRI perfusion imaging in brain tumours is most widely performed by DSC BV imaging [39, 40]. Meta-analyses of DSC studies have reported pooled sensitivity and specificity of 83–88%, although at variable relative BV cut-offs [6, 41, 42]. Traditionally, DCE imaging has focused on quantification of permeability from a 2-parameter model (Tofts’ model) by estimation of Ve and of $^{K_{\text{trans}}}$, a mixed measure of permeability and blood flow. More recent studies have, in the right mesial frontal lobe. PET/MR showed mildly increased $^{[18F]}$FET uptake below the cut-off, but clearly increased permeability and BV above the cut-off. Surgery confirmed recurrent GBM. Lower row: A patient with grade III astrocytoma, IDH mutated, 4 years after last surgery and radiotherapy. PET/MR was performed due to new punctate enhancing lesions (arrow) but stable non-enhancing signal changes (not shown). DCE showed mildly increased blood volume below the cut-off visually difficult to separate from the vascular signal, while $^{[18F]}$FET uptake was markedly increased. Subsequent surgery confirmed recurrent grade III astrocytoma.

Fig. 4 Examples of $^{[18F]}$FET PET and DCE BV imaging providing complementary information. Upper row: IDH wild-type GBM, MRI 11 months after radiotherapy show a progressive large stellate enhancing lesion in the left temporal lobe. PET/MR shows high $^{[18F]}$FET uptake and increased permeability, but only focally increased blood volume (BV) below the cut-off. The patient had a prior history of histologically confirmed pseudo-progression 5 months earlier and was followed with frequent imaging. At MRI follow-up after 2 months, the enhancing lesion had regressed. Middle row: IDH wild-type GBM, progressive enhancing lesion 9 months after radiotherapy. Lower row: A patient with grade III astrocytoma, IDH mutated, 4 years after last surgery and radiotherapy. PET/MR was performed due to new punctate enhancing lesions (arrow) but stable non-enhancing signal changes (not shown). DCE showed mildly increased blood volume below the cut-off visually difficult to separate from the vascular signal, while $^{[18F]}$FET uptake was markedly increased. Subsequent surgery confirmed recurrent grade III astrocytoma.
general, applied a 3-parameter model (the extended Tofts’ model) also estimating the plasma volume, Vp. The overall sensitivity/specificity/ROC AUC of 77%/84%/0.80 of BVmax in the present study is somewhat lower than that of normalised Vp (nVp, 92%/77%/0.87) reported in a mixed population of gliomas and brain metastases following radiotherapy [43]. Of note, diagnostic performance in the glioma subgroup (with only 2/29 with radiation necrosis) was not reported. Other studies have found lower [44, 45] or even no [46] diagnostic value of nVp in suspected recurrent high-grade gliomas. A previous smaller study (n = 16) applying Patlak plot analysis of DCE data reported that an enhancing tumour absolute mean BV value of 2.0 ml/100 g provided 100% specificity and sensitivity [47]. Although we could not reproduce this excellent accuracy, it should be noted that the optimal absolute median BV cut-off of 2.5 ml/100 g in CE lesions in the present study is not very different. For clinical use, robustness is also of key importance. Based on
the information provided in Fig. 1, the technical failure rate among 413 scans with DCE performed can be estimated to be 1.9% which is acceptable, but slightly higher than for [18F]FET PET (0.7%). Our data, thus, suggests that the diagnostic accuracy of BV determined by the 2CXM approach applied is probably within the upper range of prior DCE studies reporting Vp, and also within the range, but not superior to that, of prior DCE and DSC studies in general [6, 41, 42], and may thus provide a viable alternative to other MRI perfusion techniques when amino acid PET is not available.

As opposed to DSC, DCE using 2CXM allows absolute quantification of both blood volume and permeability in addition to blood flow. Although the present analysis

| Table 2 | Empirical optimal cut-offs according to ROC analysis |
|------------------|------------------|------------------|------------------|------------------|
|                | TBR$_{\text{max}}$ | BV$_{\text{max}}$ (ml/100 g) | nBV$_{\text{max}}$ | Combined† |
| Overall (n=76) | 0.89             | 0.80             | 0.79             | 0.90         |
| Cut-off         | 2.27             | 10.43*           | 6.23             |
| Sensitivity     | 86.4 (72.6–94.8) | 70.5 (54.8–83.2) | 81.8 (67.3–91.8) | 72.7 (57.2–85.0) |
| Specificity     | 87.5 (71.0–96.5) | 90.6 (75.0–98.0) | 71.9 (53.3–86.3) | 90.6 (75.0–98.0) |
| Odds ratio      | 44.3 (11.7–166.5) | 23.1 (6.2–83.4) | 11.5 (3.9–33.6) | 25.8 (6.9–94.0) |
| PPV             | 90.5 (77.4–97.3) | 91.2 (76.3–98.1) | 80.0 (65.4–90.4) | 91.4 (76.9–98.2) |
| NPV             | 82.4 (65.5–93.2) | 69.0 (52.9–82.4) | 74.2 (55.4–88.1) | 70.7 (54.5–83.9) |
| Enhancing lesions (n=67) |              |                  |                  |              |
| ROC AUC         | 0.91             | 0.81             | 0.79             | 0.92         |
| Cut-off         | 2.27             | 10.43*           | 6.75             |
| Sensitivity     | 92.5 (79.6–98.4) | 77.5 (61.5–89.2) | 85 (70.2–94.3)  | 75 (58.8–87.3) |
| Specificity     | 85.2 (66.3–95.8) | 85.2 (66.3–95.8) | 66.7 (46.6–83.5) | 96.3 (81–99.9) |
| Odds ratio      | 70.9 (15.1–330)  | 19.8 (5.6–69.4)  | 11.3 (3.6–36.1)  | 78 (15.5–n.a.) |
| PPV             | 90.2 (76.9–97.3) | 88.6 (73.3–96.8) | 79.1 (64–90)     | 96.8 (83.3–99.9) |
| NPV             | 88.5 (69.8–97.6) | 71.9 (53.3–86.3) | 75 (53.3–90.2)  | 72.2 (54.8–85.8) |
| Non-enhancing lesions (n=9) |              |                  |                  |              |
| ROC AUC         | 0.70             | 0.70             | 0.90             | 0.80         |
| Cut-off         | 1.52             | 2.28             | 4.11*            |
| Sensitivity     | 75 (19.4–99.4)   | 75 (19.4–99.4)   | 75 (19.4–99.4)   | 75 (19.4–99.4) |
| Specificity     | 80 (28.4–99.5)   | 80 (28.4–99.5)   | 100 (47.8–100)   | 100 (47.8–100) |
| Odds ratio      | 12 (0.67–n.a.)   | 12 (0.67–n.a.)   | n.a. (1.81–n.a.) | n.a. (1.81–n.a.) |
| PPV             | 75 (19.4–97.4)   | 75 (19.4–97.4)   | 100 (29.2–100)   | 100 (29.2–100) |
| NPV             | 80 (28.4–99.5)   | 80 (28.4–99.5)   | 83.3 (35.9–99.6) | 83.3 (35.9–99.6) |
| Combined criteria (n=67/9) |              |                  |                  |              |
| Cut-off (CE / non-CE) | 2.27/1.52     | 10.43*/2.28      | 6.75/4.11*       |
| Sensitivity     | 90.9 (78.3–97.5) | 77.3 (62.2–99.4) | 84.1 (69.9–93.4) | 75 (59.7–86.8) |
| Specificity     | 84.4 (67.2–94.7) | 87.4 (71–96.5)   | 71.9 (53.3–86.3) | 96.9 (83.8–99.9) |
| Odds ratio      | 54 (13.7–213)    | 23.8 (6.9–80.7)  | 13.5 (4.4–49.6)  | 93 (14–n.a.) |
| PPV             | 88.9 (75.9–96.3) | 89.5 (75.2–97.1) | 80.4 (66.1–90.6) | 97.1 (84.7–99.9) |
| NPV             | 87.1 (70.2–96.4) | 73.7 (56.9–86.6) | 76.7 (57.7–90.1) | 73.8 (58–86.1) |
| Patient-wise (n=59) |              |                  |                  |              |
| ROC AUC         | 0.96             | 0.84             | 0.82             | 0.96         |
| Cut-off         | 2.27             | 10.43            | 5.33*            |
| Sensitivity     | 88.4 (74.9–96.1) | 69.8 (53.9–82.8) | 90.7 (77.9–97.4) | 86.0 (72.1–94.7) |
| Specificity     | 100 (79.4–100)   | 87.5 (61.7–98.4) | 68.8 (41.3–89.)  | 100 (79.4–100) |
| Odds ratio      | n.a. (26.6–n.a.) | 16.2 (3.5–n.a.)  | 21.5 (5.1–90.5)  | n.a. (22.2–n.a.) |
| PPV             | 100 (91–100)     | 93.8 (79.2–99.2) | 88.6 (75.4–96.2) | 100 (90.5–100) |
| NPV             | 76.2 (52.8–91.8) | 51.9 (31.9–71.3) | 73.3 (44.9–92.2) | 72.7 (49.8–89.3) |

Estimates are shown with a 95% confidence interval in parenthesis. †Combination of TBR$_{\text{max}}$ and best-performing BV cut-offs (indicated with*) ROC AUC, area under receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value; n.a. indicates that values could not be calculated; CE, contrast-enhancing lesions.
has focused on blood volume measurements, which have been more widely applied in clinical glioma imaging, we also assessed the diagnostic yield of other DCE parameters. Blood flow (F) measured by DCE appeared to have a diagnostic accuracy similar to that of BV in enhancing lesions, probably reflecting that the perfusion estimate is a diagnostic accuracy similar to that of BV in enhancing lesions, and further that the diagnostic yield of other DCE parameters is too small to make firm conclusions, it is noteworthy that in non-enhancing lesions, the optimal cut-offs of both TBRmax and BV parameters are markedly lower than in enhancing lesions, and further that the diagnostic performance of DCE BV was similar to that of \([18F]FET\) PET. This could suggest that in lesions with apparently intact BBB, any augmented FET uptake or increased BV, also below standard thresholds, could be indicative of an active tumour. Further studies investigating the potential value of DCE imaging in non-enhancing lesions are warranted.

The present study is among the largest studies of diagnostic yield of simultaneous amino acid PET and MRI BV imaging using hybrid PET/MRI systems. The use of hybrid PET/MRI secures simultaneous measurements and that between-modality variability is not caused by tumour progression, and that measurements are performed under identical physiological conditions and plasma levels of chemotherapy. In agreement with prior smaller studies using DSC, we found that combined BV and \([18F]FET\) PET imaging increased specificity compared to \([18F]FET\) PET imaging alone \([20, 22, 23, 28]\), although at the expense of lower sensitivity. Similar results have been found for combined \([18F]FDG\) PET and DSC BV imaging \([43, 48, 49]\). In a very recent large retrospective analysis of a heterogeneous sample of 104 patients comprising both low- and high-grade gliomas, the authors also found higher sensitivity of \([18F]FET\) PET and higher specificity of DSC BV obtained up to 3 months apart \([27]\). A large PET/MR study of 105 patients with suspected recurrence of predominantly high-grade gliomas found static \([18F]FET\) imaging to provide the highest diagnostic accuracy (79%) along with contrast enhancement (80%) as single modalities, whereas the diagnostic accuracies of both DSC (64%) and spectroscopy (53%) were lower \([25]\). Other hybrid PET/MRI studies have investigated various combinations of PET and advanced MRI techniques including spectroscopy and/or diffusion-weighted imaging \([20, 22, 23, 48, 50, 51]\). No single modality is expected to provide 100% accuracy, but as the various imaging modalities depict different aspects of tumour biology, multimodal imaging may provide means to overcome the limitation of single modalities. Although multimodal imaging studies, in general, suggest increased accuracy, the gain in accuracy is often marginal compared to that of the best-performing single modality \([52]\). Interpretation of multiparametric imaging

### Table 3 Frequency of progression according to combined optimal empirical cut-off

|          | BV < cut-off | BV > cut-off | Total     |
|----------|--------------|--------------|-----------|
| Lesion-wise |              |              |           |
| \([18F]FET\) < cut-off | 3/28 (11%) | 1/3 (33%) | 4/31 (13%) |
| \([18F]FET\) > cut-off | 7/11 (64%) | 33/34 (97%) | 40/45 (89%) |
| Total     | 10/39 (26%) | 34/37 (92%) | 44/76 (59%) |
| Patient-wise |            |              |           |
| \([18F]FET\) < cut-off | 3/14 (21%) | 2/7 (29%) | 5/21 (24%) |
| \([18F]FET\) > cut-off | 1/1 (100%) | 37/37 (100%) | 38/38 (100%) |
| Total     | 4/15 (27%) | 39/44 (89%) | 43/59 (73%) |

Numbers refer to fraction (%) with progression.

### Table 4 ROC analysis median parameters values in CE volumes

| Parameter | TBRmed | BVmed (ml/100 g) | Fmed (ml/100 g/min) | KImed (ml/100 g/min) |
|-----------|--------|-----------------|--------------------|---------------------|
| ROC AUC   | 0.91   | 0.76            | 0.78               | 0.68                |
| Cut-off   | 1.82   | 2.51            | 14.2               | 5.6                 |
| Sensitivity | 77.5 (61.5–89.2) | 65 (48.3–79.4) | 92.5 (79.6–98.4) | 72.5 (56.1–85.4) |
| Specificity | 92.6 (74.7–99.1) | 85.2 (66.3–95.8) | 59.3 (38.8–77.6) | 66.7 (46–83.5) |
| Odds ratio | 43.1 (9.21–n.a.) | 10.6 (3.2–35.4) | 17.9 (4.6–68.1) | 5.3 (1.9–15.0) |
| PPV       | 93.9 (79.8–99.3) | 86.7 (69.3–96.2) | 77.1 (62.7–88.7) | 76.3 (59.8–88.6) |
| NPV       | 73.5 (55.6–87.1) | 62.2 (44.8–77.5) | 84.2 (60.4–96.6) | 62.1 (42.3–79.3) |

Estimates are shown with a 95% confidence interval in parenthesis. ROC AUC, area under receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value.
may be complex, and the optimal combination of modalities and criteria of interpretation has not been established. Here, we have stratified lesions into a $2 \times 2$ matrix according to simplified single modality cut-offs. Others have applied a simple scoring system [53], or analysis of radiomic features [54] in order to extract and combine information from multiple modalities.

Although perfusion MRI and amino acid PET are often considered complementary modalities, it appears from a decision-making perspective that the incremental value of $[^{18}\text{F}]$FET PET added to DCE BV is greater than that of DCE BV added to $[^{18}\text{F}]$FET PET, as illustrated by more progressive lesions being positive on only $[^{18}\text{F}]$FET PET than only on DCE BV imaging. In many centres, hybrid PET/MR is not available, and perfusion MRI and PET imaging must be obtained on separate MR and PET systems. Although same-day combined evaluation could be achieved by separate scans and subsequent software image registration, the high-positive predictive value of DCE BV shown here could suggest a sequential imaging strategy with $[^{18}\text{F}]$FET PET only required if DCE BV is negative. Based on data presented in Table 3, 37/76 (49%) of lesions and 44/59 (75%) of patients would accordingly not require $[^{18}\text{F}]$FET PET and thus reduce overall costs substantially at the expense of a minor decrease in the fraction of correctly classified lesions to 86.7% (sensitivity 93.2% and specificity 78.1%) compared to $[^{18}\text{F}]$FET PET (88.2%) in all lesions. This is in line with a recent study of DSC BV and FET PET, suggesting that such a strategy could reduce the need for $[^{18}\text{F}]$FET PET by 42%. [27]

Similar to others, we applied a combined outcome measure based on a follow-up including histology and MRI follow-up. The present study lacks histopathological confirmation in 2/3 of lesions, which may be seen as a limitation. However, retrospective data that select only patients with tissue as a reference may suffer from verification bias, as the decision to resect or biopsy may be influenced by the PET result, among other factors [18]. In treated tumours, both imaging and tissue samples may represent heterogeneous pathology with both tumour and treatment effects. In the absence of image-correlated stereo-biopsies, it is not possible directly to link the tissue examined with imaging features within the lesion. Also, the study population may differ from that of routine imaging and also from studies involving MR only which may allow consecutive imaging without referral bias, as opposed to PET/MR relying on the fraction of patients not managed by MRI alone. To ensure a homogenous study population, we applied relatively strict criteria in terms of histology and prior treatment and furthermore only included patients with evaluable outcomes after the scan, thus excluding also those in whom second-line treatment was initiated after the scan without histopathological confirmation. The imaging protocol did not include dynamic $[^{18}\text{F}]$FET PET imaging which has been reported to improve diagnostic accuracy [20, 38]. However, the added value of dynamic imaging may be modest [20, 55], and as dynamic characteristics may be related to tumour perfusion [56, 57], we expect that the incremental diagnostic value of dynamic imaging would be relatively small when added to combined static $[^{18}\text{F}]$FET PET and perfusion imaging. Finally, the present analysis was based on simplified metrics not taking into account morphology or prior imaging, which are key elements of clinical reading. Due to these limitations, diagnostic accuracies reported here should be interpreted with caution, and future prospective studies should investigate the diagnostic performance in a well-controlled, multi-reader set-up. Still, we believe that the comparison of diagnostic performance between modalities is valid due to the common outcome measure.

Conclusions

The present study shows a good diagnostic performance of DCE BV imaging using the 2CXM approach with maximal BV providing the highest accuracy among investigated metrics, but also confirms higher overall diagnostic accuracy of $[^{18}\text{F}]$FET PET for differentiation of tumour progression from treatment-related effects in patients with anaplastic astrocytoma and glioblastoma. Combined imaging did not improve the diagnostic accuracy of $[^{18}\text{F}]$FET PET, but may increase specificity and allow better risk stratification of $[^{18}\text{F}]$FET PET avid lesions.

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Data Availability Meta-data are available as Supplementary information in Online resource 2. Additional used and/or analysed during the current study are available from the corresponding author on request.

Code availability Not applicable.
Declarations

Ethics approval Retrospective use of clinical data from 2016 to 2019 was approved by the Danish Patient Safety Authority (reference no. 3–3013-1957/1) and for data after January 2020 by the local hospital administration. A subset of patients participated in prospective studies approved by the local ethics committee (H-17040888) in accordance with the Helsinki Declaration.

Consent to participate Patients included in the prospective study gave informed written consent prior to the scan.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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