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Comparison of visual and semiquantitative analysis of ^{18}F-FDOPA-PET/CT for recurrence detection in glioblastoma patients

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Background. Amino acid transport imaging with ^{18}F-FDOPA PET is increasingly used for detection of glioblastoma recurrence. However, a standardized image interpretation for ^{18}F-FDOPA brain PET studies has not yet been established. This study compares visual and semiquantitative analysis parameters for detection of tumor recurrence and correlates them with progression-free survival (PFS).

Methods. One-hundred ten patients (72 male:38 female) with suspected tumor recurrence who underwent ^{18}F-FDOPA PET imaging were studied. PET scans were analyzed visually (5-point scale) and semiquantitatively (lesion-to-striatum- and lesion- to-normal-brain-tissue ratios using both SUV_{mean} and SUV_{max}). Accuracies for recurrence detection were calculated using histopathology and clinical follow-up for validation. Receiving operator characteristic and Kaplan-Meier survival analysis were performed to derive imaging-based prediction of PFS and overall survival (OS).

Results. Accuracies for detection of glioblastoma recurrence were similar for visual (82%) and semiquantitative (range, 77%–82%) analysis. Both visual and semiquantitative indices were significant predictors of PFS, with mean lesion-to normal brain tissue ratios providing the best discriminator (mean survival, 39.4 vs 9.3 months; $P < .001$). None of the investigated parameters was predictive for OS.

Conclusions. Both visual and semiquantitative indices detected glioblastoma recurrence with high accuracy and were predictive for PFS. Lesion-to-normal-tissue ratios were the best discriminators of PFS; however, none of the investigated parameters predicted OS. These retrospectively established analysis parameters need to be confirmed prospectively.

Keywords: glioblastoma, ^{18}F-FDOPA, recurrence detection.

Twenty-two thousand nine hundred new cases of primary tumors of the brain and central nervous system were expected in the United States in 2012,[1] with glioblastoma accounting for around 40% of the malignant tumors.[2] Advances in diagnosis and therapy are modest, and the outcome of patients with glioblastoma remains abysmal with 4-year survival rates of 12%.[3]

Magnetic resonance imaging (MRI) is the modality of choice for brain tumor imaging, while computed tomography (CT) is reserved for those patients who cannot tolerate MRI scans.[4] As differentiation between treatment-related changes and residual or recurrent tumor is difficult using anatomic imaging modalities such as MRI and CT, brain PET "may be useful in differentiating tumor from radiation necrosis," but the "accuracy of interpretation" is considered to be a relevant limitation.[4] A number of PET tracers probing glucose metabolism, amino acid transport, phospholipid metabolism, tumor blood flow, hypoxia, proliferations, and others have been tested for detecting primary and recurrent brain tumors.[5]

Recent studies suggest that probes of amino acid transport could play an important role in brain tumor assessments.[6] Whereas ^{18}F-fluoroethyltyrosine (^{18}F-FET) and ^{11}C-methionine are used clinically in Europe,[7–10] our group has previously demonstrated good detection of primary and recurrent glioblastomas with L-3,4-dihydroxy-6-^{18}F-fluoro-phenyl-alanine (^{18}F-FDOPA) as well as a considerable impact on patient management.[11–14]

The dopamine precursor ^{18}F-FDOPA accumulates in the basal ganglia as a marker of presynaptic aromatic amino acid decarboxylase (AADC) activity and shows only minimal uptake in the

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normal cerebral cortex and white matter. The metabolic fate of ^{18}F-FDOPA in brain tumors has been described before.[15] In brief, brain tumor uptake of ^{18}F-FDOPA is predominantly determined by expression and activity of the L- amino acid transporters (LAT) and is largely independent of the blood-brain barrier integrity. Thus ^{18}F-FDOPA detects both contrast-enhancing and nonenhancing brain tumors.[11] A retrospective analysis revealed that a tumor-to-striatum ratio $\geq$1.0 was the best threshold for confirming or ruling out tumor recurrence.[11] ^{18}F-FDOPA PET also correctly identified tumor that was not visible on MRI[13] and predicted response in recurrent malignant gliomas treated with bevacizumab using parametric response maps.[12] A questionnaire study reported change of intended management based on the ^{18}F-FDOPA PET reports in 41% of patients with brain tumors.[14]

The aim of the current study was to identify the ^{18}F-FDOPA PET imaging parameters that most accurately identify recurrence and best predict progression-free survival (PSF) and overall survival (OS) in patients with suspected brain tumor recurrence.

Materials and Methods

Patient Population

One hundred ten patients (72 males:38 females; mean age, 51.7 $\pm$ 12.1 years; median age, 52.5 years; age range 23–80 years) underwent ^{18}F-FDOPA PET ($n = 41$) or ^{18}F-FDOPA PET/CT ($n = 69$) for suspected glioblastoma recurrence based on contrast enhancement on MRI scans. Four patients had been included in a previous publication.[13] Since 10 patients had multiple PET scans only the first scan performed for suspected recurrence was analyzed. Because of the retrospective nature of the study, the informed consent requirement was waived by the UCLA Institutional Review Board.

Image Acquisition and Reconstruction

^{18}F-FDOPA was synthesized as described previously[16] and injected intravenously at a dose of 3.62 $\pm$ 0.82 mCi. Based on a previous analysis,[15] the emission scan was started 10 minutes after tracer injection. Images were acquired for 20 minutes in the 3-dimensional mode. Image data acquired between 10 and 30 minutes after injection were summed to obtain a 20-minute static image. Several PET (high-resolution full-ring ECAT HR [$n = 5$] or ECAT HR+ PET [$n = 43$]) and PET/CT scanners (Biograph Duo [$n = 10$], Biograph 64 [$n = 9$] or Biograph mCT [$n = 43$]) were used as previously reported.[13,14] In patients undergoing PET scans, 5-minute transmission scans were acquired after the static emission scans to correct for photon attenuation. In patients undergoing PET/CT scans, a dedicated CT scan of the brain (120 kV, 80 mAs, 1-s tube rotation, 3-mm slice collimation) was acquired for attenuation correction. PET Images were reconstructed using an iterative algorithm (OSEM, 6 iterations, 8 subsets).[17] The CT data were used for attenuation correction and lesion localization.[18]

Image Interpretation

All ^{18}F-FDOPA PET/CT studies were interpreted by an experienced, blinded nuclear medicine physician (W.C.) using MRI images acquired within one week prior to PET as a reference. Images were first inspected visually. The axial PET image slice displaying the maximum lesion ^{18}F-FDOPA uptake was selected and compared with the axial PET image slice with the maximum striatal ^{18}F-FDOPA uptake. Both quantitative and qualitative approaches were applied for image analysis.

For quantitative analysis, a 10 mm circular region was placed over the area exhibiting the peak tracer activity. This region of interest (ROI) was used to derive maximum (SUV_{max}) and mean standardized uptake values (SUV_{mean}). A normal reference brain region was defined by drawing an ROI involving the contralateral striatum to derive maximum and mean lesion-to-striatum (max L/S, mean L/S) uptake ratios. When the contralateral striatum was tumor, a region was placed in contralateral normal brain tissue to derive maximum and mean lesion-to-normal-brain (max L/NB, mean L/NB) ratios. SUV_{mean} and SUV_{max} were calculated to derive lesion-to-striatum and lesion-to-normal-tissue ratios.

A 5-point visual scale was used to qualify lesions as follows: -2 = lesion nonvisible on PET; -1 = lesion visible but $<$ than striatal uptake; 0 = lesion and striatal uptakes appear isointense; 1 = lesion uptake $>$ than striatal uptake, 2 = lesion much greater than striatal uptake (Fig. 1).

Outcome Assessment

Clinical follow-up of patients was performed at least every 3 months or at shorter intervals as clinically indicated. Clinical reassessment consisted of standard evaluations including imaging (MRI and/or CT) and assessment of neurological symptoms. Scan findings were validated against histopathology ($n = 41$; 37.3%) or clinical follow-up within 6 months of the PET scan. In cases without histopathological verification, PET scans were rated true positive if clinical symptoms worsened, MRI scans showed progression of contrast enhancement, or clinical management changes were documented in medical records, which were checked. In contrast, a PET scan was considered false positive if either histopathology was negative or the clinical situation was stable for at least 6 months.

OS and PS were calculated from date of the baseline PET scan to the date of death/progression or the date of last follow-up. For calculation of time of follow-up, baseline PET and May 31, 2012 (last update of patient outcome) were used.

Statistical Analysis

Quantitative data are presented as median, range, and mean $\pm$ SD. The Wilcoxon signed rank test and the Mann-Whitney test were used for paired and unpaired comparisons of quantitative parameters. Corresponding accuracies for recurrence detection were calculated using histopathology and clinical follow-up for validation. The chi-square or Fisher exact test was conducted for comparison of frequency data between independent subgroups. Receiver operating characteristic (ROC) curves were used to determine optimal cut-off values for defining disease recurrence and predicting survival. The Fisher 'exact test was used to assess association of 2 categorical variables. Survival probabilities were calculated according to the Kaplan-Meier method, and the log-rank test was used for statistical comparison of survival curves between independent subgroups. Multivariate survival analysis was performed by Cox proportional hazards regression, and corresponding hazard ratio estimates were provided with 95% confidence intervals.

Statistical analyses were performed using SPSS, version 19.0 (SPSS). All statistical tests were performed 2-sided, and a P value $<.05$ was considered to indicate statistical significance. No correction of P values was applied to adjust for multiple tests.[19]

Results

Patient Information

All patients were referred to PET scanning for suspected disease recurrence. Initially, all patients had grade III ($n = 33$; 30.0%) or grade IV ($n = 77$; 70.0%) disease. The time between first surgery and PET scan averaged 37.3 $\pm$ 36.3 months (median, 20.4 months). Histopathology data were available for 41 patients (37.3%), which confirmed tumor recurrence in 37 patients, and ruled out disease progression in 4 patients. Clinical follow-up

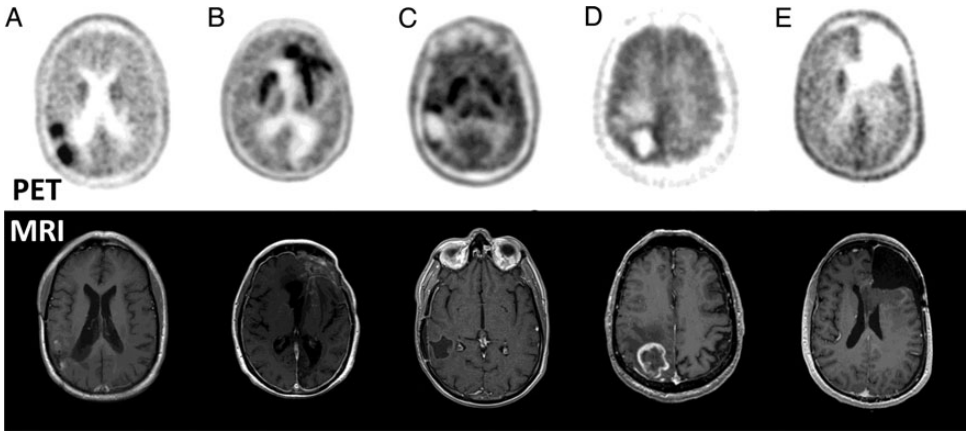

Fig. 1. Axial views of PET and corresponding MRI images of 5 patients with suspected glioblastoma recurrences. Examples represent each of the 5 scoring options (2 = lesion uptake much greater than striatal uptake; 1 = lesion uptake greater than striatal uptake; 0 = lesion and striatal uptake appears isointense; −1 = lesion visible but < than striatal uptake; −2 = lesion nonvisible on PET). (A) ^{18}F-DOPA-PET and MRI images of a 62-year-old male. FDOPA uptake was scored as 2. Lesion /striatum and lesion/normal brain SUV_{mean} ratios were 1.92 and 3.51, respectively. Recurrence was confirmed by histopathology, and the patient died within 3 months of the PET study. (B) ^{18}F-DOPA-PET and MRI images of a 50-year-old male. FDOPA uptake was rated as 1. Lesion/striatum and lesion/normal brain SUV_{mean} ratios were 1.30 and 2.78, respectively. Histopathological verification was not available, and the patient died within 7 months of PET scan. (C) ^{18}F-DOPA-PET and MRI images of a 47-year-old male. FDOPA uptake was rated as 0. Lesion/striatum and lesion/normal brain SUV_{mean} ratios were 0.94 and 1.53, respectively. Recurrence was confirmed by histopathology, and the patient died within 9 months of PET scan. D: ^{18}F-DOPA-PET and MRI images of a 72-year-old male. FDOPA uptake was scored as -1. Lesion/striatum and lesion/normal brain SUV_{mean} ratios were 0.87 and 1.47, respectively Subsequent histopathology revealed necrosis; the patient died 12 months after the PET scan. E: ^{18}F-DOPA-PET and MRI images of a 41-year-old male. FDOPA uptake was scored as -2. Lesion/striatum and lesion/normal brain SUV_{mean} ratios were 0.75 and 1.32, respectively. Histopathological verification was not available; the patient was alive 15 months after the PET scan.

and/or follow-up imaging ($n = 69$, 62.7%) revealed recurrence in 44 patients; there were no signs of disease progression in 25 patients. In summary, 81 patients (73.6%) presented with recurrent tumor, and 29 patients (26.4%) were progression-free at the time of the PET scan.

Patient Follow-up

Clinical follow-up of patients was performed at the discretion of the treating physicians. Mean follow-up duration was 40.6 months (median, 34.9 months; range, 4.2–111.6 months). During follow-up, a total of 70 deaths (63.6%) occurred, and disease progression was found in 87 patients (79.1%). Mean PFS was 7.5 months (median, 1.9 months; range, 0–107.9 months). The mean OS was 17.0 months (median, 11.4 months; range, 1.0–107.9 months).

Visual PET Image Analysis

PET scans were rated using a 5-point scale with 10 scans rated as −2 (9.1%), 23 scans as −1 (20.9%), 18 scans as 0 (16.4%), 11 scans as 1 (10.0%), and 48 scans as 2 (43.6%), respectively. When data were dichotomized (scores of 0, 1, and 2 being positive and scores of −1 and −2 being negative), 77 scans (70.0%) were rated as positive and 33 scans (30.0%) as negative. This binary assessment resulted in a sensitivity of 85.2% (69:81), a specificity of 72.4% (21:29), and accuracy, positive and negative predictive values of 81.8% (90:110), 89.6% (69:77) and 63.4% (21:33), respectively.

Semiquantitative PET Image Analysis

Lesion SUV_{max} and SUV_{mean} averaged 3.3 ± 1.5 (range, 0.8–7.9) and 2.8 ± 1.3 (range,: 0.7–7.3), respectively. Both SUV_{max} and SUV_{mean} were significantly higher in patients with verified disease progression at time of PET scan than in those without progression (SUV_{max}, 3.6 ± 1.5 vs 2.5 ± 1.2; $P = .001$; SUV_{mean}: 3.0 ± 1.3 vs 2.1 ± 1.2; $P < .001$).

Mean uptake values for normal reference brain and striatum were 1.1 ± 0.4 and 2.4 ± 0.8 and were similar in patients with and without progressive disease. Maximum and mean lesion-to-striatum SUV ratios (max L/S and mean L/S ratios) averaged 1.4 ± 0.5 (range, 0.4–2.9) and 1.2 ± 0.4 (range, 0.3–2.2), respectively. Both maximum and mean L/S ratios were significantly higher in patients with verified disease progression at time of PET scan (max L/S ratio, 1.5 ± 0.5 vs 1.0 ± 0.4; $P < .001$; mean L/S ratio, 1.3 ± 0.4 vs 0.9 ± 0.3; $P < .001$).

Maximum and mean lesion-to-normal brain ratios (max L/NB and mean L/NB ratios) were 3.2 ± 1.6 (range, 1.0–9.9) and 2.7 ± 1.4 (range, 0.7–7.6), respectively. These ratios were significantly higher in progressive than in nonprogressive patients (max L/NB ratio, 3.5 ± 1.7 vs 2.4 ± 1.3, $P = .002$; mean L/NB ratio, 2.9 ± 1.4 vs 2.0 ± 1.1, $P = .001$) (Table 1).

Validation of PET Parameters

Semiquantitative image analysis did not improve accuracy over visual PET image analysis. ROC analyses of lesion-to-striatum and lesion-to-normal brain ratios revealed areas under the curve ranging from 0.77 to 0.82 (Table 2), while visual scores resulted in

Table 1. PET uptake values for all patients as well the subgroups of patients with and without progression during follow-up

Parameter	Mean Value All Patients	SD	Range	Mean Value Progression	SD	Mean Value No Progression	SD	P value
SUV_{max}	3.3	1.5	0.8–7.9	3.6	1.5	2.5	1.2	.001
SUV_{mean}	2.8	1.3	0.7–7.3	3.0	1.3	2.1	1.1	<.001
SUVnormal	1.1	0.4	0.5–3.0	1.1	0.4	1.1	0.4	.909
SUVstriatum	2.4	0.8	1.0–5.0	2.4	0.8	2.4	0.8	.988
SUV_{max}-to-Striatum	1.4	0.5	0.4–2.9	1.5	0.5	1.0	0.4	<.001
SUV_{mean}-to-striatum	1.2	0.4	0.3–2.2	1.3	0.4	0.9	0.3	<.001
SUV_{max}-to-normal	3.2	1.6	1.0–9.9	3.5	1.7	2.4	1.3	.002
SUV_{mean}-to-normal	2.7	1.4	0.7–7.6	2.9	1.4	2.0	1.1	.001

Abbreviation: SD, standard deviation.

Table 2. Receiver operating characteristic analyses of different parameters for prediction of outcome

Parameter	AUC	95% CI
Visual scale	0.82	0.72–0.92
SUV_{max}-to-striatum	0.81	0.72–0.91
SUV_{mean}-to-striatum	0.82	0.72–0.91
SUV_{max}-to-normal	0.77	0.65–0.88
SUV_{mean}-to-normal	0.78	0.68–0.89

Abbreviations: AUC, area under the curve; CI, confidence interval.

an area under the curve (AUC) of 0.82. The previously published threshold[11] of a max L/S-ratio ≥1.0 resulted in a sensitivity of 84.0% (68:81), a specificity of 62.1% (18:29), and an accuracy of 78% (86:110).

PET Based Predictions of Progression-free Survival

AUC values of L/S and L/NB ratios (Fig. 2) for prediction of PFS ranged from 0.74 to 0.76 (Table 3). ROC analysis for the visual scale resulted in an AUC of 0.78. Kaplan-Meier analysis, using the visual scale as discriminator, resulted in a significantly longer mean PFS in patients with a visually negative PET scan (23.8 months vs 11.0; log-rank test $P < .001$) (Fig. 3). Among the semiquantitative parameters, mean L/NB-ratio discriminated best (log-rank test $P < .001$), resulting in a mean PFS of 39.4 months if the mean L/NB-ratio was <1.8 (9.3 months if mean L/NB-ratio was ≥1.8) (Fig. 3). The previously published threshold[11] was also a significant predictor for PFS (mean PFS if max L/S-ratio ≥1.0; 15.8 months vs 18.9 months for max L/S-ratio <1.0; log-rank test $P = .015$). Mean PFS for all parameters tested are shown in Table 3.

AUC values of semiquantitative parameters for prediction of PFS were 0.71 for SUV_{max} and 0.73 for SUV_{mean}, respectively. Both parameters were significant discriminators for predicting PFS (SUV_{max}, 31.5 vs 9.6 months; log-rank test $P < .001$; SUV_{mean}, 39.4 vs 12.3 months; log-rank test $P < .001$) (Table 3).

PET Parameters for Predicting Overall Survival

AUC values of all semiquantitative parameters including L/S and L/NB ratios, initial SUV_{max} and SUV_{mean}, as well as visual scale, ranged between 0.48 and 0.61 (Fig. 2). As none of the investigated parameters was predictive for OS, no Kaplan-Meier analyses were performed.

Discussion

This is the first study to examine the value of ^{18}F-FDOPA uptake in regions of suspected glioblastoma recurrence in predicting PFS and OS. First, this study demonstrates that ^{18}F-FDOPA PET in the setting of suspected recurrence (by MRI) shows a significant diagnostic accuracy of 82% (sensitivity, 89.6%; specificity, 72.4%) in distinguishing recurrent disease from treatment-related changes (Fig. 1). Second, ^{18}F-FDOPA PET is highly prognostic of PFS. Patients with positive ^{18}F-FDOPA PET scans had a 4.2 times longer median survival than patients with positive ^{18}F-FDOPA PET (39.4 months vs 9.3 months; $P < .001$). Third, this prognostic information was derived equally well from visual and semiquantitative image analysis. Lastly, none of the investigated parameters was a significant predictor for OS.

Only a few studies have investigated the prognostic value of PET probe uptake in suspected glioma recurrence.[20–24] The first showed that visual analysis of ^{18}F-FDG-PET was a significant predictor of survival ($P = .019$) in 55 patients with recurrence of high-grade glioma.[20] In a more recent publication, baseline ^{18}F-FDG PET significantly predicted PFS and OS in recurrent high-grade glioma patients scheduled to undergo treatment with bevacizumab and irinotecan if a cut-off of SUV_{max} of 7 or an L/NB-ratio of 1.35 were used.[21] In contrast, others observed no prognostic value of ^{18}F-FDG PET or ^{11}C-Methionine (^{11}C-MET) PET in 28 patients with suspected glioblastoma recurrence.[24] The only other study investigating the prognostic value of ^{11}C-MET in recurrent high-grade glioma reported that the survival of patients undergoing stereotactic fractionated radiotherapy is longer if ^{11}C-MET PET information is integrated into the treatment planning compared with MRI/CT alone.[22] The prognostic value of ^{18}F-tyrosine (FET) has been recently studied in 56 patients with recurrent malignant glioma scheduled to undergo re-irradiation.[23] L/NB ratios did not predict PFS or OS. However, kinetic analysis provided independent predictions for OS but not PFS.

This study indicates that visible ^{18}F-FDOPA-tumor uptake predicts PFS but not OS. Similar results were reported for dynamic ^{18}F-FET-PET used for radiation treatment planning in primary glioblastoma.[25] One potential explanation is the large variety of available treatments even in patients with multiple recurrences. In

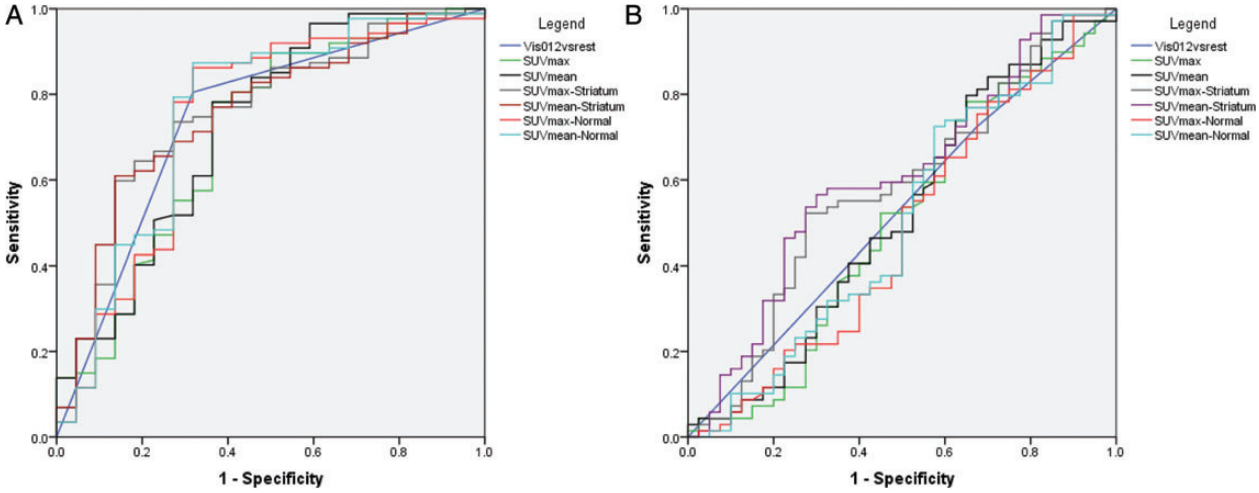

Fig. 2. ROC analysis of semiquantitative and visual parameters for prediction of (A) progression-free survival and (B) overall survival.

Table 3. Receiver operating characteristic analyses for different parameters for prediction of progression-free survival and corresponding cutoffs

Parameter	AUC	Cutoff	Log-rank P value	Mean PFS for 0	Mean PFS for 1
Visual scale	0.78	NA	<.001	23.8	11.0
SUV_{max}-to-striatum	0.76	1.11	<.001	27.6	11.5
SUV_{mean}-to-striatum	0.76	1.06	<.001	24.5	7.6
SUV_{max}-to-normal	0.74	2.05	<.001	38.0	9.3
SUV_{mean}-to-normal	0.76	1.81	<.001	39.4	9.3
SUV_{max}-to-striatum	0.76	1.00	.015	18.9	15.8
SUV_{max}	0.71	2.47	<.001	31.5	9.6
SUV_{mean}	0.73	2.01	<.001	39.4	12.3

Abbreviations: AUC, area under the curve; PFS, progression-free survival; NA, not applicable.

addition, it is likely that patients with evidence for recurrence were treated more aggressively, which might have reduced the prognostic value of ^{18}F-FDOPA PET scans. Therefore, PFS might be a more appropriate outcome marker for the validation of prognostic PET biomarkers in glioblastoma. Furthermore, it is quite possible that in patients with aggressive recurrent disease, blood-brain barrier breakdown might alter ^{18}F-FDOPA uptake, which in turn may affect the prognostic value of ^{18}F-FDOPA, especially in patients with multiple treatments.

We had previously reported that the best diagnostic discriminator was an ^{18}F-FDOPA L/S ratio >1.0, which resulted in prospective and retrospective diagnostic accuracy of 88% and 97%, respectively. These values compared favorably with the current accuracy of 78% when the same threshold was applied.[11] Using the visual analysis approach, the current accuracy was 82%. These values are inferior to those recently reported by others, who reported an accuracy of 96% in 28 patients with suspected glioblastoma recurrence.[26] The reason for this difference in accuracy might be

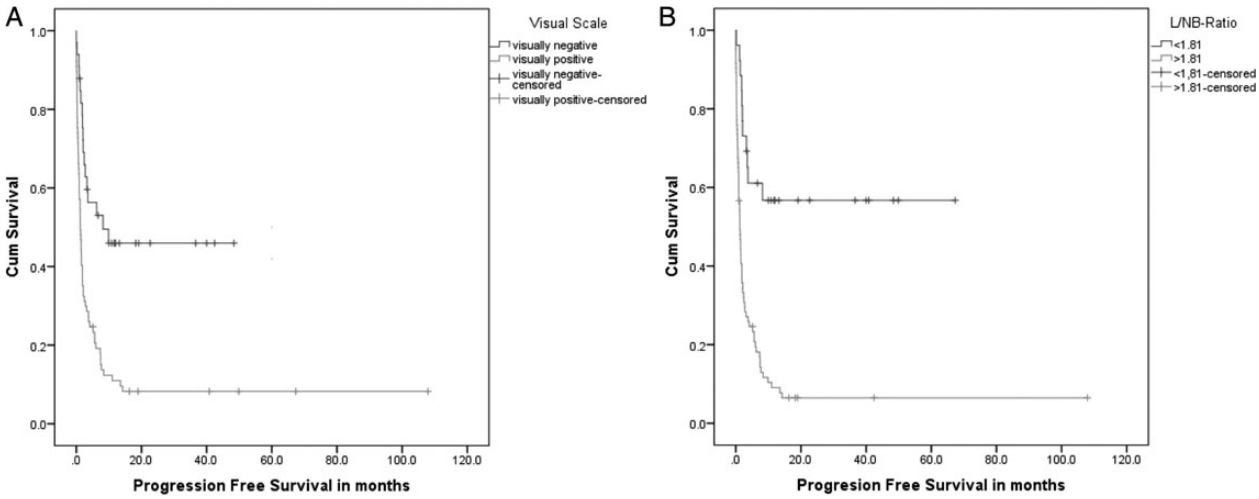

Fig. 3. Kaplan Meier survival analysis plots for prediction of progression-free survival using (A) visual scale, and (B) mean lesion-to-normal brain ratios as discriminators. Corresponding log-rank test *P* values are $P < .001$ for both, respectively.

explained by different patient populations studied. Our previous study investigated a mixed population of newly diagnosed and recurrent tumors as well as patients with tumors of different grades. In our pilot prospective study, there was a mixed population of newly diagnosed (7:30, 23.3%) as well as recurrent tumors (23:30, 76.7%) with 50% recurrent glioblastoma (15:30) (*11*). The subsequent prospective study included 41.2% patients with recurrent glioblastoma (21:51) (*11*). In the recently published study with 28 patients, there was again only 46.4% of patients with recurrent glioblastoma (13/28) (*25*). It is possible that a different diagnostic discriminator should be used for recurrent tumors of different grades. ^{18}F-FDOPA PET might have a higher diagnostic accuracy in lower-grade recurrent gliomas than in glioblastoma because patients with glioblastoma recurrence undergo more aggressive treatments, which potentially affects the prognostic value of ^{18}F-FDOPA PET.

Interestingly, visual scale performed as well as any semiquantitative parameter (Table 2). In fact, visual analysis had the highest AUC value of investigated parameters including all semiquantitative indices. This is in agreement with recently published data[26] and enables easy translation into the clinical setting.

The current study has several limitations: First, the current retrospective data need to be confirmed prospectively. Second, different PET systems were used, which might have affected SUV measurements. However, we performed phantom measurements to verify that SUVs from different scanners were comparable. Third, kinetic analysis may have improved ^{18}F-FDOPA-based outcome predictions even though we have previously shown that this is not necessarily the case.[15] Lastly, as patients were selected based on positive MRI diagnosis of recurrent disease, there is potentially a selection bias. However, an important strength of our study is the high number of enrolled patients.

In summary, both visual and semiquantitative analysis of ^{18}F-FDOPA tumor uptake accurately predicted PFS in patients with recurrent glioblastoma. However, neither parameter was predictive for OS. These promising and easily clinically applicable results need to be confirmed prospectively.

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Conflict of interest statement. None declared.

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