



Heterogeneous parameters based on ^{18}F -FET PET imaging can non-invasively predict tumor grade and isocitrate dehydrogenase gene 1 mutation in untreated gliomas

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Background: The present study aimed to explore the efficacy of easily obtained intratumoral heterogeneous parameters, other than regular semi-quantitative parameters, based on static O-(2-[^{18}F]fluoroethyl)-l-tyrosine (^{18}F -FET) positron emission tomography (PET) imaging in glioma grade and isocitrate dehydrogenase (*IDH*) gene 1 mutation prediction.

Methods: Fifty-eight adult patients with untreated glioma (grades II–IV) who underwent preoperative ^{18}F -FET PET/computed tomography (CT) imaging were enrolled in the present study. Eight semi-automatically obtained static PET imaging parameters after lesion delineation were chosen for analysis. These were: maximal tumor-to-background ratio (TBR_{max}), peak tumor-to-background ratio (TBR_{peak}), mean tumor-to-background ratio (TBR_{mean}), coefficient of variation (COV), heterogeneity index (HI), the standard deviation of lesion standardized uptake value (SUV_{sd}), metabolic tumor volume (MTV), and total lesion tracer standardized uptake (TLU). Pathological and immunohistochemical results were used as a reference. The receiver-operating characteristic analysis was used to investigate the predictive efficacy of these parameters in glioma grade and *IDH1* mutation status.

Results: TLU [area under the curve (AUC): 0.841, $P < 0.0001$], TBR_{peak} (AUC: 0.832, $P < 0.0001$), and HI (AUC: 0.826, $P < 0.0001$) had the top 3 single-parameter predictive performance between grade II or III and grade IV glioma patients. Combinations of TBR_{max}, SUV_{sd}, and TBR_{mean} (AUC: 0.850, $P < 0.0001$); HI, SUV_{sd}, and MTV (AUC: 0.848, $P < 0.0001$); and HI, SUV_{sd}, and TLU (AUC: 0.848, $P < 0.0001$) had the top 3 multiple-parameter predictive performance. SUV_{sd} (AUC: 0.710, $P = 0.0028$), TLU (AUC: 0.698, $P = 0.0074$), and HI (AUC: 0.676, $P = 0.0159$) had the top 3 single-parameter predictive performance in the *IDH1* genotype. Combinations of TBR_{max}, SUV_{sd}, and TBR_{mean} (AUC: 0.821, $P < 0.0001$); SUV_{sd} and TBR_{mean} (AUC: 0.804, $P < 0.0001$); and SUV_{sd}, HI, and TBR_{mean} (AUC: 0.799, $P < 0.0001$) had the top 3 multiple-parameter predictive performance.

Conclusions: These easily obtained and highly repetitive heterogeneous parameters based on static ^{18}F -FET PET/CT imaging can non-invasively predict glioma grade and *IDH1* mutation, crucial in treatment planning, and prognostic evaluation.

Keywords: O-(2-[^{18}F]fluoroethyl)-l-tyrosine (^{18}F -FET); glioma; heterogeneity; isocitrate dehydrogenase gene mutation (*IDH* gene mutation); positron emission tomography (PET); adults

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Introduction

Prognostication and treatment monitoring are related to glioma grade. Patients with different glioma grades have different natural histories and treatments. Isocitrate dehydrogenase (*IDH*) gene mutation is frequently observed in grades II and III glioma and secondary glioblastoma patients. In contrast, only limited *IDH* mutations are observed in primary glioblastoma patients (1,2). *IDH*-mutated gliomas have different biologic behavior and better treatment response and prognosis than *IDH* wild-type gliomas (3). Both glioma grade and *IDH* mutation status need to be confirmed by pathological results based on surgical resection or biopsy tissues. Non-invasive glioma grade and *IDH* mutation status prediction are crucial for treatment decision-making and prognostic evaluation in untreated glioma patients (4).

Amino acid tracer positron emission tomography (PET) imaging focuses on the metabolic status of glioma cells and could be used as an effective complementary diagnostic modality besides magnetic resonance imaging (5). O-(2-[^{18}F]fluoroethyl)-l-tyrosine (^{18}F -FET) is an amino acid tracer that generally has significant uptake in glioma tissues and lower uptake in background brain tissues. The characteristic of ^{18}F -FET PET imaging has led to wide clinical application, including grading (6,7), differential diagnosis (8,9), delineation of tumors (10,11), treatment plan decision-making (12-14), and prognostication (15,16), and has been recommended for use during all phases of glioma diagnosis and treatment (17,18).

Diagnostic semi-quantitative parameters, including maximal tumor-to-background ratio (TBR_{max}) and mean tumor-to-background ratio (TBR_{mean}), can be obtained from static ^{18}F -FET imaging. Volumetric parameters, such as metabolic tumor volume (MTV) and total lesion tracer standardized uptake (TLU), which is similar to total lesion glycolysis in ^{18}F -fluorodeoxyglucose (FDG) imaging, are widely used in tumor imaging analysis (19,20). Dynamic ^{18}F -FET imaging could provide extra tracer uptake information other than static imaging (21). Further imaging analyses, such as texture analyses and radiomics, can be used for imaging data mining to extract a vast amount of imaging features for analysis; however, these techniques are complicated and not suitable for routine clinical imaging analysis and diagnosis.

Heterogeneity is a feature of malignant tumors. Intratumoral heterogeneous parameters based on ^{18}F -FDG PET imaging, such as the heterogeneity index (HI) and

coefficient of variation (COV) of the tumor lesion, have been used in predicting treatment response and prognosis, and in the differentiation between benign and malignant lymph nodes in different tumors (22-25). Based on their nature, these intratumoral, heterogeneous, semi-quantitative parameters have the potential to predict glioma grade and *IDH* mutation status.

The purpose of the present study was to investigate the non-invasive predictive efficacy of heterogeneous parameters, other than the regular static parameters of ^{18}F -FET PET imaging, in glioma grade and *IDH1* mutation.

Methods

The institutional ethics board approved the present study of Huashan Hospital, Fudan University (No. 2017-332). Due to the retrospective nature of the study and anonymous clinical data, written informed consent from enrolled patients was waived. The design and methods involved in this research complied with the Declaration of Helsinki and its amendments.

Patients

In this single-center research study, we retrospectively reviewed 280 consecutive adult ^{18}F -FET PET/computed tomography (CT) patients referred to the PET Center of Huashan Hospital, Fudan University, from November 2017 to December 2018. The inclusion criteria were as follows: (I) adult patients with an untreated brain lesion; (II) positive ^{18}F -FET PET imaging findings without artifacts; and (III) a confirmed histological diagnosis of glioma and *IDH* mutation status after ^{18}F -FET PET imaging. The exclusion criteria were as follows: (I) any diagnostic and/or treatment procedures before ^{18}F -FET PET investigation; (II) patients without a pathological diagnosis after ^{18}F -FET PET imaging; and (III) negative or background-like ^{18}F -FET PET uptake of a tumor lesion. The interval between ^{18}F -FET PET imaging and following surgical resection or biopsy was no more than 90 days for grade II or III glioma patients, and no more than 30 days for grade IV glioma patients. Based on these criteria, 58 adult patients with untreated gliomas were enrolled in the present study.

Patient information was obtained and reviewed, including demographic and clinical data, treatment plan, and pathological diagnosis.

¹⁸F-FET PET/CT imaging and analysis

¹⁸F-FET PET scan was performed using a Biograph 64 PET/CT system (Siemens, Erlangen, Germany). Patients fasted for at least 4 h before ¹⁸F-FET PET imaging, and 370±20 MBq ¹⁸F-FET was intravenously injected before the PET/CT scan. A static scan was performed 20 min after the tracer injection and lasted for 20 min. In total, 8 of 58 patients underwent dynamic ¹⁸F-FET PET scanning. The dynamic scan was performed for >40 min after the tracer injection; 20–40-min images were reconstructed for diagnosis and analysis. Attenuation correction was performed using a low-dose CT (120 KV, 150 mA, Acq. 64 mm × 0.6 mm, 3-mm slice thickness, and 0.55 pitch) before the emission scan. PET images were reconstructed using the iterative 3D method with a Gaussian filter (6 iterations, 14 subsets, full width at half maximum: 2 mm, zoom: 2), which resulted in axial, coronal, and sagittal brain imaging of PET, CT, and PET/CT fusion for diagnosis and analysis.

The Syngo.via workstation (Siemens, Erlangen, Germany) was used to analyze the ¹⁸F-FET PET/CT imaging. Background mean standardized uptake value was measured in a crescent-shape area, including gray and white matter on the contralateral hemisphere (26). Tumor maximal standardized uptake value (SUVmax), peak standardized uptake value (SUVpeak), mean standardized uptake value (SUVmean), the standard deviation of lesion standardized uptake value (SUVsd), and MTV of the tumor lesion were semi-automatically obtained after glioma volume of interest (VOI) delineation, with a threshold of 1.6 times that of background SUVmean (27). Background brain tissue SUVmean and glioma lesion VOI delineation were determined by 2 experienced nuclear medicine physicians (TH: 10 years' experience, WZ: 5 years' experience) using 2 separate measurements. Each physician applied the same lesion delineation procedures, and the other physician ensured that the procedures were carried out appropriately. After the first physician completed the procedures, the physicians switched roles and repeated the lesion delineation procedure. We also analyzed the interobserver agreement indices in order to reach measurement consensus. TBRmax, peak tumor-to-background ratio (TBRpeak), and TBRmean were calculated by the division of tumor SUVmax, SUVpeak, and SUVmean with background SUVmean. The SUVsd of lesion VOI divided by lesion SUVmean was used to obtain the COV of the lesion. Lesion SUVmax

divided by lesion SUVmean was applied to obtain the lesion HI. TLU was calculated as MTV×lesion SUVmean.

Pathological diagnosis

Glioma tissues obtained from surgical resection or stereotactic biopsy were used for the pathological diagnosis. Hematoxylin-eosin staining results and *IDH1* R132H immunohistochemical staining results were combined for the pathological diagnosis. The 2016 World Health Organization glioma classification was incorporated in the diagnosis if the necessary molecular biomarker data were complete. All pathological diagnoses were completed in the Pathology Department of Huashan Hospital, Fudan University (Shanghai, China).

Statistical analysis

Means and standard deviations or medians and ranges were calculated in continuous variables. Percentages were used for dichotomous and categorical variables. Logistic regression was used to investigate the predictive efficacy of the parameters; the variance inflation factor was observed to control multicollinearity. Receiver-operating characteristic curve analysis was applied to evaluate different predictive models. A reasonable cutoff was decided when the combination of sensitivity and specificity reached its maximum. The area under the curve (AUC) was calculated to compare predictive efficacy. The Hosmer-Lemeshow goodness-of-fit test was used for the calibration of models. Student's *t*-test was used to compare continuous variables between 2 groups if the variables were normally distributed and adjustment was considered based on equal or unequal variances; Wilcoxon rank-sum test was performed if the normal distribution of variables was not met. One-way analysis of variance was used to compare continuous variables between different glioma grades; non-parametric Kruskal-Wallis tests were used if the normal distribution or equal variance criteria were not met. *P*<0.05 was considered statistically significant. Interobserver agreements of ¹⁸F-FET PET parameter measurements were evaluated with interclass correlation coefficients (ICC), defined as poor (<0.2), fair (0.21–0.4), moderate (0.41–0.6), good (0.61–0.8), and very good (0.81–1.0). Statistical analyses were completed with STATA version 14.1 (College Station, TX, USA) and MedCalc version 13.1.0 (<https://www.mdcalc.com/>).

Table 1 Patient demographic and clinical characteristics

Characteristics	Data
Age (years)	17–70 (41.74±14.58)
Sex	
Female	21 (36.21%)
Male	37 (63.79%)
2016 World Health Organization grade	
II	33 (56.90%)
Diffuse astrocytoma	<i>IDH1</i> wild-type 13 (39.39%) <i>IDH1</i> mutation 6 (18.18%)
Oligodendroglioma	<i>IDH1</i> mutation 13 (39.39%)
Astrocytoma	<i>IDH1</i> wild-type 1 (3.03%)
III	13 (22.41%)
Anaplastic astrocytoma	<i>IDH1</i> wild-type 11 (84.62%) <i>IDH1</i> mutation 2 (15.38%)
IV	12 (20.69%)
Glioblastoma	<i>IDH1</i> wild-type 11 (91.67%)
Diffuse midline glioma	<i>IDH1</i> wild-type 1 (8.33%)
Tumor location	
Frontal lobe	28 (48.28%)
Temporal lobe	7 (12.07%)
Parietal lobe	2 (3.45%)
Occipital lobe	0 (0.00%)
Multiple lobes	6 (10.34%)
Cerebellum	2 (3.45%)
Deep brain regions	13 (22.41%)
Surgical treatment	
Resection	39 (81.03%)
Total resection	20 (51.28%)
Partial resection	19 (49.72%)
Stereotactic biopsy	19 (18.97%)
<i>IDH1</i> status	
Wild type	37 (63.79%)
Mutation	21 (36.21%)

Range, mean, and standard deviation of age are provided. Other dichotomous and categorical items are shown as percentages. *IDH1*, isocitrate dehydrogenase gene 1.

Results

Patient characteristics

Patients' demographic and clinical data are summarized in *Table 1*. There were 33, 13, and 12 patients with grades II, III, and IV gliomas, respectively. Interested reader can find the detailed data in a supplementary appendix online (*Table S1*).

Interobserver agreement results

The ICC showed satisfactory agreement for the ¹⁸F-FET PET semi-quantitative parameter measurement results between the 2 physicians (ICC >0.95, P<0.01). Based on those findings, the first physician's measurement results (TH) were used for the following analysis. The means and standard deviations of the semi-quantitative parameters among the different glioma grades and the *IDH1* status are shown in *Table 2*.

Predictive efficacy of gliomas between grade II or III and grade IV

All 8 semi-quantitative parameters (TBRmax, TBRpeak, TBRmean, HI, COV, SUVsd, MTV, and TLU) could significantly differentiate between grade II or III and grade IV gliomas (P<0.0001). TLU (AUC: 0.841, P<0.0001), followed by TBRpeak (AUC: 0.832, P<0.0001) and HI (AUC: 0.826, P<0.0001), had the top 3 single-parameter predictive performance. Combinations of TBRmax, SUVsd, and TBRmean (AUC: 0.850, P<0.0001); HI, SUVsd, and MTV (AUC: 0.848, P<0.0001); and HI, SUVsd, and TLU (AUC: 0.848, P<0.0001) had the top 3 multiple-parameter predictive performance (*Figure 1* and *Table 3*).

The P value of the difference between the top 3 combined models and the top 3 single-parameter predictive models was insignificant (P=0.752). The Hosmer-Lemeshow goodness-of-fit test results indicated that, for these models, P>0.05, indicating satisfactory calibration (*Tables S2,S3*).

*Predictive efficacy of *IDH1* mutation based on immunohistochemical analysis*

Five of the 8 parameters (SUVsd, TLU, HI, MTV, and TBRmax) could significantly predict the *IDH1* mutation,

Table 2 Means and standard deviations of the semi-quantitative parameters of glioma volume of interest (VOI) delineation based on static O-(2-[18F]fluoroethyl)-l-tyrosine positron emission tomography imaging in different tumor grades and isocitrate dehydrogenase gene 1 (*IDH1*) status

Parameters	Grades II and III	Grade IV	IDH wild type	IDH mutation
TBRmax	2.82±1.04	4.63±1.92	3.49±1.63	2.68±0.91
TBRpeak	2.44±0.88	4.01±1.53	3.00±1.35	2.36±0.79
TBRmean	1.92±0.28	2.32±0.45	2.06±0.39	1.91±0.26
COV*100	12.72±9.15	26.05±12.7	17.72±12.15	11.53±8.43
HI	1.43±0.31	1.94±0.54	1.62±0.46	1.37±0.28
MTV	20.96±37.63	50.88±44.89	30.12±35.10	21.93±49.57
TLU	39.81±67.68	108.84±88.51	63.29±71.86	37.88±84.59
SUVsd	0.258±0.230	0.618±0.385	0.407±0.336	0.200±0.173

COV, coefficient of variation; HI, heterogeneity index; MTV, metabolic tumor volume; SUVsd, standard deviation of lesion standardized uptake value; TBRmax, maximal tumor-to-background ratio; TBRmean, mean tumor-to-background ratio; TBRpeak, peak tumor-to-background ratio; TLU, total lesion tracer standardized uptake.

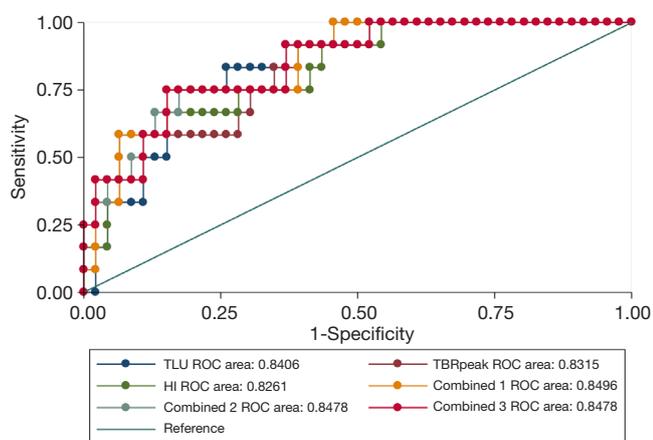


Figure 1 Predictive efficacy comparisons of the top 3 single-parameter models and top 3 multiple-parameter models between glioma grade II or III and grade IV. Receiver-operating characteristic curve analysis showed that total lesion tracer standardized uptake (TLU), peak tumor-to-background ratio, and heterogeneity index (HI) had the top 3 single-parameter model performance in glioma grade prediction; area under the curve (AUC) was 0.841, 0.832, and 0.826, respectively. Combined model 1 was the combination of maximal tumor-to-background ratio, the standard deviation of lesion standardized uptake value (SUVsd), and mean tumor-to-background ratio; AUC was 0.850. Combined model 2 was the combination of HI, SUVsd, and metabolic tumor volume; AUC was 0.848. Combined model 3 was the combination of HI, SUVsd, and TLU; AUC was 0.848.

whereas the predictive efficacy of COV, TBRpeak, and TBRmean was around borderline. SUVsd (AUC: 0.710, $P=0.0028$), TLU (AUC: 0.698, $P=0.0074$), and HI (AUC: 0.676, $P=0.0159$) had the top 3 single-parameter predictive performance. Combinations of TBRmax, SUVsd, and TBRmean (AUC: 0.821, $P<0.0001$), SUVsd and TBRmean (AUC: 0.804, $P<0.0001$), and SUVsd, HI, and TBRmean (AUC: 0.799, $P<0.0001$) had the top 3 multiple-parameter predictive performance (Figure 2 and Table 4).

The P value of the difference between the top 3 combined models and the top 3 single-parameter predictive models was insignificant ($P=0.155$). The Hosmer-Lemeshow goodness-of-fit test results indicated that, for these models, $P>0.05$, indicating satisfactory calibration (Tables S4,S5).

Grading efficacy of the semi-quantitative parameters

A descriptive statistical analysis was performed to investigate the efficacy of these parameters. All 8 semi-quantitative parameters showed statistical significance between grade II or III and grade IV gliomas (Table 5). For differentiation between grades II and III gliomas, none of these 8 parameters could significantly differentiate between these 2 groups. For differentiation between grades II and IV gliomas, all 8 parameters could significantly differentiate between these 2 groups. For differentiation between grades

Table 3 Receiver-operating characteristic curve analysis results for the differentiation between grade II or III and grade IV gliomas

Parameters	AUC (95% CI)	P value	Cutoff	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
TBRmax	0.824 (0.702–0.912)	<0.0001	2.67	92	61	67	38	97
TBRpeak	0.832 (0.710–0.917)	<0.0001	2.35	92	61	67	38	97
TBRmean	0.791 (0.664–0.886)	<0.0001	2.31	58	93	86	70	90
COV	0.808 (0.683–0.900)	<0.0001	27.21	58	91	84	63	89
HI	0.826 (0.704–0.913)	<0.0001	1.77	67	87	83	57	91
MTV	0.801 (0.675–0.894)	<0.0001	20.13	75	80	79	50	93
TLU	0.841 (0.721–0.923)	<0.0001	50.93	75	83	81	53	93
SUVsd	0.816 (0.693–0.906)	<0.0001	0.45	67	87	83	57	91
Com1	0.850 (0.731–0.930)	<0.0001	–	75	85	83	56	93
Com2	0.848 (0.727–0.927)	<0.0001	–	75	83	81	54	93
Com3	0.848 (0.727–0.927)	<0.0001	–	75	84	81	54	93

AUC, area under curve; CI, confidence interval; Com1, the combined model of TBRmax, SUVsd, and TBRmean; Com2, the combined model of HI, SUVsd, and MTV; Com3, the combined model of HI, SUVsd, and TLU; COV, coefficient of variation; HI, heterogeneity index; MTV, metabolic tumor volume; NPV, negative predictive value; PPV, positive predictive value; SUVsd, standard deviation of lesion standardized uptake value; TBRmax, maximal tumor-to-background ratio; TBRmean, mean tumor-to-background ratio; TBRpeak, peak tumor-to-background ratio; TLU, total lesion tracer standardized uptake.

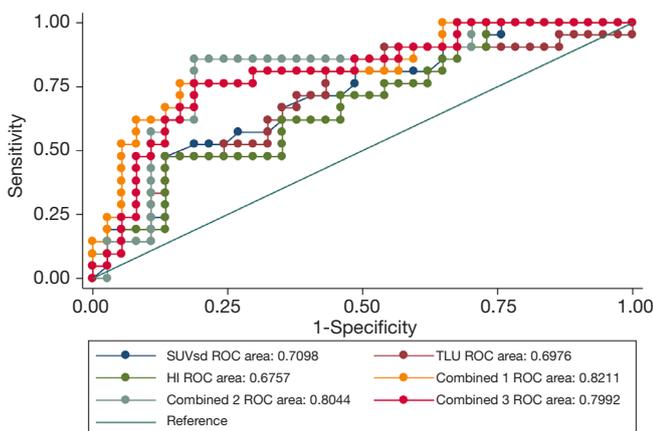


Figure 2 Predictive efficacy comparisons of top 3 single-parameter models and top 3 multiple-parameter models between different glioma isocitrate dehydrogenase gene 1 (*IDH1*) status. Receiver-operating characteristic curve analysis showed the standard deviation of lesion standardized uptake value (SUVsd), total lesion tracer standardized uptake (TLU), and heterogeneity index (HI) had the top 3 single-parameter model performance in *IDH1* status prediction; area under the curve (AUC) 0.710, 0.698, and 0.676, respectively. Combined model 1 was maximal tumor-to-background ratio (TBRmax), SUVsd, and mean tumor-to-background ratio; AUC was 0.821. Combined model 2 was the combination of SUVsd and TBRmean; AUC was 0.804. Combined model 3 was the combination of SUVsd, HI, and TBRmean; AUC was 0.799.

III and IV gliomas, TBRpeak, TBRmax, and HI showed a significant difference between these 2 groups, whereas the COV P value was around borderline (*Table 5*).

Discussion

In the present study, we investigated the non-invasive predictive efficacy of some easily obtained and highly repetitive intratumoral heterogeneous parameters, other than the commonly used semi-quantitative parameters, after lesion delineation based on static ^{18}F -FET PET/CT imaging in glioma patients. To the best of our knowledge, this is the first report demonstrating how these extra intratumoral heterogeneous parameters could predict glioma grade and *IDH1* mutation status based on static ^{18}F -FET PET imaging analysis.

The main findings of the present study are as follows. First, all the semi-quantitative parameters based on static ^{18}F -FET PET imaging could significantly differentiate between glioma grade II or III and grade IV. TLU, TBRpeak, and HI had the top 3 single-parameter predictive performance, and combinations of TBRmax, SUVsd, and TBRmean had the best multiple-parameter predictive performance. Second, SUVsd, TLU, HI, MTV, and TBRmax could significantly predict *IDH1* mutation status

Table 4 Receiver-operating characteristic curve analysis results for the prediction of isocitrate dehydrogenase gene 1 mutation based on immunohistochemical analysis

Parameters	AUC (95% CI)	P value	Cutoff	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
TBRmax	0.658 (0.521–0.777)	0.0364	2.21	48	87	72	67	74
TBRpeak	0.638 (0.502–0.760)	0.0701	2.15	57	73	67	55	75
TBRmean	0.633 (0.496–0.755)	0.0827	1.84	62	68	66	52	76
COV	0.650 (0.513–0.771)	0.0446	8.85	52	76	67	55	74
HI	0.676 (0.540–0.793)	0.0159	1.26	48	87	72	67	74
MTV	0.660 (0.524–0.779)	0.0342	19.48	90	46	62	49	90
TLU	0.698 (0.563–0.811)	0.0074	28.95	81	57	66	52	84
SUVsd	0.710 (0.576–0.821)	0.0028	0.11	47	57	66	52	84
Com1	0.821 (0.698–0.909)	<0.0001	–	76	84	81	73	86
Com2	0.804 (0.679–0.897)	<0.0001	–	86	81	83	72	91
Com3	0.799 (0.673–0.893)	<0.0001	–	76	84	81	73	85

AUC, area under curve; CI, confidence interval; Com1, the combined model of TBRmax, SUVsd, and TBRmean; Com2, the combined model of SUVsd and TBRmean; Com3, the combined model of SUVsd, HI and TBRmean; COV, coefficient of variation; HI, heterogeneity index; MTV, metabolic tumor volume; NPV, negative predictive value; PPV, positive predictive value; SUVsd, standard deviation of lesion standardized uptake value; TBRmax, maximal tumor-to-background ratio; TBRmean, mean tumor-to-background ratio; TBRpeak, peak tumor-to-background ratio; TLU, total lesion tracer standardized uptake.

Table 5 Grading efficacy of parameters based on static O-(2-[18F]fluoroethyl)-L-tyrosine positron emission tomography imaging between different glioma grades

Parameters	Grades II+III vs. IV	Grade II vs. III	Grade II vs. IV	Grade III vs. IV
TBRmax	0.0006*	0.348451	0.000324**	0.005331**
TBRpeak	0.0004*	0.429037	0.000305**	0.003077**
TBRmean	0.0021*	0.328791	0.001021**	0.012724
COV	0.001*	0.303379	0.000521**	0.009635***
HI	0.0005*	0.318267	0.000278**	0.005861**
MTV	0.0014*	0.178946	0.000456**	0.020645
TLU	0.0003*	0.144722	0.000085**	0.010712
SUVsd	0.0045*	0.195083	0.000273**	0.010712

*, P<0.05 indicated statistical significance based on Wilcoxon rank sum test results. **, adjusted P<0.008333 indicated statistical significance based on the Kruskal-Wallis test results. ***, adjusted P=0.009635 indicated around statistical borderline based on the Kruskal-Wallis test results. COV, coefficient of variation; HI, heterogeneity index; MTV, metabolic tumor volume; SUVsd, standard deviation of lesion standardized uptake value; TBRmax, maximal tumor-to-background ratio; TBRmean, mean tumor-to-background ratio; TBRpeak, peak tumor-to-background ratio; TLU, total lesion tracer standardized uptake.

based on the immunohistochemical analysis results, whereas the combination of TBRmax, SUVsd, and TBRmean had the best multiple-parameter predictive performance. Third, the 8 semi-quantitative parameters demonstrating grading efficacy in grades II, III, and IV gliomas to some degree.

SUVpeak can be defined as the highest mean SUV from a fixed 1-cm³ spherical volume centered over the highest metabolic part of the tumor VOI. SUVsd is the parameter describing the standard deviation of lesion delineation standardized uptake value. TBRpeak, HI, COV, and SUVsd,

further describe the intratumoral imaging heterogeneity features, other than those commonly used, such as TBRmax and TBRmean. During the static ^{18}F -FET imaging analysis of glioma patients, well-accepted procedures of lesion VOI delineation can be semi-automatically completed with the aid of 1.6 times the background SUVmean (27). As a result, all 8 semi-quantitative parameters could be conveniently obtained and reproduced after lesion delineation, which will help routine clinical imaging diagnoses and further imaging analyses.

The multiple-parameter models showed some efficacy enhancement in both glioma grade and *IDH1* status prediction, but the probability value indicated that there was no significant difference between the models. A large number of patients and complete molecular biomarker status information are warranted to investigate further the efficacy of these intratumoral heterogeneous parameters based on ^{18}F -FET PET imaging.

Different cell groups in malignant tumors could have different behaviors and treatment responses, and the heterogeneity of malignant tumors is related to oxygen consumption and glucose metabolism (28). Previous studies have demonstrated that heterogeneous parameters, such as HI and COV in ^{18}F -FDG PET imaging, could benefit treatment response evaluation and patient outcomes in non-small cell lung cancer, rectal carcinoma, and nasopharyngeal carcinoma (29-31). The findings of the present study confirm the potential of these intratumoral heterogeneous semi-quantitative parameters after lesion delineation procedures based on static ^{18}F -FET PET/CT imaging, which could also contribute to the further understanding of glioma heterogeneity mechanisms in amino acid tracer imaging.

The *IDH* mutation status of glioma patients is an important prognostic factor. In some glioma classifications, the *IDH* mutation could indicate better treatment response and prognosis (32). Our findings demonstrated that SUVsd, TLU, HI, MTV, and TBRmax have significant predictive efficacy in *IDH1* mutation, which indicates that these semi-quantitative parameters could also contribute to the non-invasive prediction of the *IDH1* mutation status of glioma patients, other than the most commonly used TBRmax. SUVsd and HI demonstrated reasonable predictive efficacy in *IDH1* mutation status in our research, indicating that the intratumoral heterogeneity of glioma ^{18}F -FET PET/CT imaging could be related to glioma *IDH1* mutation status. TLU and MTV are metabolic volumetric semi-quantitative parameters often associated with tumor treatment response

and prognosis (19,20). An interesting finding of our research was that these volumetric semi-quantitative parameters had shown potential in *IDH1* mutation status prediction. *IDH1* mutation status in glioma patients could affect tumor growth and ^{18}F -FET metabolic patterns, which, as a result, could lead to different treatment results and prognoses.

Although these static semi-quantitative parameters have many benefits, there are still challenges in ^{18}F -FET PET imaging, such as the need for better non-invasive predictive efficacy in the *IDH1* genotype and glioma grade, as well as the need for better grading efficacy between grades II and III gliomas. Dynamic ^{18}F -FET PET imaging could provide additional valuable parameters, such as lesion time activity curve pattern, time to peak, and slope (21). Moreover, dynamic imaging parameters of amino acid tracer PET could also enhance the performance of static imaging parameters for *IDH* mutation detection (33). More complicated texture and radiomics analysis could also be applied in glioma imaging research (34-36). We believe that these easily applied and relatively stable parameters could be used in combination with dynamic ^{18}F -FET PET imaging parameters and other more complicated methods for glioma imaging prediction analyses.

The present study has some limitations. The retrospective nature of the study, the relatively low number of patients, and incomplete molecular pathological diagnostic data limit the strength of the results. To avoid a false-negative *IDH* mutation status, *IDH* sequencing should be used for negative *IDH* immunohistochemical analysis results. A larger number of patients and more comprehensive pathological biomarker status information are needed in further studies of the non-invasive predictive efficacy of static ^{18}F -FET PET imaging parameters in adults with untreated gliomas.

These convenient heterogeneous semi-quantitative parameters based on static ^{18}F -FET PET imaging could benefit the non-invasive prediction of glioma grade and *IDH1* mutation status in adults with untreated gliomas, which could influence treatment decision-making and the prognostic evaluation.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/qims-20-723>). The authors have no conflicts of interest to declare.

Ethical Statement: The ethical committee approved the present study of Huashan Hospital, Fudan University (No. 2017-332). Due to the retrospective nature of the study and anonymous clinical data, written informed consent from enrolled patients was waived. The design and methods involved in this research complied with the Declaration of Helsinki and its amendments.

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Table S1 Clinical data, pathology, and treatment plan information for the 58 glioma patients

n	Sex	Age (years)	Location	Pathology	WHO grade	IDH1 status	Treatment	Pretreatment
1	F	41	Frontal, right	Diffuse astrocytoma	II	Wild type	Total resection	None
2	M	63	Temporal, right	Diffuse astrocytoma	II	Wild type	Subtotal resection	None
3	M	48	Frontal, right	Oligodendroglioma, NOS	II	R132H mutation	Total resection	None
4	M	30	Brain stem	Astrocytoma	II	Wild type	Stereotactic biopsy	None
5	F	36	Frontal, left	Diffuse astrocytoma	II	R132H mutation	Subtotal resection	None
6	F	35	Frontal, left	Diffuse astrocytoma	II	Wild type	Subtotal resection	None
7	F	60	Frontal, left	Oligodendroglioma, NOS	II	R132H mutation	Total resection	None
8	F	49	Temporal, left	Diffuse astrocytoma	II	Wild type	Partial resection	None
9	F	49	Cerebellum, left	Diffuse astrocytoma	II	Wild type	Stereotactic biopsy	None
10	M	56	Frontal, left	Oligodendroglioma, NOS	II	R132H mutation	Subtotal resection	None
11	F	29	Frontal, left	Diffuse astrocytoma	II	R132H mutation	Total resection	None
12	F	35	Frontal, left	Oligodendroglioma, NOS	II	R132H mutation	Total resection	None
13	M	49	Frontal, left	Oligodendroglioma, NOS	II	R132H mutation	Subtotal resection	None
14	F	51	Frontal, left	Diffuse astrocytoma	II	Wild type (twice)	Total resection	None
15	M	51	Temporal, left	Diffuse astrocytoma	II	Wild type	Subtotal resection	None
16	M	29	Temporal, right	Oligodendroglioma, NOS	II	R132H mutation	Subtotal resection	None
17	F	32	Frontal-parietal, right	Diffuse astrocytoma	II	Wild type	Subtotal resection	None
18	M	24	Frontal, left	Diffuse astrocytoma	II	Wild type	Total resection	None
19	M	52	Parietal, right	Oligodendroglioma, NOS	II	R132H mutation	Subtotal resection	None
20	F	29	Frontal, left	Oligodendroglioma, NOS	II	R132H mutation	Total resection	None
21	F	31	Frontal, left	Diffuse astrocytoma	II	R132H mutation	Total resection	None
22	M	28	Thalamus, left	Diffuse astrocytoma	II	Wild type	Stereotactic biopsy	None
23	F	51	Frontal, left	Oligodendroglioma, NOS	II	R132H mutation	Total resection	None
24	M	54	Frontal, right	Diffuse astrocytoma	II	Wild type	Stereotactic biopsy	None
25	F	45	Parietal, right	Diffuse astrocytoma	II	Wild type (twice)	Stereotactic biopsy	None
26	M	39	Temporal, right	Oligodendroglioma, NOS	II	R132H mutation	Total resection	None
27	F	44	Temporal-insular, right	Oligodendroglioma, NOS	II	R132H mutation	Subtotal resection	None
28	M	28	Frontal, left	Diffuse astrocytoma	II	R132H mutation	Stereotactic biopsy	None
29	M	39	Frontal, right	Diffuse astrocytoma	II	R132H mutation	Total resection	None
30	M	42	Frontal, left	Oligodendroglioma, NOS	II	R132H mutation	Total resection	None
31	M	52	Frontal-temporal-insular, right	Oligodendroglioma, NOS	II	R132H mutation	Subtotal resection	None
32	M	24	Frontal-temporal, left	Diffuse astrocytoma	II	R132H mutation	Total resection	None
33	F	45	Frontal, left	Diffuse astrocytoma	II	Wild type	Stereotactic biopsy	None
34	M	29	Frontal-temporal-insular, left	Anaplastic astrocytoma	III	Wild type	Partial resection	None
35	M	66	Brain stem	Anaplastic astrocytoma	III	Wild type	Stereotactic biopsy	None
36	M	63	Frontal, right	Anaplastic astrocytoma	III	Wild type	Subtotal resection	None
37	M	52	Frontal, left	Anaplastic astrocytoma	III	Wild type	Total resection	None
38	M	38	Corpus callosum	Anaplastic astrocytoma	III	Wild type	Stereotactic biopsy	None
39	M	55	Frontal, left	Anaplastic astrocytoma	III	R132H mutation	Stereotactic biopsy	None
40	F	67	Temporal-insular, left	Anaplastic astrocytoma	III	Wild type	Total resection	None
41	M	31	Thalamus, right	Anaplastic astrocytoma	III	Wild type	Stereotactic biopsy	None
42	F	20	Basal ganglia, left	Anaplastic astrocytoma	III	Wild type	Stereotactic biopsy	None
43	F	30	Thalamus bilateral	Anaplastic astrocytoma	III	Wild type	Stereotactic biopsy	None
44	M	68	Frontal, right	Anaplastic astrocytoma	III	R132H mutation	Total resection	None
45	M	62	Basal ganglia, right	Anaplastic astrocytoma	III	Wild type	Stereotactic biopsy	None
46	F	24	Frontal, left	Anaplastic astrocytoma	III	Wild type	Stereotactic biopsy	None
47	M	17	Cerebellum, right	Glioblastoma	IV	Wild type	Partial resection	None
48	F	70	Frontal, left	Glioblastoma	IV	Wild type	Total resection	None
49	M	46	Temporal, right	Glioblastoma	IV	Wild type	Total resection	None
50	M	29	Thalamus, right	Diffuse midline glioma, H3K27M mutant	IV	Wild type	Stereotactic biopsy	None
51	M	30	Thalamus, left	Glioblastoma	IV	Wild type	Stereotactic biopsy	None
52	M	57	Basal ganglia, left	Glioblastoma	IV	Wild type	Subtotal resection	None
53	M	51	Basal ganglia, right	Glioblastoma	IV	Wild type	Stereotactic biopsy	None
54	M	19	Frontal, right	Glioblastoma	IV	Wild type	Total resection	None
55	M	61	Frontal, right	Glioblastoma	IV	Wild type	Subtotal resection	None
56	M	29	Frontal, left	Glioblastoma	IV	Wild type	Total resection	None
57	M	18	Basal ganglia, right	Glioblastoma	IV	Wild type	Stereotactic biopsy	None
58	M	27	Temporal, right	Glioblastoma	IV	Wild type	Partial resection	None

F, female; IDH1, isocitrate dehydrogenase gene 1; M, male; NOS, not otherwise specified; WHO, World Health Organization.

Table S2 Efficacy comparisons between top models in glioma grade prediction

Model	Observations (n)	ROC area	Standard error	95% CI
TLU	58	0.8406	0.0548	0.73309–0.94807
TBRpeak	58	0.8315	0.0625	0.70903–0.95402
HI	58	0.8261	0.0642	0.70022–0.95195
Com1	58	0.8496	0.0576	0.7368–0.96244
Com2	58	0.8478	0.0588	0.7325–0.96306
Com3	58	0.8478	0.0589	0.7323–0.96330

χ^2 -test [5]=2.66 Prob> χ^2 -test=0.7516. CI, confidence interval; Com1, the combined model of TBRmax, SUVsd, and TBRmean; Com2, the combined model of HI, SUVsd, and MTV; Com3, the combined model of HI, SUVsd, and TLU; HI, heterogeneity index; MTV, metabolic tumor volume; ROC, receiver-operating characteristic; SUVsd, standard deviation of lesion standardized uptake value; TBRmax, maximal tumor-to-background ratio; TBRmean, mean tumor-to-background ratio; TBRpeak, peak tumor-to-background ratio; TLU, total lesion tracer standardized uptake.

Table S3 Hosmer-Lemeshow goodness-of-fit test results for models in glioma grade prediction

Parameters	Observations (n)	Groups (n)	Hosmer-Lemeshow χ^2 -test	P value
TBRmax	58	10	5.74	0.676
TBRpeak	58	10	7.44	0.490
TBRmean	58	10	11.89	0.156
COV	58	10	8.44	0.392
HI	58	10	4.48	0.812
SUVsd	58	10	8.55	0.382
MTV	58	10	8.10	0.423
TLU	58	10	7.79	0.454
Com1	58	10	6.21	0.624
Com2	58	10	7.83	0.450
Com3	58	10	8.02	0.432

Com1, the combined model of TBRmax, SUVsd, and TBRmean; Com2, the combined model of HI, SUVsd, and MTV; Com3, the combined model of HI, SUVsd, and TLU; COV, coefficient of variation; HI, heterogeneity index; MTV, metabolic tumor volume; SUVsd, standard deviation of lesion standardized uptake value; TBRmax, maximal tumor-to-background ratio; TBRmean, mean tumor-to-background ratio; TBRpeak, peak tumor-to-background ratio; TLU, total lesion tracer standardized uptake.

Table S4 Efficacy comparisons between top models in isocitrate dehydrogenase gene 1 status prediction

Model	Observations (n)	ROC area	Standard error	95% CI
SUVsd	58	0.7098	0.0701	0.57247–0.84710
TLU	58	0.6976	0.0737	0.55303–0.84208
HI	58	0.6757	0.0729	0.53286–0.81849
Com1	58	0.8211	0.0596	0.70430–0.93792
Com2	58	0.8044	0.0623	0.68234–0.92641
Com3	58	0.7992	0.0613	0.67901–0.91945

χ^2 -test [5]=8.03 Prob> χ^2 -test=0.1547. CI, confidence interval; Com1, the combined model of TBRmax, SUVsd, and TBRmean; Com2, the combined model of SUVsd and TBRmean; Com3, the combined model of SUVsd, HI, and TBRmean; HI, heterogeneity index; ROC, receiver-operating characteristic; SUVsd, standard deviation of lesion standardized uptake value; TBRmax, maximal tumor-to-background ratio; TBRmean, mean tumor-to-background ratio; TLU, total lesion tracer standardized uptake.

Table S5 Hosmer-Lemeshow goodness-of-fit test results for models in isocitrate dehydrogenase gene 1 status prediction

Parameter	Observations (n)	Groups (n)	Hosmer-Lemeshow χ^2 -test	P value
TBRmax	58	10	7.12	0.524
TBRpeak	58	10	10.53	0.230
TBRmean	58	10	9.75	0.283
COV	58	10	9.06	0.337
HI	58	10	7.53	0.481
MTV	58	10	9.57	0.297
TLU	58	10	9.21	0.325
SUVsd	58	10	12.24	0.141
Com1	58	10	12.38	0.135
Com2	58	10	8.59	0.378
Com3	58	10	7.71	0.463

Com1, the combined model of TBRmax, SUVsd, and TBRmean; Com2, the combined model of SUVsd, and TBRmean; Com3, the combined model of SUVsd, HI, and TBRmean; COV, coefficient of variation; HI, heterogeneity index; MTV, metabolic tumor volume; SUVsd, standard deviation of lesion standardized uptake value; TBRmax, maximal tumor-to-background ratio; TBRmean, mean tumor-to-background ratio; TBRpeak, peak tumor-to-background ratio; TLU, total lesion tracer standardized uptake.