

Prognostic stratification of newly diagnosed *IDH*-mutant gliomas by [¹⁸F]fluoroethyltyrosine and [¹¹C]methionine PET: A retrospective, bicentric cohort study

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Abstract

Background. Improved prognostic stratification, including imaging-based parameters, is needed to guide treatment decisions in *IDH*-mutant glioma.

Methods. In this bicentric retrospective study, 457 patients with *IDH*-mutant glioma and [¹⁸F]fluoroethyltyrosine or [¹¹C]methionine positron emission tomography (PET) prior to radiotherapy or systemic treatment were included. Associations of maximum and mean tumor-to-background ratios (TBR_{max}/TBR_{mean}) and PET-positive volume (PET volume) with time to next intervention (TTNI) and overall survival (OS) were analyzed.

Results. Overall, 251 (54.9%) patients with astrocytoma and 206 (45.1%) with oligodendroglioma were included. In patients with astrocytoma who underwent PET before resection, measurable disease according to PET RANO 1.0 criteria was associated with shorter TTNI compared to no/non-measurable disease (median 46.0 vs. 67.9 months; $P = .004$). Univariable analysis showed an association of TTNI with TBR_{max} , TBR_{mean} , and PET volume in astrocytoma and PET volume in oligodendroglioma. Multivariable analyses including age, WHO grade, extent of resection, post-operative treatment, and magnetic resonance imaging (MRI)-based tumor extent indicated an association of TTNI with TBR_{max} (HR 1.48 [95%CI: 1.09–2.01]) and TBR_{mean} (HR 1.93 [95%CI: 1.14–3.27]) in astrocytoma and PET volume (HR [10 ml increase]: 1.18 [95%CI: 1.03–1.36]) in oligodendroglioma. In astrocytoma, also OS was related to TBR_{max} (HR: 1.40 [95%CI: 1.13–1.74]), TBR_{mean} (HR: 1.97 [95%CI: 1.21–3.22]), and PET volume (HR: 1.23 [95%CI: 1.10–1.37]) in univariable analysis. Further analyses considering timepoint of PET showed consistent results.

Conclusions. In this retrospective study, amino acid PET parameters were associated with outcome in newly diagnosed *IDH*-mutant glioma. Future clinical trials should include PET imaging to define imaging-based prognostic signatures.

Key Points

- Higher PET uptake is associated with shorter TTNI and OS in astrocytoma.
- Larger PET volumes are associated with shorter TTNI in oligodendroglioma.
- Associations with TTNI were confirmed after adjusting for known prognostic factors.

Diffuse gliomas harboring mutations in isocitrate dehydrogenase 1/2 (*IDH1/2*) genes are a heterogeneous group of glial neoplasms in adults.¹ While their prognosis is more favorable

than that of *IDH*-wildtype glioblastoma, they are characterized by a diffusely infiltrating growth pattern, leading to high recurrence rates. Therefore, postoperative treatment approaches including

Importance of the Study

Postoperative treatment decisions in *IDH*-mutant glioma remain challenging, particularly given the recent approval of the *IDH* inhibitor vorasidenib. According to guidelines, clinical factors such as age, residual tumor, neurological deficits, and WHO grade are considered as the basis for postsurgical management, but the underlying data are derived from historical post-hoc analyses of clinical trials. Positron emission tomography (PET) imaging using amino acid tracers is increasingly used for treatment planning and response assessment, but its

value for prognostic assessment remains insufficiently established in molecularly defined glioma subgroups. In the present retrospective analysis, we observed that high uptake intensities and large PET-positive volumes are associated with shorter time to next intervention in astrocytomas and oligodendrogliomas after adjusting for known prognostic factors. Our results suggest a potential role of PET in prognostic stratification in these patients and emphasize the need to include PET imaging in prospective clinical trials of *IDH*-mutant glioma.

radiotherapy, systemic treatment, or a combination of both may be required.² However, given the long survival times of up to more than 10 years and the relatively young patient population, potential long-term sequelae of treatment must be considered.^{3,4} To date, decisions on postoperative treatment are based on clinical factors such as age, extent of resection, neurological deficits, and WHO grade. These factors stem from historical post-hoc analyses of clinical trials performed in the pre-molecular era.⁵ Accordingly, a watch-and-wait approach may be followed in low-risk situations, whereas postoperative radio-chemotherapy may be needed in patients with higher age, incomplete resection, presence of neurological symptoms, and higher WHO grade. Still, proper validation of these factors in molecularly defined glioma subgroups is lacking.⁶ Moreover, the recent approval of vorasidenib based on the INDIGO trial adds an additional treatment option, allowing deferral of radio-chemotherapy in patients without immediate need for radio-chemotherapy.⁷ Given ongoing changes in the treatment landscape, rational estimation of prognosis is needed in this population to guide therapeutic decisions and facilitate counseling of patients and caregivers. Previous work on prognostic models incorporating imaging-based biomarkers is merely based on magnetic resonance imaging (MRI)-based tumor volumes and contrast enhancement, and molecularly defined glioma subgroups of all grades as defined by the 2021 WHO classification are frequently not included.^{8–10}

Positron emission tomography (PET) imaging is increasingly used to guide the management of brain tumors. Whereas MRI still represents the cornerstone of imaging in glioma, PET imaging with amino acid tracers visualizes metabolic activity irrespective of blood brain barrier disruption and thereby delivers valuable information for surgical planning, the distinction of tumor recurrence from post-therapeutic changes, and response assessment.¹¹ To this end, the Response Assessment in Neuro-Oncology (RANO) Working Group has issued recommendations for standardized assessment of amino acid PET in diffuse gliomas (PET RANO 1.0 criteria).¹² However, these are mainly based on expert consensus and primarily retrospective analyses of cohorts lacking integrated molecular classification and meaningful clinical annotation.

To address this gap in knowledge, we conducted this retrospective, bicentric study to test our hypothesis that high uptake in O-(2-[¹⁸F]-fluoroethyl)-L-tyrosine ([¹⁸F]FET) and [¹¹C]-methyl-L-methionine ([¹¹C]methionine) PET is

associated with worse prognosis in newly diagnosed *IDH*-mutant gliomas.

Patients and Methods

Patient Cohort

This is a retrospective, bicentric study including adult patients with a diagnosis of diffuse glioma between 01/2001 and 07/2024 who underwent amino acid PET in clinical routine at the LMU University Hospital (LMU Munich, Germany) or the Medical University of Vienna (Vienna, Austria). Amino acid PET examinations were performed before any postoperative treatment (radiotherapy and/or chemotherapy) and within one year before or after histological diagnosis (surgical resection or biopsy). Patients undergoing amino acid PET after prior radiotherapy and/or chemotherapy were excluded. In order to analyze the prognostic value of initial tumor uptake in PET prior to any therapeutic intervention, patients undergoing PET after surgical resection were analyzed separately. Histological diagnoses were performed by a board-certified neuropathologist. Molecular reclassification according to the WHO Classification of Central Nervous System Tumours of 2021¹³ was performed using *IDH1* R132H immunohistochemistry and/or targeted sequencing, multiplex ligation-dependent probe amplification (MLPA), fluorescent/chromogenic in situ hybridization (FISH/CISH), and/or DNA methylation analysis as described previously.¹⁴

The study has been conducted in compliance with local and national guidelines and according to the Declaration of Helsinki (1964) with all its amendments and has been approved by the ethics board of the LMU Munich (approval no. 17-656, 604-16) and the Medical University of Vienna (approval no. 2086/2023, 1166/2019).

Imaging and Data Analysis

PET imaging was performed at the Department of Nuclear Medicine, LMU Hospital or the Division of Nuclear Medicine, Medical University of Vienna upon intravenous administration of either O-(2-[¹⁸F]-fluoroethyl)-L-tyrosine ([¹⁸F]FET, 2.5–3 MBq/kg) or [¹¹C]-methyl-L-methionine ([¹¹C]methionine)¹⁵ (5–7.5 MBq/kg), depending on tracer

availability in clinical routine, after prior fasting for at least 4 h. PET images were acquired by combined PET/CT imaging employing an ECAT EXACT HR+ or Biograph-64 PET/CT scanner (Siemens, Erlangen, Germany) or a GE Advance system (GE Medical Systems, Freiburg, Germany), or combined with 3T MRI using a BrainPET insert for either static or dynamic PET scans (20–40 min post injection).

PET images were analyzed on a Hermes workstation (Hermes Medical Solutions, Stockholm, Sweden) following established methodologies and PET RANO 1.0 criteria.^{12,16} Accordingly, the mean activity of 4–6 adjacent, crescent-shaped regions of interest in the healthy contralateral hemisphere was measured as background activity.¹⁷ PET volume was segmented using a lower threshold of $1.6 \times$ mean standardized uptake values (SUV_{mean}) of background as also recommended by PET RANO 1.0 criteria and commonly used for tumor segmentation in previously published studies of gliomas and brain metastases.^{12,18} Mean and maximum SUV values (SUV_{mean} , SUV_{max}) in PET volume were measured, and maximum and mean tumor-to-background ratios (TBR_{max} , TBR_{mean}) were determined by dividing tumor SUV_{max} and SUV_{mean} by background SUV_{mean} .

Tumors with PET volume > 0.5 ml and $TBR_{max} > 1.6$ were classified as measurable disease. Tumors with PET volume < 0.5 and/or $TBR_{max} < 1.6$ but visually elevated uptake were categorized as non-measurable disease, and TBR_{max} and PET volume values were included as quantitative variables for analyses. By definition, a lack of visually elevated activity in the tumor region compared to the background VOI (ie, no measurable disease) results in equal uptake between tumor region and background. Therefore, TBR_{max} was set as 1 in such cases. As TBR_{mean} values can only be determined if a VOI with $SUV = 1.6 \times SUV_{mean}$ of background can be defined, TBR_{mean} was also set as 1 in order not to exclude these cases, given the significant proportion of such lesions in the included cohort.

Magnetic resonance imaging data within three months before/after PET imaging were analyzed, excluding those with surgery between PET and MRI. MRI-based tumor extent was measured using maximum perpendicular diameters in axial MRI in both T2-weighted/fluid-attenuated inverse recovery (FLAIR) imaging and T1-weighted with contrast enhancement (T1CE) in line with RANO 2.0 criteria.¹⁹

Statistical Analysis

Categorical variables are described as numbers and percentages, whereas their independence was assessed using chi-square test. Continuous variables are given as median and range and were compared between groups using non-parametric Mann–Whitney *U* tests. The Spearman rank correlation coefficient was used to assess the correlation between PET and MRI parameters. In line with the key secondary endpoint of the INDIGO trial,⁷ time to next intervention (TTNI) was selected as primary outcome parameter and was defined as the time between histological diagnosis (first resection or biopsy) and either (A) first intervention for recurrence or progression after first-line management (including re-surgery, postoperative radio- and/or chemotherapy, or watch-and-wait) or (B) last follow-up. If no intervention was documented (eg, lost to follow-up after

multidisciplinary decision for treatment at progression), the date of imaging leading to such treatment decisions was used. Overall survival (OS) was defined as the time between histological diagnosis and death or last follow-up as appropriate. Survival probabilities were calculated and illustrated using the Kaplan–Meier method, and comparisons between groups were performed using the log-rank test. Univariable analyses on categorical/continuous parameters were performed using Cox proportional hazard models. The proportional hazards assumption was evaluated using Schoenfeld residuals and by visually inspecting Kaplan–Meier curves. To evaluate whether integration of time between PET and surgery improves model fit, likelihood ratio tests (LRT) between models containing quantitative PET parameters (TBR_{max} , TBR_{mean} , PET volume) and additional models including time between PET and surgery, as well as respective interaction terms, were performed. For multivariable analysis, variable selection was performed using LASSO-penalized Cox regression with 10-fold cross-validation to determine the optimal penalty (λ). Bootstrapping (1000 resamples) was used to estimate the selection frequency of each variable. To account for the fact that LASSO estimates are inherently biased, we also fitted an unpenalized (“global”) Cox proportional hazards model including all candidate predictors for comparison. Optimal thresholds for TBR_{max} , TBR_{mean} , and PET volume were determined by the maximally selected rank statistic using the *surv_cutpoint* function from *survminer*. To assess the stability of the chosen threshold, we performed bootstrapping with 1000 resamples, recalculating the maximally selected rank statistic in each replicate and summarizing the resulting distribution of cutpoints.

To mitigate the issue of multiple comparisons in the context of a hypothesis-generating study, statistically significant results were defined as $P \leq .01$.²⁰ Statistical analysis has been conducted using R 4.4.1 (The R Foundation for Statistical Computing, Vienna, Austria) using the packages *dplyr*, *tidyr*, *survival*, *survminer*, *ggplot2*, and *ggpubr* as well as GraphPad Prism 10 (GraphPad Software, La Jolla, CA, USA).

Results

Baseline Characteristics

Overall, 457 patients were included, of whom 352 (77.0%) were treated in Munich and 105 (23.0%) in Vienna. Median age at first surgery was 40 years (range: 18–81). In total, 251/457 (54.9%) patients were diagnosed with astrocytoma, whereas 206/457 (45.1%) patients had oligodendroglial tumors. PET was performed before surgery (resection/biopsy) in 389/457 (85.1%) patients (Supplementary Figure 1). Of note, 414/457 (90.6%) of patients underwent PET within 3 months before/after surgery. Of the 68 patients (14.9%) undergoing their first PET after surgery, 29 patients (42.6%) had a biopsy, and 39 (57.4%) underwent resection. In total, 13 patients had both pre- and post-surgical PET. Median time to next intervention (TTNI) was 66.5 months (95%CI: 60.4–79), whereas overall survival (OS) was not reached. Further baseline characteristics are given in Table 1.

Table 1. Baseline Characteristics

n = 457

Sex	
-male	246 (53.8%)
-female	211 (46.2%)
Age at first surgery (median, range)	40 years (18–81)
Tumor entities	
-Astrocytoma, <i>IDH</i> -mutant, CNS WHO 2	144 (31.5%)
-Astrocytoma, <i>IDH</i> -mutant, CNS WHO 3	73 (15.9%)
-Astrocytoma, <i>IDH</i> -mutant, CNS WHO 4	33 (7.2%)
-Astrocytoma, <i>IDH</i> -mutant, grading inconclusive	1 (0.2%)
-Oligodendroglioma, <i>IDH</i> -mutant, 1p/19q-codeleted, CNS WHO 2	150 (32.8%)
-Oligodendroglioma, <i>IDH</i> -mutant, 1p/19q-codeleted, CNS WHO 3	56 (12.3%)
MGMT promoter methylation	
-Methylated	376 (82.3%)
-Unmethylated	59 (12.9%)
-unknown	22 (4.8%)
Extent of resection at diagnosis	
-Gross total resection (GTR)	109 (23.9%)
-Subtotal resection (STR)	105 (23.0%)
-Resection of unknown extent (excluding biopsy)	25 (5.5%)
-Biopsy	218 (47.7%)
Postoperative treatment	
-Observation	184 (40.3%)
-RT only	32 (7.0%)
-ChT only	118 (25.8%)
-R-ChT	98 (21.4%)
- ¹²⁵ I seeds	19 (4.2%)
-Unknown/lost to follow-up	6 (1.3%)
Median follow-up	71.7 months (95%CI: 65–80.2)
Median time to next intervention (TTNI)	66.5 months (95%CI: 60.4–79)
Deceased patients	59 (12.9%)
Patients undergoing an intervention for recurrence or progression after first-line management	223 (48.8%)
Patients experiencing neither next intervention nor death until end of follow-up	222 (48.6%)
Timepoint of PET	
-PET before surgical intervention	389 (85.1%)
-PET after biopsy	29 (6.3%)
-PET after resection	39 (8.5%)
Time elapsed between PET and surgery	
-Median (range)	2 days (-364–337)
->6 months before surgery	6 (1.5%)
-3–6 months before surgery	7 (1.3%)
-1–3 months before surgery	45 (9.8%)
-Within 1 month before surgery	226 (49.5%)
-Within 1 month after surgery	79 (17.3%)
-1–3 months after surgery	64 (14.0%)
-3–6 months after surgery	25 (5.5%)
->6 months after surgery	5 (1.1%)
Used tracer	
- ¹⁸ F]FET	412 (90.2%)

Table 1. Continued

n = 457	
- [¹¹ C]methionine	45 (9.8%)
PET RANO 1.0 measurable disease definition	
-Measurable disease	317 (69.4%)
-Non-measurable disease	67 (14.7%)
-No measurable disease	73 (16.0%)
Product of maximum perpendicular diameters in T2/FLAIR (median, range)	14.57 cm ² (0–73.81)
Product of maximum perpendicular diameters in contrast-enhanced MRI (median, range)	0.00 cm ² (0–50.4)
[¹⁸ F]FET = O-(2-[¹⁸ F]-fluoroethyl)-L-tyrosine; ChT = chemotherapy; CNS = Central Nervous System; GTR = gross total resection; MGMT = O6-methylguanine methyltransferase; PET = positron emission tomography; RT = radiotherapy; R-ChT = radio-chemotherapy; STR = sub-total resection; WHO = World Health Organization.	

Overall, 471 lesions from 457 patients were evaluated. On the patient level, 317/457 (69.4%) had measurable disease according to the PET RANO 1.0 definition, whereas 67/457 (14.7%) were defined as non-measurable disease, and 73/457 patients (16.0%) had no measurable disease. Measurable disease was more frequent in oligodendroglioma (181/206, 87.9%) compared to astrocytoma (136/251, 54.2%; $P < .001$, Chi square test). Descriptive statistics of SUV_{max} , SUV_{mean} , TBR_{max} , TBR_{mean} , and PET-positive volumes (PET volume) across histological subgroups are given in [Supplementary Table 1](#) and [Supplementary Figure 2](#). Correlation analysis between quantitative PET parameters (TBR_{max} , TBR_{mean} , PET volume) and MRI-based tumor extent (product of maximum perpendicular diameters in T2/FLAIR and contrast-enhanced MRI) revealed overall weak to medium correlations ([Supplementary Table 2](#)).

Due to significantly higher uptake and PET volumes in oligodendroglioma compared to astrocytoma, further analyses were conducted separately.

Prognostic Impact of Pre-resection Amino Acid PET in Astrocytoma

Overall, 229 patients with astrocytoma underwent amino acid PET before resection or before/after biopsy. Median TTNI in this cohort was 59.8 months (95%CI: 48–67.9 months). Of these patients, 121 (52.8%) had measurable disease, 43 (18.8%) non-measurable disease, and 65 (28.4%) no measurable disease according to PET RANO 1.0 criteria. Measurable disease was more frequent at higher WHO grades (CNS WHO 2: 58/134 [43.3%]; CNS WHO 3: 44/70 [62.9%]; CNS WHO 4: 19/24 [79.2%]; $P < .001$, Fisher's exact test). TTNI of patients with measurable disease was shorter than that of those with no or non-measurable disease (median: 46.0 [95%CI: 37.1–62.4] vs. 67.9 months [95%CI: 60.4–109.2]; $P = .004$, log-rank test; [Figure 1A](#)).

Among quantitative PET parameters, TBR_{max} was associated with survival in univariable analysis (Hazard ratio [HR]: 1.44 [95%CI: 1.23–1.68; $P < .001$), as were TBR_{mean} (HR: 1.91 [95%CI: 1.34–2.71]; $P < .001$) and PET volume (HR for 10 ml increase: 1.16 [95%CI: 1.07–1.26]; $P < .001$; [Table 2](#)). Subgroup analysis including only patients who underwent [¹⁸F]FET PET confirmed these findings ([Supplementary](#)

[Table 3](#)). To test whether the time between PET and surgery impacts these associations, LRT with models integrating the time between PET and surgery as well as respective interaction terms were performed. These showed no improvement in model fit for TBR_{max} ($P = .528$), TBR_{mean} ($P = .589$), and PET volume ($P = .180$) when incorporating time-interaction covariates, indicating no significant influence of time between PET and surgery.

Multivariable analysis including clinical variables such as age, WHO grade, MGMT promoter methylation status, extent of resection, and postoperative treatment as well as MRI-based tumor extent in T2/FLAIR and T1CE resulted in a HR of 1.48 for TBR_{max} (95%CI: 1.09–2.01, $P = .011$) and a HR of 1.03 for T2/FLAIR extent (95%CI: 1.02–1.05, $P < .001$; [Table 2](#)). LASSO-penalized Cox regression with bootstrapping selected TBR_{max} in 93.4% and T2/FLAIR extent in 99.0% of resamples, supporting the relevance of both as prognostic factors when adjusting for other variables ([Supplementary Table 4](#)). In a similar model including TBR_{mean} instead of TBR_{max} , an HR of 1.93 (95%CI: 1.14–3.27, $P = .014$) was determined for TBR_{mean} . Again, in 93.6% and 98.4% of resamples, TBR_{mean} and T2/FLAIR extent were selected in LASSO-penalized Cox regression with bootstrapping ([Supplementary Table 5](#)). Results for included covariates did not change substantially when omitting PET-based quantitative parameters ([Supplementary Table 6](#)). Although the LRT between the models including and omitting both TBR_{max} and PET volume was not significant ($P = .051$), indicating no clear overall fit improvement, the concordance index (C-index) increased from 0.6950 to 0.7183. This indicates that adding PET-based parameters enhanced the model's ability to rank patients by risk.

For TBR_{max} , a value of 1.93 (bootstrap median: 1.93; 95%CI: 1.20–4.01) was identified as the optimal prognostic threshold. For TBR_{mean} , the optimal threshold was 1.94 (bootstrap median: 1.93; 95%CI: 1.58–2.23). The optimal threshold of PET volume was 2.3 mL (bootstrap median: 2.79; 95%CI: 0.01–31.3). TTNI comparisons in this cohort based on these thresholds are illustrated in [Figure 2A](#), [2C](#), and [2E](#), while comparisons based on optimal T2/FLAIR and T1CE thresholds are shown in [Supplementary Figure 3A](#) and [3C](#).

TTNI analysis, including WHO grade (CNS WHO grade 2 vs. 3), showed survival differences according to TBR_{mean}

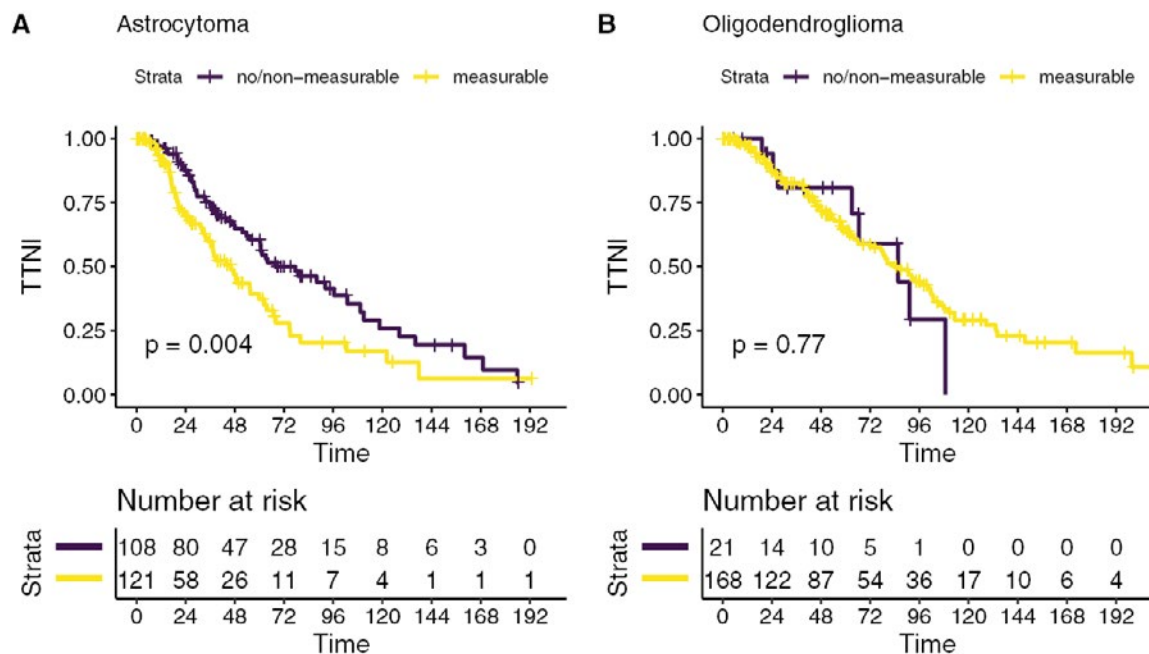


Figure 1. Time to next intervention (TTNI) by measurable disease definition according to PET RANO 1.0 criteria in patients with unresected astrocytoma (A) and oligodendroglioma (B). P-values as determined by log-rank test.

while there was considerable overlap within TBR_{mean} categories at different WHO grades (Figure 3A).

Furthermore, also OS was associated with TBR_{max} (HR: 1.40 [95%CI: 1.13–1.74]; $P = .002$), TBR_{mean} (HR: 1.21–3.22; $P = .007$), and PET volume (HR: 1.23 [95%CI: 1.10–1.37]; $P < .001$) in univariable analyses. In comparison, univariable OS analysis resulted in an HR of 1.03 (95%CI: 1.00–1.05; $P = .019$) for T2/FLAIR and an HR of 1.07 (95%CI: 0.97–1.17; $P = .176$) for T1CE extent. Multivariable OS analysis was not feasible due to a limited number of events ($n = 40$).

Prognostic Impact of Pre-resection Amino Acid PET in Oligodendroglioma

In total, 189 patients with oligodendroglioma underwent amino acid PET before resection or before/after biopsy. Median TTNI was 85.6 months (95%CI: 71.9–102 months). In this cohort, 168 (88.9%) had measurable disease, 17 (9.0%) non-measurable disease, and 4 (2.1%) had no measurable disease. There was no association of measurable disease with WHO grade (measurable disease in CNS WHO 2: 120/139 [86.3%] vs. CNS WHO 3: 48/50 [96.0%]; $P = .194$, Fisher's exact test). Moreover, there was no difference in TTNI between patients with measurable disease and those with no or non-measurable disease (median: 83.6 [95%CI: 71.9–102] vs. 85.6 months [95%CI: 63.0–not reached]; $P = .77$, log-rank test; Figure 1B).

TBR_{max} (HR: 1.17 [95%CI: 0.95–1.44; $P = .134$) and TBR_{mean} (HR: 1.31 [95%CI: 0.68–2.51]; $P = 0.415$) were not associated with TTNI in univariable analysis. However, there was a correlation between TTNI and PET volume (HR for

10 mL increase: 1.11 [95%CI: 1.05–1.19]; $P < .001$; Table 2). Subgroup analysis including only patients who underwent [^{18}F]FET PET confirmed these findings (Supplementary Table 3). To test whether the time between PET and surgery impacts these associations, LRT with models integrating the time between PET and surgery, as well as respective interaction terms, were performed. These showed no improvement in model fit for TBR_{max} ($P = .560$), TBR_{mean} ($P = .518$), and PET volume ($P = .424$) when incorporating time-interaction covariates, indicating no significant influence of time between PET and surgery.

Multivariable analysis, including the same clinical factors as in astrocytoma, resulted in an HR of 1.18 (95%CI: 1.03–1.36, $P = .017$) for PET volume. LASSO-penalized Cox regression with bootstrapping selected PET volume in 90.2% of resamples, supporting its relevance as a prognostic factor when adjusting for other variables (Supplementary Table 4). In a similar model including TBR_{mean} instead of TBR_{max} , an HR of 1.19 (95%CI: 1.05–1.34, $P = .007$) was observed for PET volume. Again, in 90.6% of resamples in LASSO-penalized Cox regression with bootstrapping, PET volume was selected (Supplementary Table 5). Results for included covariates did not change substantially when omitting PET-based quantitative parameters (Supplementary Table 6). However, LRT between the models including and omitting TBR_{max} and PET volume resulted in a p-value of 0.032, while the C-indices were similar (0.7379 vs. 0.7374). These findings suggest that adding PET parameters improved the overall fit while not improving the model's ability to rank patients by risk.

For TBR_{max} , a value of 4.18 (bootstrap median: 3.63; 95%CI: 1.79–4.36) was identified as the optimal prognostic

Table 2. Uni- and Multivariable TTNi Analysis in Patients with Astrocytoma and Oligodendroglioma Undergoing Amino Acid PET Before Surgical Resection.

	Astrocytoma (n = 229)				Oligodendroglioma (n = 189)			
	Univariable analysis		Multivariable analysis (n = 178)		Univariable analysis		Multivariable analysis (n = 134)	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
Age at diagnosis	n = 229				n = 189			
	0.98 (0.97–1.00)	0.050	0.98 (0.96–1.00)	0.059	0.98 (0.96–1.00)	0.108	0.98 (0.96–1.00)	0.040
WHO grade	n = 228				n = 189			
-CNS WHO 2	Reference				Reference			
-CNS WHO 3	0.90 (0.60–1.37)	0.632	1.27 (0.70–2.30)	0.428	0.76 (0.46–1.24)	0.272	2.81 (1.36–5.80)	0.005
-CNS WHO 4	1.00 (0.53–1.87)	0.992	0.80 (0.30–2.11)	0.654				
MGMT	n = 229				n = 189			
-methylated	Reference				Reference			
-unmethylated	0.81 (0.47–1.39)	0.439	0.63 (0.31–1.26)	0.187	0.37 (0.09–1.54)	0.169	0.06 (0.01–0.59)	0.016
-unknown	0.57 (0.14–2.32)	0.433	0.74 (0.17–3.18)	0.682	0.46 (0.19–1.14)	0.094	0.83 (0.31–2.19)	0.704
Extent of resection	n = 229				n = 189			
-Gross total resection (GTR)	Reference				Reference			
-Subtotal resection (STR)	2.33 (1.26–4.30)	0.007	1.09 (0.51–2.36)	0.820	1.18 (0.59–2.35)	0.637	0.92 (0.40–2.12)	0.844
-Resection of unknown extent (excluding biopsy)	1.53 (0.71–3.29)	0.274	0.88 (0.32–2.43)	0.802	0.81 (0.23–2.82)	0.739	0.23 (0.05–1.07)	0.061
-Biopsy	1.88 (1.13–3.11)	0.015	1.60 (0.85–3.01)	0.144	1.38 (0.79–2.42)	0.258	1.08 (0.50–2.35)	0.849
Postoperative treatment	n = 225				n = 187			
-observation	Reference				Reference			
-RT only	1.02 (0.51–2.02)	0.962	0.63 (0.24–1.62)	0.337	1.75 (0.54–5.72)	0.354	2.08 (0.51–8.52)	0.307
-ChT only	1.17 (0.75–1.83)	0.478	0.72 (0.38–1.37)	0.323	0.76 (0.48–1.20)	0.244	0.53 (0.28–1.01)	0.055
-R-ChT	0.68 (0.36–1.29)	0.235	0.37 (0.16–0.89)	0.026	0.18 (0.07–0.44)	<0.001	0.05 (0.01–0.21)	<0.001
-[¹²⁵ I] seeds	1.42 (0.71–2.82)	0.317	0.99 (0.42–2.32)	0.987	0.80 (0.25–2.58)	0.707	1.23 (0.26–5.86)	0.794
Product of maximum perpendicular diameters in T2/FLAIR (unit: 1 cm²)	n = 198				n = 148			
	1.03 (1.02–1.05)	<0.001	1.03 (1.02–1.05)	<0.001	1.02 (0.99–1.04)	0.160	1.02 (0.99–1.05)	0.273
Product of maximum perpendicular diameters in T1CE (unit: 1 cm²)	n = 199				n = 170			
	1.12 (1.04–1.20)	0.004	1.06 (0.93–1.20)	0.371	1.01 (0.96–1.06)	0.708	1.01 (0.96–1.06)	0.759
TBR_{max}	n = 229				n = 189			
	1.44 (1.23–1.68)	<0.001	1.48 (1.09–2.01)	0.011	1.17 (0.95–1.44)	0.134	0.94 (0.67–1.32)	0.732
TBR_{mean}	n = 229				n = 189			
	1.91 (1.34–2.71)	<0.001			1.31 (0.68–2.51)	0.415		
PET volume (unit: 10 ml)	n = 229				n = 189			

Table 2. Continued

Astrocytoma (n = 229)				Oligodendroglioma (n = 189)			
Univariable analysis		Multivariable analysis (n = 178)		Univariable analysis		Multivariable analysis (n = 134)	
HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
1.16 (1.07–1.26)	<0.001	0.88 (0.73–1.06)	0.180	1.11 (1.05–1.19)	<0.001	1.18 (1.03–1.36)	0.017

ChT = chemotherapy; CNS = Central Nervous System; HR = hazard ratio; MGMT = O6-methylguanine methyltransferase; PET = positron emission tomography; RT = radiotherapy; R-ChT = radio-chemotherapy; TBR_{max} / TBR_{mean} = maximum/mean tumor-to-background ratios; WHO = World Health Organization; 95%CI = 95% confidence interval.

threshold. For TBR_{mean} , the optimal threshold was 2.15 (bootstrap median: 2.09; 95%CI: 1.67–2.36). The optimal threshold of PET volume was 43.1 ml (bootstrap median: 41.99; 95%CI: 9–43.1). TTNI comparisons in this cohort based on these thresholds are illustrated in Figure 2B, 2D, and 2F, while comparisons based on optimal T2/FLAIR and T1CE thresholds are shown in Supplementary Figure 3B and 3D.

TTNI analysis, including WHO grade, showed significant survival differences according to PET volumes, while there was considerable overlap within PET volume categories with different WHO grades (Figure 3B). OS analysis in these patients was not feasible due to a limited number of survival events ($n = 17$).

Subgroup Analysis According to Type of Surgery and Timepoint of PET

To correct for the potentially confounding factor of surgical resection of PET-positive volume on TTNI, we performed univariable subgroup analyses according to type of surgery (resection vs. biopsy) and the timepoint of PET in resected patients (before or after resection or biopsy). In astrocytoma, TBR_{max} , TBR_{mean} , and PET volume showed a consistent association with TTNI across subgroups except in patients where PET was performed after resection (Figure 4A, 4C, and 4E). In oligodendroglioma, a correlation between TBR_{max} and TBR_{mean} could not be shown in any of these subgroups (Figure 4B and 4D), whereas PET volume was associated with TTNI in all subgroups except for patients who underwent resection (Figure 4F).

Discussion

In this large retrospective cohort of patients with newly diagnosed *IDH*-mutant glioma treated at two high-volume academic centers in Germany and Austria, we evaluated the prognostic value of amino acid PET. To our knowledge, this is the largest study investigating the prognostic impact of PET in *IDH*-mutant glioma diagnosed by the 2021 WHO classification. Here, we observed associations of prognosis with quantitative PET parameters such as TBR_{max} and TBR_{mean} values in astrocytoma and PET volume in oligodendroglioma after adjusting for known prognostic

factors. While our results corroborate prior reports suggesting a prognostic value of amino acid PET, previous data were primarily based on histological classification of the pre-molecular era, included unselected glioma cohorts of varying grades, did not incorporate clinical factors to test for the independence of their prognostic impact, or were unable to evaluate associations with overall survival due to limited sample size.^{21–30} Moreover, the evaluation of PET imaging in our cohort was consistently based on the standardized framework of the recently proposed PET RANO 1.0 criteria,¹² which was further validated by showing a prognostic impact of PET-measurable disease classification in untreated patients with astrocytoma.

Notably, associations with prognosis remained after adjusting for clinical factors, including MRI-based tumor extent, which frequently influence clinical decision-making in the postoperative setting, suggesting an additive layer of information by amino acid PET. For instance, histological grading remains a cornerstone for prognostic stratification, as a watch-and-wait approach is frequently pursued in WHO grade 2 gliomas, whereas upfront treatment is generally recommended in WHO grade 3 gliomas.^{31,32} In our study, WHO grade had limited prognostic value as previously reported in other cohorts.^{33,34} To date, grading is still primarily based on histomorphological criteria such as anaplastic features or arbitrary cut-offs on mitotic count, which are, however, not well validated for *IDH*-mutant tumors.^{33,35} Given the ill-defined boundary, particularly between WHO grades 2 and 3, previous studies have shown considerable inter- and intra-observer variability,^{36,37} highlighting the need for refined stratification frameworks that reflect tumor biology. Indeed, novel approaches incorporate DNA methylation profiles and propose continuous grading frameworks that align with underlying biological mechanisms such as cell differentiation, cell cycle regulation, and extracellular matrix remodeling.^{34,38} Consistent with our findings, differences in uptake according to WHO grades and tumor histology have been reported previously.^{22,39–41} Furthermore, the prognostic value after adjusting for clinical factors in our cohort underscores the potential of quantitative information derived from PET imaging regardless of WHO grade, extent of resection, or postoperative treatment. Further studies integrating both in-depth molecular profiling and advanced

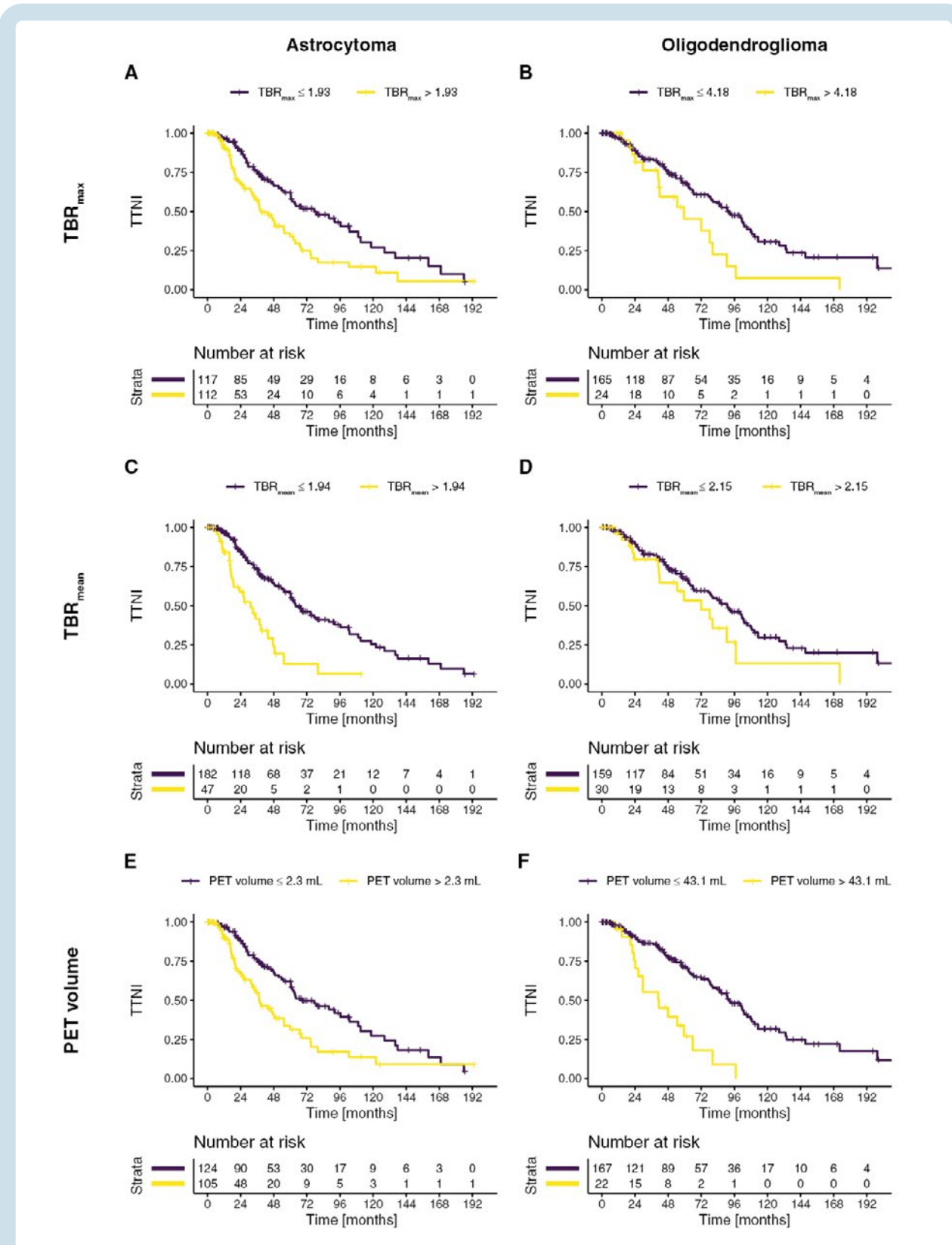


Figure 2. Time to next intervention (TTNI) by TBR_{max} (A/B), TBR_{mean} (C/D) and PET volume (E/F) in patients with unresected astrocytoma (A, C, E) and oligodendroglioma (B, D, F). Thresholds as determined by maximally selected rank statistic.

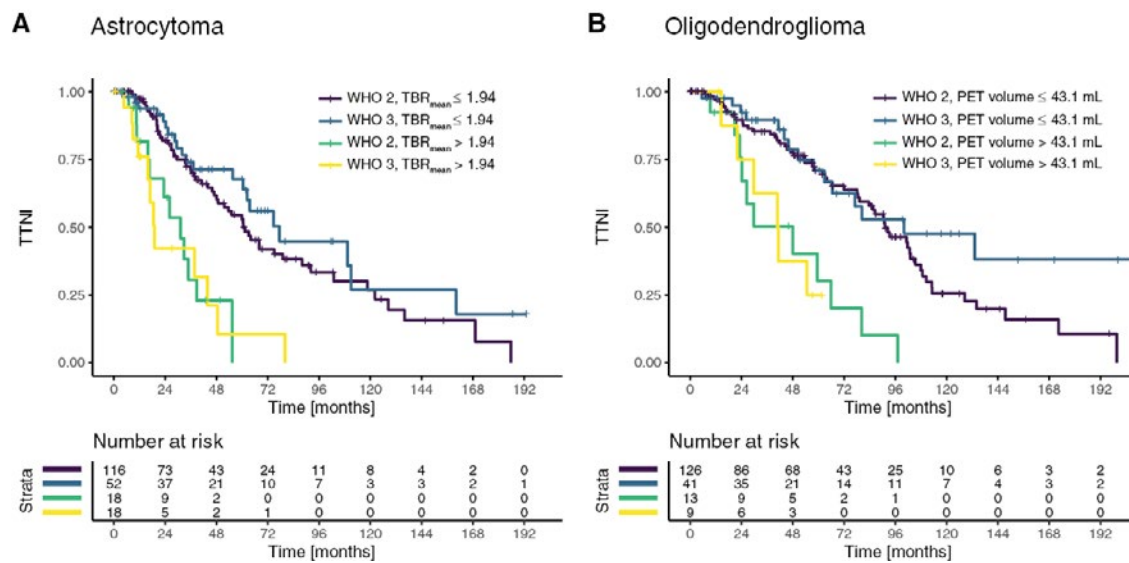


Figure 3. Time to next intervention (TTNI) by WHO grade and (A) TBR_{mean} in astrocytoma and (B) PET volume in oligodendroglioma. Thresholds as determined by maximally selected rank statistic.

imaging are needed to improve prognostic stratification and guide treatment allocation in this patient population.

In patients with oligodendroglioma, our data suggest an association between PET volume and outcome. Notably, the optimal PET volume cut-off of 43.1 mL aligns well with the optimal threshold for pre-operative tumor volume in another study based on MRI.¹⁰ However, the referenced work only included WHO grade 2 tumors and FLAIR-based volumetric assessment, resulting in larger preoperative volumes than the PET volumes measured in the present study and underscoring the challenging delineation of tumor volumes from perifocal edema in MRI. While an effect of limited sample sizes cannot be excluded, subgroup analyses revealed that the association between PET volume and outcome was not present in patients undergoing PET and subsequent resection, suggesting that residual tumor volume might be more relevant than preoperative tumor size as reported in previous studies on volumetric MRI in *IDH*-mutant glioma^{10,42,43} and glioblastoma.^{44,45} At the same time, no association between uptake intensity (TBR_{max} , TBR_{mean}) and prognosis could be detected in oligodendrogliomas, probably due to a uniformly higher uptake compared to astrocytomas as previously reported.⁴⁶ While it is assumed that amino acid PET uptake correlates with expression and activity of L-amino acid transporters (LAT), underlying biological mechanisms for higher PET uptake in oligodendrogliomas compared to astrocytomas remain unclear, particularly given the overall slower growth of oligodendrogliomas.^{47–49} Moving forward, further studies investigating the relationship between tumor growth, molecular factors, and PET uptake are needed to define the association between PET and proliferative activity in subgroups of *IDH*-mutant glioma.

Inclusion of patients treated at two distinct high-volume centers allowed for analyses in a large real-life cohort, underscoring the robustness of the presented

data. In addition, contemporary glioma classification as well as long-term follow-up are strengths of this study. Nevertheless, this study has important limitations. First, the retrospective and bicentric study design is inherently associated with missing data (particularly on performance status and MRI-based tumor volumes), limited cohort size in certain subgroups, and heterogeneity in the cohort. This also applies to heterogeneous postoperative treatments, including [¹²⁵I] seeds, which are not considered standard of care according to current guidelines.³¹ Also, administered chemotherapy was heterogeneous in the cohort and included procarbazine, lomustine (CCNU), vincristine (PCV) as well as temozolomide-based regimens. The addition of chemotherapy to radiotherapy improved outcomes across trials in *IDH*-mutant gliomas, and in line, this was included to multivariable analysis to adjust for the type of postoperative treatment. In contrast, the superiority of PCV versus temozolomide remains a matter of discussion; accordingly, the choice of chemotherapy regimen has therefore not been included as a variable. Furthermore, selection bias might affect the generalizability of our data, as amino acid PET was widely used in Munich, while patients in Vienna mainly underwent PET for hotspot delineation prior to surgery in patients not showing contrast enhancement in MRI. Nevertheless, patients' characteristics are well in line with previously published clinical trial and real-life data on *IDH*-mutant (or previously "lower-grade") gliomas.^{750–52} While TTNI is a clinically meaningful endpoint increasingly used in prospective trials, it might introduce ambiguity given that treatment patterns at suspected recurrence might differ between institutions and evolve over time. Frequently, the initiation of a therapeutic intervention at progression/recurrence is not only a result of tumor relapse, but also patient and physician preference as well as further clinical factors, including PET imaging, especially as treating physicians were not blinded in this

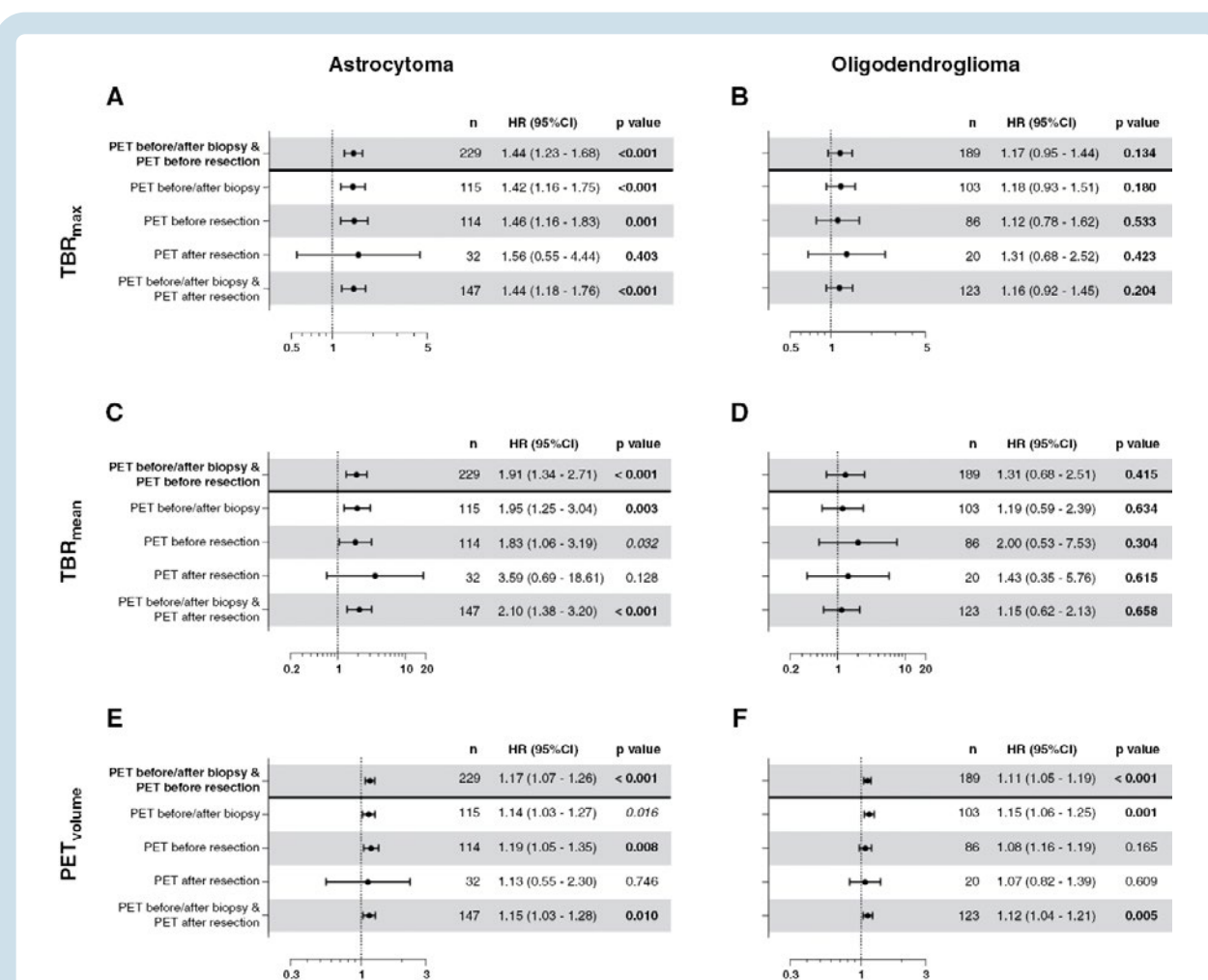


Figure 4. TTNI analysis by TBR_{max} (A/B), TBR_{mean} (C/D), and PET volume (E/F) in astrocytoma (A/C/E) and oligodendroglioma (B/D/F) subgroups according to type of surgery (biopsy vs. resection) and timepoint of PET (before/after surgery). HR (95%CI) = hazard ratio with 95% confidence interval; P values as determined by univariable Cox regression.

retrospective study. While imaging-based progression-free survival according to current RANO criteria could address these limitations, necessary imaging data were unavailable in most patients. Nevertheless, we could confirm the prognostic impact of TBR_{max} and TBR_{mean} in astrocytoma using OS as endpoint. As in many clinical trials of *IDH*-mutant glioma, OS events were limited, and longer follow-up would be ultimately needed to confirm our signals in multivariable analyses. PET imaging was acquired using different tracers and scanners, and data on dynamic PET parameters were not available in many patients. However, standardized assessment of static parameters based on the PET RANO 1.0 criteria was applied, normalizing measurements to background activity and allowing for comparable measurements across distinct tracers and devices. Lastly and given the lack of external validation, the findings should be interpreted with caution and should be validated on external, ideally prospective cohorts.

To conclude, our data indicate an association of amino acid PET parameters with outcome in *IDH*-mutant glioma

after adjusting for known prognostic factors, suggesting an added value of amino acid PET in prognostic stratification and postoperative treatment allocation. Moving forward, the inclusion of amino acid PET should be considered in prospective clinical trials and well-annotated registries to further evaluate its prognostic and predictive values.

Supplementary material

Supplementary material is available online at *Neuro-Oncology* (<https://academic.oup.com/neuro-oncology>).

KeyWords:

glioma | astrocytoma | oligodendroglioma | positron emission tomography | prognosis

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Author Contributions

Study design: MJM, MP, NLA; Implementation and data acquisition: MJM, JMW, JW, EB, SK, JI, TA, RS, JH, JR, HCP, TS, BK, GW, AW, TN, MH, JF, SS, PNH, LvB, ASB, NT, MP, NLA; Data analysis and interpretation: MJM, LB, JMW, MP, NLA; Writing of first draft: MJM, NLA; All authors edited, read, and approved the final manuscript.

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Ethics Approval

The study has been conducted in compliance with local and national guidelines and according to the Declaration of Helsinki (1964) with all its amendments and has been approved by the ethics board of the LMU Munich (approval no. 17-656, 604-16) and the Medical University of Vienna (approval no. 2086/2023, 1166/2019).

Data Availability

Data are available upon request from the corresponding author and approval from relevant regulatory authorities.

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