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The role of preoperative [^{11}C]methionine PET in defining tumor-related epilepsy and predicting short-term postoperative seizure control in temporal lobe low-grade gliomas

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OBJECTIVE Surgery is the mainstay of treatment for low-grade glioma (LGG)–related epilepsy. However, the goal of achieving both oncological radical resection and seizure freedom can be challenging. PET with [^{11}C]methionine (MET) has been recently introduced in clinical practice for the management of patients with LGGs, not only to monitor the response to treatments, but also as a preoperative tool to define the metabolic tumor extent and to predict tumor grading, type, and prognosis. Still, its role in defining tumor-related epilepsy and postoperative seizure outcomes is limited. The aim of this preliminary study was to investigate the role of MET PET in defining preoperative seizure characteristics and short-term postoperative seizure control in a cohort of patients with newly diagnosed temporal lobe low-grade gliomas (tLGGs).

METHODS Patients with newly diagnosed and histologically proven temporal lobe grade 2/3 gliomas (2021 WHO CNS tumor classification) who underwent resection at the authors' institution between July 2011 and March 2021 were included in this retrospective study. MET PET images were acquired, fused with MRI scans, and qualitatively and semiquantitatively analyzed. Any eventual PET/MRI involvement of the temporomesial area, seizure characteristics, and 1-year seizure outcomes were reported.

RESULTS A total of 52 patients with tLGGs met the inclusion criteria. MET PET was positive in 41 (79%) patients, with a median metabolic tumor volume of 14.56 cm^3 (interquartile range [IQR] 6.5–28.2 cm^3). The median maximum and mean tumor-to-background ratio (TBR_{max},TBR_{mean}) were 2.24 (IQR 1.58–2.86) and 1.53 (IQR 1.37–1.70), respectively. The metabolic tumor volume was found to be related to the presence of seizures at disease onset, but only in noncodeleted tumors ($p = 0.014$). Regarding patients with uncontrolled seizures at surgery, only the temporomesial area PET involvement showed a statistical correlation both in the univariate ($p = 0.058$) and in the multivariate analysis ($p = 0.030$). At 1-year follow-up, seizure control was correlated with MET PET–derived semiquantitative data. Particularly, higher TBR_{max} ($p = 0.0192$) and TBR_{mean} ($p = 0.0128$) values were statistically related to uncontrolled seizures 1 year after surgery.

CONCLUSIONS This preliminary study suggests that MET PET may be used as a preoperative tool to define seizure characteristics and outcomes in patients with tLGGs. These findings need to be further validated in larger series with longer epileptological follow-ups.

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KEYWORDS brain tumors; low-grade gliomas; tumor-related epilepsy; [^{11}C]methionine PET; seizure outcome

ABBREVIATIONS AED = antiepileptic drug; CR = complete resection; EOR = extent of resection; FLAIR-TV = FLAIR tumor volume; IQR = interquartile range; LGG = low-grade glioma; MET = [^{11}C]methionine; MTV = metabolic tumor volume; NTR = near total resection; PR = partial resection; STR = subtotal resection; SUP = supramaximal resection; TBR = tumor-to-background ratio; TBR_{max} = maximum TBR; TBR_{mean} = mean TBR; tLGG = temporal lobe low-grade glioma; TMa = temporomesial area; TRE = tumor-related epilepsy.

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Tumor-related epilepsy (TRE) is the most common clinical condition associated with temporal lobe low-grade gliomas (tLGGs), and is a significant cause of long-term cognitive impairment and morbidity.[1–4] Surgery is the mainstay of treatment for TRE, even though the goal of achieving both oncological radical resection and seizure freedom can be challenging. Indeed, a relatively high proportion of patients still suffers from uncontrolled seizures, even after maximal resections, and epileptological outcomes are often underestimated.[4,5] Pathophysiological mechanisms underlying TRE are still a matter of debate, although growing evidence has led investigators to argue that the epileptogenic focus (or foci) resides at the periphery of the tumor, rather than in the core.[6–9]

It is thus reasonable to think that early recognition of the peritumoral area through noninvasive imaging techniques may lead to significant benefits in terms of seizure control. In the last 2 decades, several studies have investigated the role of advanced morphological and metabolic imaging techniques in the definition of TRE and postoperative epileptological prognostication, leading to nonetheless controversial results.[5]

Amino acid PET, and particularly [^{11}C]methionine (MET) PET, is increasingly used in clinical practice for the management of patients with LGGs, both to monitor the response to treatments and as a preoperative tool to define the metabolic tumor extent prior to surgery. Moreover, it has been used to predict tumor grading, molecular subtype, and prognosis.[10–16] Nevertheless, its role in defining TRE and postoperative seizure outcomes is still limited.[14,17–20]

The aim of this exploratory study was to investigate the role of preoperative MET PET combined with other clinical and imaging data in defining the preoperative seizure characteristics and the short-term postoperative seizure control in a cohort of patients who underwent resection for newly diagnosed tLGGs.

Methods

Patients with a new histomolecular diagnosis of grade 2/3 glioma (2021 WHO CNS tumor classification)[21] who underwent resection at our institution between July 2011 and March 2021 were retrospectively included. This study was approved by our institutional ethics committee.

The inclusion criteria were as follows: 1) histopathological and molecular diagnosis of IDH-mutant grade 2/3 diffuse glioma according to the 2021 WHO CNS tumor classification; 2) no previous treatments (chemotherapy, radiotherapy, or surgery); and 3) temporal lobe tumor location. Demographic, clinical, imaging, treatment, and outcome data were retrospectively collected.

Preoperative Imaging and Epileptological Data

MRI was performed according to our institutional protocol, with volumetric T2, T2-FLAIR, and T1 pre/postcontrast sequences. MET PET images were acquired, and were qualitatively and semiquantitatively analyzed as previously described.[15] The semiquantitative data included the following: the tumor-to-background ratio (TBR), along with its maximum (TBR_{max}) and mean (TBR_{mean}) values, and the metabolic tumor volume (MTV, cm^3) for positive examinations. All PET scans were coregistered with the preoperative MRI (iPlan Cranial, Brainlab AG) to define any MTV/T2-FLAIR eventual mismatch, particularly within the temporomesial area (TMa), which is a highly epileptogenic area[4] including the amygdala and the head of the hippocampus (Fig. 1). Seizure characteristics were classified according to the 2017 International League Against Epilepsy (ILAE) recommendations.[22] Seizure control at surgery was defined as the absence of seizures within 30 days before surgery.

Surgical Technique and Extent of Resection

All patients gave their written informed consent for surgery and for the publication of their data for scientific purposes. The aim of surgery was the maximal safe resection in all cases. PET-MRI–based neuronavigation as well as intraoperative neurophysiological brain monitoring and brain mapping were used. Preoperative and postoperative FLAIR tumor volumes (FLAIR-TV) were calculated with both manual and automated tumor segmentation by using the iPlan Cranial software (Brainlab AG). Postoperative (< 72 hours) MRI scans with diffusion-weighted sequences were carefully reviewed by an experienced neuroradiologist (L.S.P.) to rule out any ischemic damage near the surgical cavity, which could have acted as a confounder in calculating any residual FLAIR-TV. The extent of resection (EOR) was then defined as [(preoperative FLAIR-TV − postoperative FLAIR-TV)/preoperative FLAIR-TV] × 100, and classified according to a recent report by Karschnia et al.[23] For the purposes of our analyses, EOR was further categorized into three groups: 1) supramaximal resection (SUP) + complete resection (CR); 2) near total resection (NTR); and 3) subtotal (STR) + partial resection (PR). Tumor biopsies have not been included because there were no cases within our sample. TMa resection was ultimately reported based on the postoperative MRI findings.

Follow-Up and Seizure Outcomes

The follow-up consisted of scheduled neurological examinations and MRI scans every 3–6 months after surgery. The indication for any postoperative adjuvant treatment was defined following a multidisciplinary evaluation. Tumor recurrence and/or progression was defined according to the Response Assessment in Neuro-Oncology (RANO) criteria.[24] Seizure outcome was evaluated 1 year after surgery and at tumor recurrence/progression (when it occurred) by using the Engel classification system.[25,26] Results were further dichotomized as controlled seizures (class I) and uncontrolled seizures (class II–IV).

Statistical Analysis

Stata MP software, version 14.0 (StataCorp LP), was used for the statistical analysis. In the descriptive analysis, quantitative variables were tested for normal distribution by the Shapiro-Wilk test. In the case of normal distribution the mean and standard deviation were reported, whereas in the case of nonnormal distribution the median and interquartile range (IQR) were used. The Kruskal-Wallis H test was used to compare the median of quantitative vari-

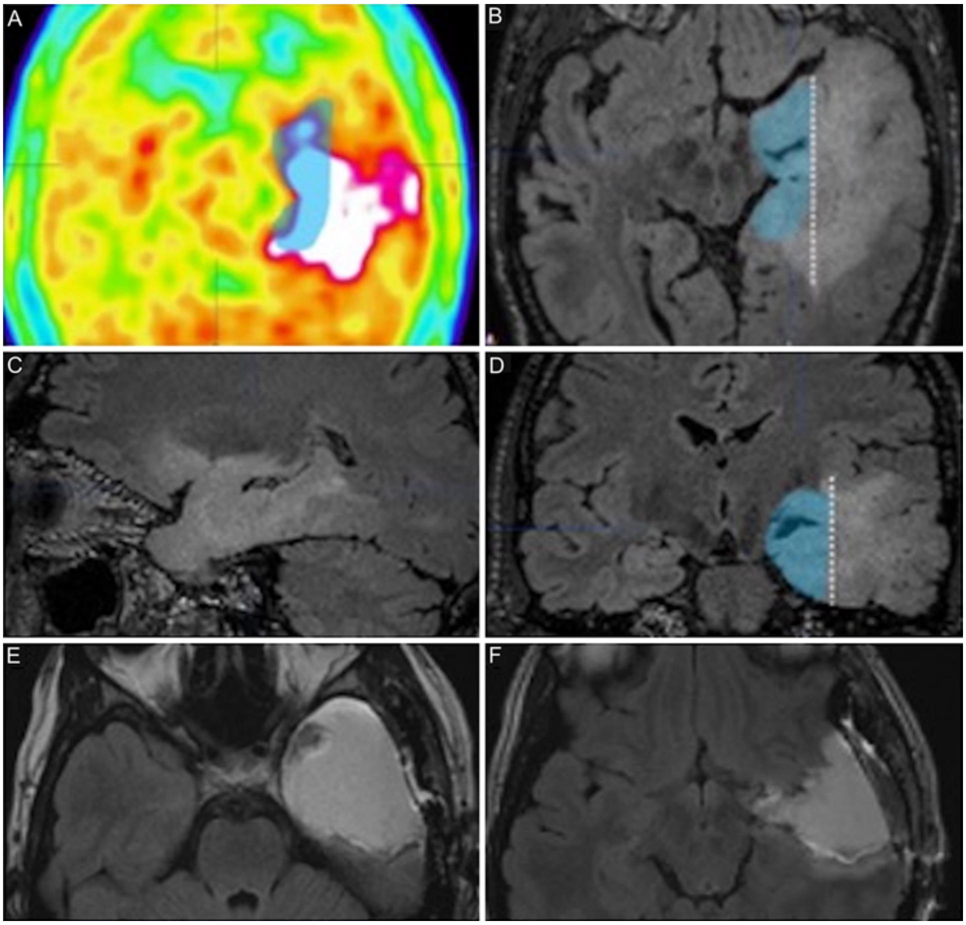

FIG. 1. A–D: Preoperative PET-MRI FLAIR sequences obtained in a 27-year-old woman with a left IDH-mutant grade 2 astrocytoma and uncontrolled seizures at surgery (sudden feeling of anxiety and fear, déjà vu, visual hallucinations) despite triple AED treatment. Axial MET PET scan showing high radiotracer uptake within the left TMa (A). MRI FLAIR sequences with axial (B), sagittal (C), and coronal (D) images showing the tumor. The TMa is delimited laterally by a line passing just medial to the collateral sulcus (*white dotted line*), including the amygdala and the hippocampus (head and first portion of the body). PET-MRI TMa overlap is highlighted in *light blue* (panels A, B, and D). **E and F:** Postoperative axial MRI FLAIR sequences obtained in the same patient, showing the complete resection of the tumor. The patient experienced no postoperative deficit except a transient superolateral visual field impairment, and she was completely seizure free 1 year after surgery (Engel class I).

ables. Ordinal and categorical variables were compared using the chi-square test. Probability values < 0.05 were considered statistically significant. Univariate and multivariate logistic regression analyses were used to test the association of clinical, histomolecular, and imaging data with the pre- and postoperative presence of seizures.

Results

A total of 52 patients with tLGG, 31 (60%) men and 21 (40%) women, met the inclusion criteria. IDH-mutant 1p/19q-codeleted and -noncodeleted molecular types were observed in 28 (54%) and 24 (46%) patients, respectively. Tumor grading followed the same distribution among the patient cohort, with 28 (54%) grade 2 and 24 (46%) grade 3 tumors.

Imaging, Clinical, and Histomolecular Data Related to Preoperative Seizure Characteristics

The median preoperative FLAIR-TV was 43.9 cm^3 (IQR 28.5–65.8 cm^3) and the TMa was involved in 34 (65%) patients on FLAIR sequences. MET PET examinations were positive in 41 (79%) patients, with a median MTV of 14.56 cm^3 (IQR 6.5–28.2 cm^3). The median TBR_{max} was 2.24 (IQR 1.58–2.86), and the median TBR_{mean} was 1.53 (IQR 1.37–1.70). TMa PET involvement was observed in 18 (35%) cases. Seizures were the presenting symptom in 40 (77%) cases. All patients except for one began the antiepileptic drug (AED) therapy before surgery. Fourteen subjects, including one not on antiseizure medications, had no fully controlled secondary epilepsy at surgery.

The IDH-mutant 1p/19q-codeleted molecular subtype and the FLAIR TMa involvement were found to be statistically related to the presence of seizures at disease onset ($p = 0.022$ and $p = 0.049$, respectively), as well as the MTV in noncodeleted tumors ($p = 0.014$). Other PET qualitative (positive/negative) and semiquantitative ($TBR_{max/mean}$ and MTV) data did not correlate to preoperative seizure characteristics. Regarding the occurrence of uncontrolled sei-

TABLE 1. Main demographic, histomolecular, and imaging data subdivided according to the patient's clinical presentation

Variable	All, n = 52	Szs at Onset, n = 40	No Szs at Onset, n = 12	p Value
Age in yrs at surgery, median (IQR)	39 (32–48)	40 (36–48)	31 (27–59)	0.1813
2021 WHO grade, no. (%)				0.722
2	28 (54%)	21 (53%)	7 (58%)	
3	24 (46%)	19 (47%)	5 (42%)	
LGG type, no. (%)				**0.022**
IDH-mutant, 1p/19q-codeleted	28 (54%)	25 (63%)	3 (25%)	
IDH-mutant, 1p/19q-noncodeleted	24 (46%)	15 (37%)	9 (75%)	
Side, no. (%)				0.450
Lt	35 (67%)	28 (70%)	7 (58%)	
Rt	17 (33%)	12 (30%)	5 (42%)	
PET qualitative, no. (%)				0.239
Positive	41 (79%)	33 (83%)	8 (67%)	
Negative	11 (21%)	7 (17%)	4 (33%)	
TMa PET involvement, no. (%)				0.915
Yes	18 (35%)	14 (35%)	4 (33%)	
No	34 (65%)	26 (65%)	8 (67%)	
TMa FLAIR involvement, no. (%)				**0.049**
Yes	34 (65%)	29 (73%)	5 (42%)	
No	18 (35%)	11 (27%)	7 (58%)	

Szs = seizures.
Boldface type indicates statistical significance.

zures at surgery, only the TMa PET involvement showed an independent predictive value in the multivariate analysis (p = 0.030). The TMa FLAIR/PET mismatch did not correlate either with epileptological presentation or with seizure control at surgery. Clinical, histomolecular, and radiological data are summarized in the tables, with patient's clinical presentation (Table 1) and seizure control at surgery (Table 2).

TABLE 2. Main demographic, histomolecular, and imaging data subdivided according to seizure control at surgery

Variable	All, n = 39	Sz Free at Surgery, n = 25	Non–Sz Free at Surgery, n = 14	p Value
Age in yrs at surgery, median (IQR)	39 (36–47)	38 (36–43)	44 (36–48)	0.7978
2021 WHO grade, no. (%)				0.757
2	21 (54%)	13 (52%)	8 (57%)	
3	18 (46%)	12 (48%)	6 (43%)	
LGG type, no. (%)				0.169
IDH-mutant, 1p/19q-codeleted	25 (64%)	18 (72%)	7 (50%)	
IDH-mutant, 1p/19q-noncodeleted	14 (36%)	7 (28%)	7 (50%)	
Side, no. (%)				0.617
Lt	27 (69%)	18 (72%)	9 (64%)	
Rt	12 (31%)	7 (28%)	5 (36%)	
PET qualitative, no. (%)				0.656
Positive	32 (82%)	20 (80%)	12 (86%)	
Negative	7 (18%)	5 (20%)	2 (14%)	
TMa PET involvement, no. (%)				0.345
Yes	13 (33%)	7 (28%)	6 (43%)	
No	26 (67%)	18 (72%)	8 (57%)	
TMa FLAIR involvement, no. (%)				0.970
Yes	28 (72%)	18 (72%)	10 (71%)	
No	11 (28%)	7 (28%)	4 (29%)	

TABLE 3. Main imaging and EOR data in relation to 1-year seizure outcomes (Engel I vs Engel II–IV)

Variable	All, n = 41	Engel I Sz Free at 1 Yr, n = 33	Engel II–IV Non–Sz Free at 1 Yr, n = 8	p Value
Age in yrs at surgery, median (IQR)	39 (32–48)	38 (32–47)	40 (35–49)	0.8307
2021 WHO grade, no. (%)				0.177
2	22 (54%)	16 (48%)	6 (75%)	
3	19 (46%)	17 (52%)	2 (25%)	
LGG type, no. (%)				0.134
IDH-mutant, 1p/19q-codeleted	21 (51%)	15 (45%)	6 (75%)	
IDH-mutant, 1p/19q-noncodeleted	20 (49%)	18 (55%)	2 (25%)	
Side, no. (%)				0.695
Lt	28 (68%)	23 (70%)	5 (62.5%)	
Rt	13 (32%)	10 (30%)	3 (37.5%)	
PET qualitative, no. (%)				0.095
Positive	32 (78%)	24 (73%)	8 (100%)	
Negative	9 (22%)	9 (27%)	0	
MTV in cm^3, median (IQR), n = 30	14.56 (6.5–28.2)	13.6 (4.9–21.7)	16.7 (12.3–29.9)	0.3643
TBR_{max}, median (IQR), n = 39	2.24 (1.58–2.86)	2.15 (1.44–2.61)	3.09 (2.37–4.19)	**0.0192**
TBR_{mean}, median (IQR), n = 39	1.53 (1.37–1.70)	1.51 (1.10–1.62)	1.82 (1.59–2.01)	**0.0128**
Preop FLAIR vol in cm^3, median (IQR)	43.9 (28.5–65.8)	44.4 (29.1–65.3)	51.5 (36.1–68.1)	0.5986
Postop FLAIR vol in cm^3, median (IQR)	3.3 (0–8.7)	3.2 (0.03–8.3)	2.6 (0–3.8)	0.5760
EOR, no. (%)				0.4179
SUP/CR	13 (32%)	9 (27.3%)	4 (50%)	
NTR	12 (29%)	9 (27.3%)	3 (37.5%)	
STR/PR	16 (39%)	15 (45.4%)	1 (12.5%)	
TMa PET involvement, no. (%)				0.650
Yes	13 (32%)	11 (33%)	2 (25%)	
No	28 (68%)	22 (67%)	6 (75%)	
TMa FLAIR involvement, no. (%)				**0.007**
Yes	27 (66%)	25 (76%)	2 (25%)	
No	14 (34%)	8 (24%)	6 (75%)	
TMa PET-FLAIR mismatch, no. (%)				0.230
Yes	18 (44%)	16 (48%)	2 (25%)	
No	23 (56%)	17 (52%)	6 (75%)	
TMa resection, no. (%)				0.237
Yes	23 (56%)	20 (61%)	3 (37.5%)	
No	18 (44%)	13 (39%)	5 (62.5%)	

Boldface type indicates statistical significance.

EOR, Imaging, Clinical, and Histomolecular Data Related to Postoperative Seizure Control

The median postoperative FLAIR-TV was 3.3 cm^3 (IQR 0–8.7 cm^3). SUP + CR was achieved in 13 (32%) patients, and NTR was achieved in 12 (29%) and STR + PR in 16 (39%). Four known cases of tumor recurrences were observed within 1 year. The 1-year seizure outcome data are available for 41/52 patients; 11 subjects were lost during follow-up.

One year after surgery, all patients were on AEDs. Thirty-three (80%) were seizure free (Engel class I), whereas 8 (20%) had uncontrolled seizures (7 Engel class II, 1 Engel class IV) despite surgery and medical therapy. A positive correlation between EOR and seizure control was found, although it was not statistically significant (p = 0.089). TMa resection was performed in 23 (56%) patients, including 17 (74%) with TMa FLAIR and 11 (48%) with TMa PET involvement. Sixteen of 17 (94%) patients with TMa FLAIR involvement and 9/11 (82%) with PET TMa involvement who underwent TMa resection had controlled seizures 1 year after surgery. A strong positive relation between the TMa FLAIR involvement and 1-year seizure control was found (p = 0.007) and confirmed in the univariate analysis (p = 0.005). Seizure control also strongly correlated with MET PET–derived semiquantitative data. Particularly, higher TBR values were statistically related to uncontrolled seizures, and that was true for both the TBR_{max} (p = 0.0192) and the TBR_{mean} (p = 0.0128). Moreover, higher TBR_{max} values at preoperative MET PET were independent predictors of uncontrolled seizures at

TABLE 4. Univariate and multivariate analyses regarding clinical presentation (seizures vs nonseizures)

	Univariate Analysis			Multivariate Analysis*		
Variable	OR	95% CI	p Value	OR	95% CI	p Value
Age	0.977	0.924–1.033	0.407			
Grade (grade 2 vs grade 3)†	1.143	0.273–4.786	0.855			
Type (1p/19q-codeleted vs 1p/19q-noncodeleted)†	0.510	0.119–2.188	0.365			
Preop FLAIR-TV†	1.033	0.996–1.072	0.082			
PET qualitative (PET+ vs PET−)	1	0.167–5.985	1.000			
MTV	1.019	0.976–1.063	0.394			
TBR_{max}†	1.302	0.663–2.560	0.444			
TBR_{mean}	1.286	0.245–6.757	0.767			
TMa MET PET involvement (yes vs no)†	0.848	0.175–4.103	0.838			
TMa FLAIR involvement (yes vs no)†	1.333	0.305–5.830	0.702			

* No variable proved to be statistically significant at multivariate analysis.
† Variables selected for the multivariate analysis.

multivariate analysis. The main results regarding imaging data and EOR in relation to postoperative seizure control are reported in Table 3, whereas details regarding univariate and multivariate analyses can be found in Tables 4–6.

Discussion

Our results, investigating the role of preoperative MET PET together with other clinical and imaging variables in defining tumor-related epilepsy and postoperative seizure control in a cohort of patients with LGG (grade 2 and 3) IDH-mutant diffuse gliomas involving the temporal lobe, showed a correlation between MET PET and uncontrolled seizures both at and postsurgery.

Seizure outcome is often underestimated in patients with LGGs. In fact, considering their relatively long survival (in contrast with high-grade tumors), the persistence of seizures despite surgical treatment—still the most important oncological and functional prognostic factor—can significantly impact the quality of life and long-term morbidity, especially when the temporal lobe is involved.[4,27] The reasons for seizure persistence after resection are multifactorial and still under investigation, but they seem to be related to the persistence of epileptogenic foci that are located outside the MRI-FLAIR tumor mass, especially when the highly epileptogenic mesial temporal structures are involved.[8] In these circumstances, advanced preoperative noninvasive imaging techniques could help to modify and tailor the surgical management, by identifying those patients who are not likely to respond to standard surgical lesionectomy.[5,28–32]

In our study we observed that seizures were the most common presenting symptom in patients affected by the IDH-mutant, 1p/19q-codeleted LGG type, and with TMa FLAIR involvement at MRI. These findings are concordant with previous studies demonstrating that oligodendrogliomas carry a higher risk of epilepsy compared to astrocytomas,[33] and that the TMa has an intrinsic epileptogenicity.[34]

Moreover, we found that TMa FLAIR involvement at preoperative MRI was significantly associated with better

TABLE 5. Univariate and multivariate analyses regarding seizure control at surgery (controlled vs noncontrolled)

	Univariate Analysis			Multivariate Analysis		
Variable	OR	95% CI	p Value	OR	95% CI	p Value
Age	0.994	0.946–1.043	0.799			
Grade (grade 2 vs grade 3)*	1.481	0.425–5.161	0.537			
Type (1p/19q-codeleted vs 1p/19q-noncodeleted)*	0.448	0.126–1.589	0.214			
Preop FLAIR-TV	0.999	0.985–1.012	0.829			
PET qualitative (PET+ vs PET−)	1.667	0.340–8.175	0.529			
MTV*	1.022	0.988–1.056	0.208			
TBR_{max}	1.108	0.659–1.864	0.699			
TBR_{mean}	0.943	0.223–3.986	0.936			
TMa MET PET involvement (yes vs no)*	0.229	0.050–1.052	0.058	0.0830	0.009–0.787	**0.030**
TMa FLAIR involvement (yes vs no)	1.167	0.318–4.284	0.816			
AEDs (yes vs no)*	4.364	0.950–20.036	0.070	29.423	0.006–0.839	**0.036**

Boldface type indicates statistical significance.
* Variables selected for the multivariate analysis

TABLE 6. Univariate and multivariate analyses regarding 1-year seizure control (controlled vs noncontrolled)

Variable	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p Value	OR	95% CI	p Value
Age	1.025	0.960–1.094	0.457			
Grade (grade 2 vs grade 3)*	0.467	0.949–2.295	0.348			
Type (1p/19q-codeleted vs 1p/19q-noncodeleted)*	0.294	0.051–1.683	0.169			
Preop FLAIR-TV	0.999	0.983–1.016	0.913			
PET qualitative (PET+ vs PET−)	NA	NA	NA			
MTV	0.987	0.956–1.019	0.426			
TBR_{max}*	0.363	0.162–0.814	**0.014**	0.301	0.105–0.858	**0.025**
TBR_{mean}	0.039	0.002–0.676	**0.026**			
TMa MET PET involvement (yes vs no)	3.181	0.344–29.432	0.308			
TMa FLAIR involvement (yes vs no)	25	2.617–238.787	**0.005**			
EOR (SUP/CR/NTR vs STR/PR)*	6.667	0.747–59.501	0.089			
TMa resection (yes vs no)*	3.857	0.672–22.109	0.130			
Postop treatments (yes vs no)	0.487	0.085–2.800	0.420			
Disease recurrence/progression (yes vs no)*	0.375	0.042–3.355	0.380			
AEDs (yes vs no)	0.852	0.144–5.032	0.860			

NA = not applicable.
Boldface type indicates statistical significance.
* Variables selected for the multivariate analysis.

1-year seizure control at univariate analysis ($p = 0.005$). This may be explained by the fact that patients with known TMa tumor involvement at diagnosis were most likely to undergo excision of highly epileptogenic structures, including the hippocampus. Indeed, in our cohort, nearly all (94%) patients with TMa FLAIR involvement who underwent TMa resection had controlled seizures 1 year after surgery. The same hypothesis was made by Englot et al., who also reported better postoperative seizure outcomes for patients with preoperative TMa involvement.[4]

During the last decade, studies with advanced imaging modalities, including metabolic and molecular imaging techniques, have provided interesting data suggesting that epileptogenic foci associated with TRE could be identified, with particular regard to foci that can be nested within the peritumoral area and that could be undetected on conventional MRI.[35] PET neuroimaging is commonly used in the management of patients with LGG, either preoperatively to define the metabolic tumor extent or postoperatively to monitor treatment response.[10,12,15,16] Nevertheless, its role in defining TRE and postoperative seizure outcomes is still limited.[14,17–20,35] Different radiopharmaceuticals—including [^{18}F]FDG, [^{11}C]MET, [^{18}F]fluoroethyltyrosine, and [^{11}C]alpha-methyltryptophan—have been the subject of several studies of TRE, with yet controversial results.[6,35] Moreover, most of these studies included multiple sites, histologies, and tumor gradings, thus making their findings hard to reproduce and apply in the clinical scenario.

In our series, MET PET qualitative analysis did correlate with preoperative seizure characteristics, because MET PET TMa involvement was related to the presence of uncontrolled seizures at surgery, notwithstanding AED treatment; this was confirmed in the multivariate analysis ($p = 0.030$). Additionally, even though the overall MTV, as well as the TMa MET PET involvement, did not relate to seizure characteristics or control after surgery, the MTV was found to be significantly associated with the presence of seizures at diagnosis, but only in noncodeleted tumors ($p = 0.014$) (Table 7). These findings allow one to argue that the high expression of membrane amino acid trans-

TABLE 7. MET PET results for MTV (in positive examinations) and correlation with the presence of seizures at onset in IDH-mutant astrocytomas

Variable	All IDH-Mutant Astrocytomas, n = 24	Szs at Onset, n = 15	No Szs at Onset, n = 9	p Value
PET qualitative, no. (%)				0.371
Positive	16 (67%)	11 (73%)	5 (56%)	
Negative	8 (33%)	4 (27%)	4 (44%)	
MTV in cm^3, median (IQR), n = 15	6.6 (2.3–16.8)	15.2 (6.6–27.7)	2.3 (2–3.2)	**0.0143**
TBR_{max}, median (IQR), n = 23	2.03 (1.34–2.34)	2.16 (1.47–2.43)	1.46 (1.12–2.03)	0.0778
TBR_{mean}, median (IQR), n = 23	1.47 (0.95–1.59)	1.53 (1.10–1.61)	1.30 (0.95–1.52)	0.1474

Unless otherwise indicated, values are expressed as the number of patients (%) or the median (IQR).

porters, leading to the uptake of amino acid radiopharmaceuticals in the brain, may be secondary not only to the presence of neoplastic cells with a high turnover rate but also to extratumoral epileptogenic foci.[20] It is unclear whether in our cohort one phenomenon prevailed over the other in patients with positive MET PET and seizures.

Finally, in our study, PET-derived semiquantitative data were able to predict seizure outcomes 1 year after surgery. Indeed, higher TBR_{max} and TBR_{mean} values were statistically related to worse postoperative seizure control, and TBR_{max} confirmed its independent predictive value in the multivariate analysis ($p = 0.025$). These data suggest a potential role of MET PET in defining those patients who have more aggressive disease at onset and could benefit from more radical resections, whenever possible, or from alternative/adjuvant treatments or prolonged medical therapy to control secondary TRE.

Limitations

Notwithstanding the promising results, our study presents some major limitations. The first one is its retrospective observational nature. The second, and probably the most important one, is the relatively limited sample size and the loss to follow-up of 21% of patients, which may have been a source of potential bias. However, the investigated pathology is relatively rare, and MET PET is not yet routinely used as a preoperative investigation tool. Moreover, only the temporal location and IDH-mutated tumors have been included in the analyses. On the one hand, this makes the sample itself extremely homogeneous, while on the other, it inevitably affects statistical accuracy. Finally, long-term follow-up data are missing, thus making our findings worthy of more thorough analyses in the future.

Conclusions

MET PET–derived data combined with clinical and radiological information may represent a useful tool to preoperatively identify aggressive diseases and extratumoral epileptogenic foci, and thus predict postoperative seizure control in patients with LGGs. The present study suggests that MET PET qualitative and semiquantitative analysis could be used to define seizure characteristics at the time of surgery and to predict postoperative seizure outcomes in patients with tLGGs, potentially affecting the decision-making process during tumor resection and patient management. These results, however, must be further validated in larger series with longer epileptological follow-up.

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Disclosures

Dr. Chiti reported personal fees from AmGen, Novartis, Sirtex, General Electric Healthcare, and Telix outside the submitted work.

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Conception and design: Bono, Riva, Politi, Rodari, Pessina. Acquisition of data: Ninatti, Bono, Barbieri, Clerici. Analysis and interpretation of data: Ninatti, Bono, Raspagliesi, Barbieri, Politi, Rodari, Sollini, Pessina. Drafting the article: Ninatti, Bono, Riva, Raspagliesi. Critically revising the article: Bono, Riva, Raspagliesi, Navarria, Simonelli, Sollini, Chiti, Pessina. Reviewed submitted version of manuscript: Bono, Riva, Raspagliesi, Barbieri, Rodari, Chiti, Pessina. Approved the final version of the manuscript on behalf of all authors: Ninatti. Statistical analysis: Ninatti, Pessina. Study supervision: Riva, Navarria, Politi.

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