VALIDATION OF DIFFERENT STATIC [^{18}F]FET-PET PARAMETERS IN THE DISCRIMINATION OF LOW- AND HIGH-GRADE GLIOMAS

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BACKGROUND AND GOAL

Though considered rare, primary brain tumours (PBTs) contribute importantly to cancer mortality and morbidity. Proper treatment planning of PBTs relies on an accurate diagnosis, for which postoperatively acquired histopathology is the gold standard. Because biopsy and resection, two sampling methods for acquiring histopathologically validated diagnosis, bear certain risks, which ought to be avoided when possible, and since histopathological tumour evaluation is prone to bias due to tumour heterogeneity and observer variability, there is an increasing interest in non-invasive diagnostic tools to support preoperative treatment planning. Over 75 % of all malignant PBTs are either low-grade gliomas (LGG, WHO grades I and II) or high-grade gliomas (HGG, WHO grades III and IV). Hence, this retrospective cohort study aims to evaluate the role of different static O-(2-[^{18}F]fluoroethyl)-L-tyrosine ([^{18}F]FET) positron emission tomography (PET) parameters in discriminating LGG from HGG.

MATERIALS AND METHODS

Subject recruitment
33 subjects with untreated low- (n = 16) or high-grade (n = 17) glioma and with availability of at least a pretreatment [^{18}F]FET-PET scan and histopathologically validated diagnosis (type and grade) were retrospectively recruited between 1 January 2005 and 31 December 2017 at the Ghent University Hospital, a tertiary care hospital in Ghent, Belgium.

Scan processing
Maximal tumour standardised uptake value (SUV$_{max}$, in g · mL^{-1}) is determined. Mean background SUV (SUV$_{MB}$) is the averaged SUV of all voxels within a spherical volume of interest (VOI) (Ø = 3.0 cm) manually placed in unaffected brain tissue. SUV$_{peak}$ is the averaged SUV of all voxels within a spherical VOI (Ø = 1.2 cm) manually placed in the tumour, such that this averaged SUV is maximised [1]. SUV isocontours define respective VOIs (VOI$_x$), which hold all voxels with an SUV greater than or equal to the isocontour SUV value (Figure 1, Table 1):

Static parameters
An overview of the parameters determined in this study is given in **Table 1**.

Figure 1. Example of VOI definition by SUV isocontours
Transverse [^{18}F]FET-PET scan slice in a 25-year-old male subject with anaplastic astrocytoma (WHO grade III HGG) (a). The black circle in the right hemisphere represents the background VOI. The black circle in the left hemisphere represents VOI$_{peak}$. Detailed view of the tumour shows the different predefined SUV isocontours defining respective VOIs (b). Dark red, isocontour A$_{1.3}$; bright red, isocontour A$_{41}$; orange, isocontour A$_{1.5}$; yellow, isocontour A$_{1.6}$; white, isocontour A$_{50}$. VOI$_x$ is defined by all voxels externally bordered by isocontour A$_x$. A, anterior; L, left; P, posterior; R, right. Case courtesy of the Departments of Neurosurgery and Nuclear Medicine of the Ghent University Hospital, Ghent, Belgium.

Table 1. Overview of defined VOIs and associated static parameters

VOI$_x$	VOI criteria (threshold)	Mean SUV = SUV$_x$	TLU$_x$ = SUV$_x$ · MTV$_x$	TBR$_x = \dfrac{\text{SUV}_x}{\text{SUV}_{MB}}$
VOI$_{MB}$	Sphere (Ø = 3.0 cm) in unaffected tissue	SUV$_{MB}$	- *	-
VOI$_{max}$ (1 voxel)	SUV = SUV$_{max}$	SUV$_{max}$	- *	TBR$_{max}$
VOI$_{peak}$	Sphere (Ø = 1.2 cm) with maximal mean SUV	SUV$_{peak}$	- *	TBR$_{peak}$
VOI$_{1.3}$	SUV ⩾ 1.3 · SUV$_{MB}$	SUV$_{1.3}$	TLU$_{1.3}$	TBR$_{1.3}$
VOI$_{1.5}$	SUV ⩾ 1.5 · SUV$_{MB}$	SUV$_{1.5}$	TLU$_{1.5}$	TBR$_{1.5}$
VOI$_{1.6}$	SUV ⩾ 1.6 · SUV$_{MB}$	SUV$_{1.6}$	TLU$_{1.6}$	TBR$_{1.6}$
VOI$_{41}$	SUV ⩾ 41 % SUV$_{max}$	SUV$_{41}$	TLU$_{41}$	TBR$_{41}$
VOI$_{50}$	SUV ⩾ 50 % SUV$_{max}$	SUV$_{50}$	TLU$_{50}$	TBR$_{50}$

* TLU was not calculated for background, maximal, and peak VOIs, since the corresponding volumes are fixed (3.0-cm-diameter sphere, 1 voxel, and 1.2-cm-diameter sphere, respectively).
MB, mean background; SUV, standardised uptake value; TBR, tumour-to-background ratio; TLU, total lesion tracer uptake; VOI, volume of interest.

Statistical analysis
Satisfaction of parametric conditions is assessed with a Shapiro–Wilk and Levene test. Parameters are compared between LGG and HGG with an unpaired Student's t test (parametric conditions satisfied) or with a Mann–Whitney U test (parametric conditions not satisfied). Parameters significantly differing between LGG and HGG are subjected to receiver-operating characteristic (ROC) analysis. Parameter means or medians are assessed to determine whether higher values correspond to higher or lower grade. Optimal parameter cut-off value (COV) is the value at which Youden's index (J) = sensitivity (SN) + specificity (SP) − 1 is maximised. All results with $p < 0.05$ are considered significant.

RESULTS

Distributions of SUV$_{max}$, SUV$_{peak}$, SUV$_{41}$, SUV$_{50}$, TBR$_{max}$, and TBR$_{50}$ satisfy parametric conditions among both groups, while all other parameters do not ($p < 0.05$). Results of comparisons between LGG and HGG, and ROC analysis, are summarised in **Table 2**. AUC is highest for MTV$_{1.5}$ (0.85), and lowest for TBR$_{1.5}$ (0.78). At their respective optimal COV, Youden's index is highest for MTV$_{1.5}$ (J = 0.691), and lowest for TBR$_{1.3}$ (J = 0.449).

Table 2. Diagnostic strength of static PET parameters significantly differing between LGG and HGG

	Mean (SD) or median (IQR)*		p**	AUC (95 % CI)	Optimal COV	SN (%)	SP (%)
	LGG	HGG					
TBR$_{max}$	2.64 (1.16)	4.33 (1.59)	0.002	0.82 (0.68-0.97)	3.38	70.60	81.30
TBR$_{50}$	1.67 (0.69)	2.68 (0.97)	0.002	0.81 (0.66-0.96)	2.25	70.60	81.30
MTV$_{1.3}$ (mL)	4.47 (24.13)	60.08 (122.00)	0.001	0.84 (0.69-0.98)	18.53	88.20	75.00
MTV$_{1.5}$ (mL)	1.62 (18.10)	38.46 (56.70)	< 0.001	0.85 (0.71-0.99)	7.95	94.10	75.00
MTV$_{1.6}$ (mL)	0.93 (15.88)	28.58 (31.10)	0.001	0.84 (0.69-0.98)	6.68	88.20	75.00
TLU$_{1.3}$ (g)	8.01 (29.65)	90.62 (95.08)	0.002	0.81 (0.64-0.97)	15.41	94.10	68.80
TLU$_{1.5}$ (g)	2.08 (17.11)	48.66 (81.31)	0.001	0.82 (0.67-0.98)	19.76	76.50	81.30
TLU$_{1.6}$ (g)	1.48 (14.99)	31.49 (60.01)	0.002	0.81 (0.65-0.97)	16.69	76.50	81.30
TBR$_{peak}$	1.26 (1.01)	2.29 (1.32)	0.004	0.79 (0.64-0.95)	1.55	82.40	68.80
TBR$_{41}$	1.31 (0.75)	2.26 (1.31)	0.002	0.80 (0.65-0.95)	1.91	70.60	81.30
TBR$_{1.3}$	1.48 (0.33)	1.75 (0.42)	0.004	0.79 (0.63-0.94)	1.58	82.40	62.50
TBR$_{1.5}$	1.68 (0.39)	1.98 (0.40)	0.005	0.78 (0.63-0.94)	1.94	70.60	75.00
TBR$_{1.6}$	1.77 (0.41)	2.12 (0.48)	0.002	0.81 (0.67-0.96)	2.06	70.60	75.00

Parameters that did not significantly differ between LGG and HGG were excluded from this table.
* Mean (95 % CI) for TBR$_{max}$ and TBR$_{50}$, median (IQR) for all other parameters.
** Based on an unpaired Student's t test for TBR$_{max}$ and TBR$_{50}$ (equal variances assumed, p > 0.05), and on a Mann–Whitney U test for all other parameters.
AUC, area under the ROC curve; COV, cut-off value (value for which SN + SP is maximised) HGG, high-grade glioma; MTV, metabolic tumour volume; LGG, low-grade glioma; SD, standard deviation; SN, sensitivity; SP, specificity; TBR, tumour-to-background ratio; TLU, total lesion tracer uptake.

CONCLUSION

This present study suggests a potentially valuable role for at least 13 SUV-based static [^{18}F]FET-PET parameters, for the differentiation of LGG and HGG, with AUCs ranging from 0.78 to 0.85. Further statistical analyses may combine multiple such parameters into one diagnostic tool for more precise differentiation of LGG and HGG. However, due to the limited sample size and subsequent power of this study, our results must be corroborated in larger populations. We emphasise that to date, PET parameters, including those mentioned in this study, are at most semiautomatically computed, in essence still depending on manual input (such as arbitrarily chosen thresholds and manual placement of background and peak VOIs), prone to bias due to both intra- and inter-observer variability. Hence, we stress the need for fully automated diagnostic tools in the typing and staging of primary brain tumours in clinical settings, to minimise bias.

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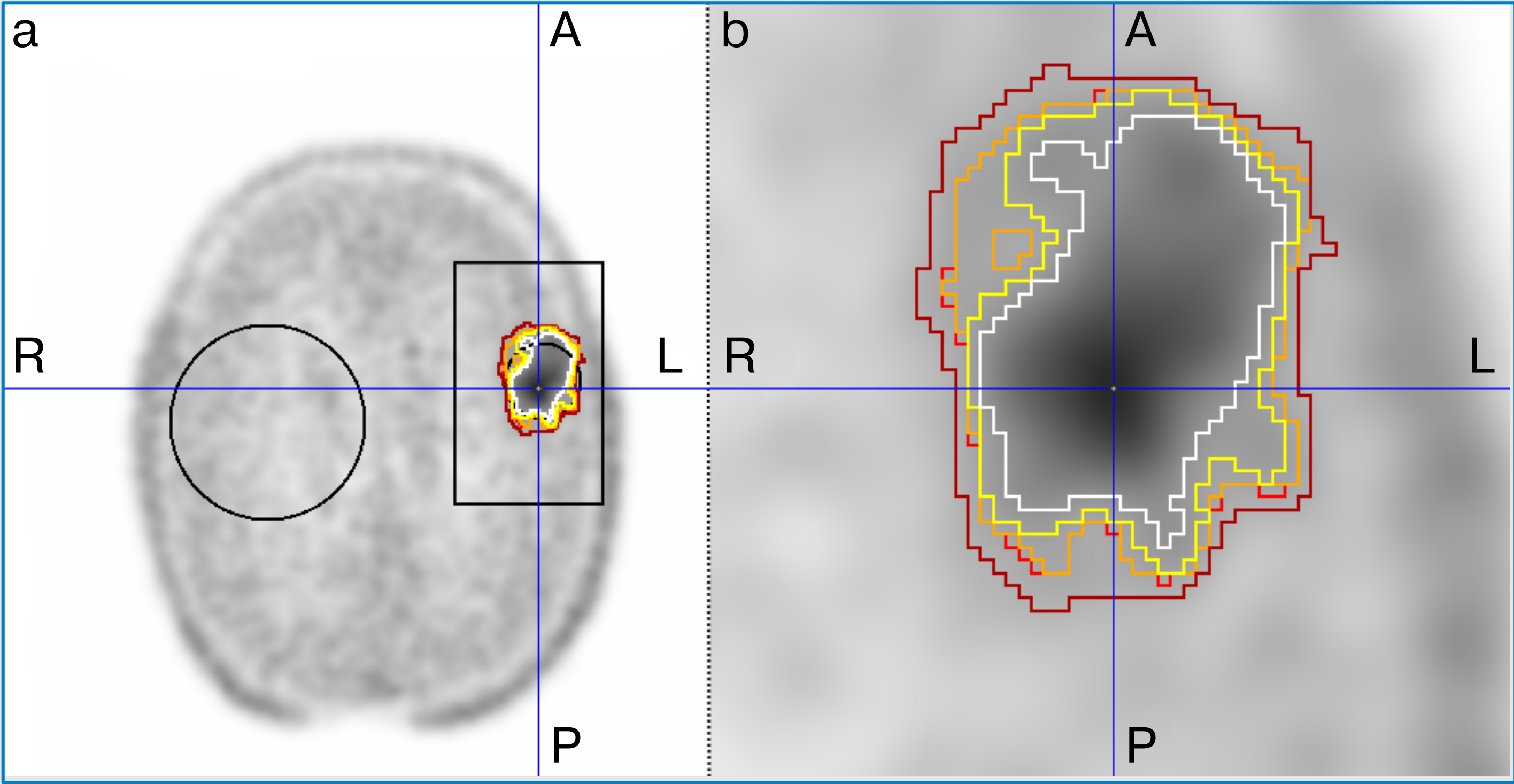
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