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Clinical Study

Semi-quantification of methionine uptake and flair signal for the evaluation of chemotherapy in low-grade oligodendroglioma

Bich-Ngoc-Thanh Tang[1], Niloufar Sadeghi[2], Fabrice Branle[3], Olivier De Witte[4], David Wikler[1] and Serge Goldman[1]
[1]*Department of Nuclear Medicine and PET/Biomedical-Cyclotron Unit;* [2]*Department of Radiology;* [3]*Department of Oncology; and* [4]*Department of Neurosurgery, Université Libre de Bruxelles-Hôpital Erasme, Brussels, Belgium*

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Summary

^{11}C-Methionine (MET) is a useful positron emission tomography (PET) tracer for the evaluation of low-grade gliomas. Among these tumors, a high percentage of low-grade oligodendrogliomas (ODG) are sensitive to chemotherapy with procarbazine, CCNU, and vincristine (PCV). We aimed at: (1) objectively assessing ODG response to PCV by a metabolic index (the Activity Volume Index or AVI) generated from an automated semi-quantification of PET with MET (PET-MET); (2) comparing AVI and quantitative magnetic resonance imaging (MRI) measurements of response to PCV.

Methods: seven patients with ODG were followed for a period of 19.9 ± 6.6 months after the completion of PCV chemotherapy. Regions of interest (ROI) were generated by covering all voxels with count values above a threshold level set at 120% of the mean cerebellar activity. On each slice, ROI volume and mean count values were calculated. AVI was calculated as the sum over all ROI of *tumor volume* × *(tumor mean count/cerebellum count)*. Tumor volume measurements on MRI, were based on signal abnormalities visually detected on fluid-attenuated inversion recovery (FLAIR) sequences.

Results: PCV therapy was associated with a drastic decrease in AVI (mean ± SD, cm^3): AVI post-PCV = 0.80 ± 1.45 vs. AVI prior PCV = 12.94 ± 11.46 ($P = 0.03$). Likewise, we observed a decrease in tumor volume estimated from the FLAIR signal (31.37 ± 11.99 post-PCV vs. 67.95 ± 39.96 prior PCV, $P = 0.03$) although AVI decrease after PCV was significantly more pronounced ($P = 0.015$).

Conclusion: This study, based on limited number of patients and follow-up period indicates that AVI may be a sensitive and observer-independent method applicable to the assessment of ODG responsiveness to PCV treatment and may offer a major added value to both clinical assessment and MRI evaluation of chemotherapeutic outcomes.

Introduction

Treatment and follow-up of low grade gliomas remain a challenge despite various approaches based on resection, radiation, drug therapies [1]. Their morbidity relates to effects on the surrounding, often infiltrated, cerebral tissue while their mortality issues from their potential anaplastic evolution. Oligodendroglioma (ODG), a glioma originating from the oligodendrocytic glial cell line, is more sensitive to chemotherapy than astrocytoma of the same grade [2,3], particularly when it combines procarbazine, CCNU and vincristine (PCV). The standards applied to assess tumor response to chemotherapy is currently based on the patient's clinical outcome combined with morphological criteria, specifically tumor size changes on magnetic resonance imaging (MRI) or enhanced computed tomography (ECT). Thus, in newly diagnosed or recurrent ODG and in mixed oligoastrocytoma, response rates to PVC as variable as 55–75% are reported [4–6]. In a study using T2 weighted-MRI criteria [7], only 28% (7/25 patients with ODG) show a partial response to PCV. To delineate ODG, MRI techniques have recognized limitations. These stem from the infiltrative nature of these tumors [8]. The typical absence of contrast enhancement in low grade ODG [9] also impedes proper MRI or ECT evaluation of tumor evolution under treatment.

Studies have shown that the amino acid tracer ^{11}C-Methionine (MET) heavily accumulates in gliomas, even when contrast enhancement is absent [10,11] and FDG uptake is low [12–14]. A stereotactic study has shown that MET uptake is locally related to histological markers of aggressiveness [15]. Hence, PET using MET (PET-MET) is a recognized tool for the clinical management of low-grade gliomas [14,16–20] but its value for the evaluation of treatment effectiveness has not been clearly defined.

In this work, we aimed at defining an index integrating activity and volume data from PET-MET analysis, in order to reliably measure the tumor load within the brain. Second, we evaluated the contribution of this index as an objective assessment tool regarding tumor responsiveness to chemotherapy. Finally, use of this index was compared to the axial turbo spin echo fluid-attenuated inversion recovery (FLAIR) MRI-based technique to evaluate ODG response to PCV treatment.

Methods

Patients

Seven patients (4 females, 3 males; mean age ± SD: 41.63 ± 14.22 years) with a known low-grade ODG primarily diagnosed by stereotactic biopsy ($n = 5$) or tumor resection ($n = 2$), were followed after the initiation of PCV treatment from April 2000 to August 2003.

Chemotherapy was proposed in these patients because extensive resection of the lesion was not achievable due to its localization or extension. Chromosome 1p/19q status or Ki67 labelling index were not used in this decision. Three of these patients received PCV as first therapy, two others as an adjuvant treatment and the two remaining patients for inoperable recurrence. Two patients completed the total session of six PCV cycles. Treatment was interrupted in the remaining patients due to neutrocytopenia developed at the end of the fourth session. The terms: (1) 'Adjuvant' treatment refers to the programmed chemotherapy following a subtotal resection; (2) 'First' treatment denotes that chemotherapy was the only medical intervention considered for the patient and (3) treatment 'for relapse' signifies that chemotherapy was administered as the only treatment proposed to the patient after a relapse. Finally, only patient 2 underwent radiotherapy.

Clinical status was highly variable in the group of patients. Clinical evaluation by Karnofsky Performance Scale (KPS) was performed prior and at the end of chemotherapy. Patients' characteristics as well as clinical outcomes are summarized in Table 1.

Each patient underwent PET-MET and MRI before and after the last of the chemotherapy cycle. MRI was obtained (mean ± SD) 0.49 ± 0.77 months from PET-MET prior PCV and 0.29 ± 0.54 months post-PCV. One patient was evaluated with the two modalities during the chemotherapy at the end of the third cycle. In five patients, several PET-MET were obtained during the long term follow-up after PCV, four of which had simultaneous MRI examinations.

PET-MET analysis

Patients in the fasted state were injected intravenously with a bolus of about 555 MBq of MET prepared following a method adapted from Comar et al. [21]. The 20 min emission scans were obtained starting 20 min post-injection.

Attenuation correction was performed by means of a transmission scan. All except one PET-MET were performed on an ECAT 962-HR+ operated in 3D mode (CTI-Siemens, Knoxville, TN). This system provides a set of 63 planes with a slice thickness of 2.4 mm. One scan was performed on an ECAT 933/08-12 (CTI-Siemens, Knoxville, TN), which provides 6.75 mm adjacent slices over an axial length of 10.5 cm. Images were reconstructed by filtered back projection, displayed and analyzed using the ECAT software. The PET-MET were obtained before and at several time

Table 1. Patient clinical characteristics

	Age at onset of PCV (years)	Follow-up duration post-PCV (months)	Tumour localisation	Successive treatments	Indication for PCV	Symptoms at PCV initiation	KPS prior initiation of PCV	KPS post-completion of PCV		Number of complete PCV cycles
								At the end of PCV	Further follow-up	
I	58	18.07	Right parietal	PCV	First intervention	Motor deficit and epilepsy	80	100	100	6
II	29	9.23	Right parieto-temporal	Surgery Surgery +RT+PCV	Adjuvant	Visual, sensitive and motor deficit	70	80	80	6
III	40	21.93	Left frontal	Surgery Surgery PCV	For relapse	Epilepsy, aphasia	70	90	90	5
IV	33	16.43	Right fronto-temporal	PCV	First intervention	Epilepsy	70	90	100	4
V	32	28.5	Right fronto-temporal	PCV	First intervention	Epilepsy	80	90	90	4
VI	65	27.1	Bilateral frontal	Surgery PCV	For relapse	None[a]	100	100	100	4
VII	33	18.53	Right frontal	Surgery+PCV	Adjuvant	Epilepsy	90	90	100	4

RT = radiation therapy.
[a] No clinical changes but evolution on PET and MRI.

points during and after the course of PCV treatment. Regions of interest (ROI) were set up independently from MRI and ECT data. First an elliptical ROI and its mirror image were placed in the cerebellar cortex considered as tissue of reference. The cerebellum was chosen as tissue of reference because it is a relatively homogeneous and large structure distant from ODG occurrence sites. The mean activity within these ROI was used to set the threshold and to normalize the activity detected in the tumors. Volume and uptake of MET in the tumor were recorded in automatically generated ROI. These ROI covered all voxels with count values above a threshold set at 120% of the weighted mean activity in the cerebellar cortex. Pretreatment tumor uptake was evaluated by the ratio of the mean counts in all tumor ROI over the mean cerebellar counts. To assess the whole tumor metabolic activity, an Activity Volume Index (AVI) was calculated as

$$\mathrm{AVI} = \sum_{i}^{\mathrm{ROI}} \frac{A^t(\mathrm{ROI}_i)V^t(\mathrm{ROI}_i)}{\overline{A}(\mathrm{cerebellum})}$$

where t is the tumor, V the volume, A the activity and $\overline{A}$ mean activity.

MRI analysis

All MRI examinations were performed using a 1.5-T whole-body MR imager (Gyroscan ACS-Power Trak 6000, Philips, Best, The Netherlands), with a maximum gradient strength of ±20 mT/m. A standard circularly polarized head coil was used. The following sequences were acquired for each patient: axial T1-weighted images with imaging parameters of 422/9 (TR/TE), slice thickness of 5 mm, field of view of 180 × 240, and matrix of 179 × 256; axial T2-weighted spin-echo images with imaging parameters of 5081/100 (TR/TE), slice thickness of 5 mm, field of view of 180 × 240, and matrix of 224 × 256. FLAIR images were acquired with imaging parameters of 6500/150/2100 (TR/TE/TI), slice thickness of 5 mm, field of view of 180 × 240, and matrix of 140 × 256.

We finally obtained contrast-enhanced, axial T1-weighted images after an intravenous injection of 0.1 mmol of gadopentetate dimeglumine per kilogram of body weight (Dotarem, Guerbet Laboratories, Aulnay-sous-Bois, France).

The volume measurement for each tumor was based on signal abnormalities detected on the set of FLAIR images. The (FLAIR) sequence has been selected to define the tumor volume as it is superior to the conventional T2-weighted sequences to demarcate intracranial tumors from non-tumor tissue [22]. First, the tumor boundaries were manually traced considering areas of high signal intensities on FLAIR images. For this process, FLAIR images were compared to the T1-weighted images in order to discard FLAIR anomalies attributable to non-tumor lesions such as hemorrhage. The total volume of each tumor was calculated as the summed volumes of all ROI traced on the set of FLAIR images.

Statistical analysis

Statistical analyses were performed using Prism 2 (GraphPad Software, San Diego, CA). Non-parametric Wilcoxon two-tailed t test was used for data analysis and the level of significance was set at $P < 0.05$.

Results

In all patients, neurological assessment showed clinical improvement after PCV treatment. This improvement either involved neurological deficits or seizure control (Table 1). The KPS before PCV and at the end of the PCV completion increased from 70 (mean; range: 70–100) to 90 (mean; range: 80–100) (Table 1).

Initial AVI evaluation using PET-MET prior to therapy commencement showed elevated tumor uptake in all patients as illustrated in Figures 1A and 2A. The timing of assessment and the data obtained are summarized in Table 2. The ratio of tumor to cerebellum activity was evaluated and showed a mean value of 1.47 ± 0.17 (mean ±SD); ranging from 1.27 to 1.73. AVI evaluated at the basal time point (12.94 ± 11.46 cm^3) was significantly reduced after PCV treatment (0.80 ± 1.45 cm^3, $P = 0.03$, Figures 1–2 and 4A). Similarly, the volume measurements on MRI decreased from 67.95 ± 39.96 cm^3 before PCV to 31.37 ± 11.99 cm^3 after treatment ($P = 0.03$, Figures 1–2 and 4B). AVI shows statistically more significant decrease than the FLAIR signal volume ($P = 0.015$, Figure 5). Using 25% decrease as cut-off value for responsiveness to therapy, six patients were considered as responders both on the basis of AVI and MRI volume measurements. As a group, they showed a mean post-therapy decrease of 96.32% in AVI and 49.86% in MRI volume measurements. The patient who did not reach the 25% cutoff decrease, AVI and tumor volume on MRI were actually increased by 27.70 and 41.11%, respectively (Figure 3). In the five patients with longer follow-up, further assessments by PET-MET showed no late AVI increase (Table 1). Volumetric measurements on MRI evaluated in four of these patients showed a continuous decrease of the FLAIR volume in two cases (12.27 and 22.13%) and less than 10% changes in the two others.

Discussion

The work here presented describes an analytical PET-based method of follow-up for low-grade ODG. We have generated an index of whole tumor MET uptake, namely AVI, with a simple automated semi-quantitative measure. This index integrates tumor volume and level of MET uptake. It is intrinsic to the metabolic imaging modality and consequently avoids subjective delineation of tumor on PET or co-registered MRI. Tested in seven patients with low-grade ODG treated

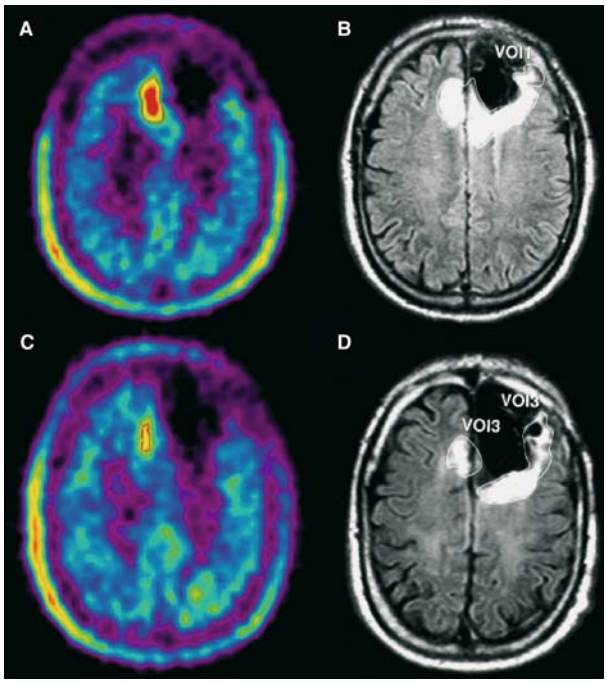

Figure 1. Patient 6 treated by PCV chemotherapy for recurrence after surgical resection of an ODG: PET-MET before chemotherapy with an area of high uptake in the right border of the resection cavity (A). On the corresponding MR images (B), the posterior and left borders of the resection cavity present high intensity of FLAIR signal where no metabolic activity is detected. PET-MET (C) and MRI images (D) demonstrate the tumor response after treatment completion. ROI on the PET-MET slices are obtained by a thresholding method (red line). Boundaries of the tumor are traced considering areas of high signal intensities on FLAIR images (white line).

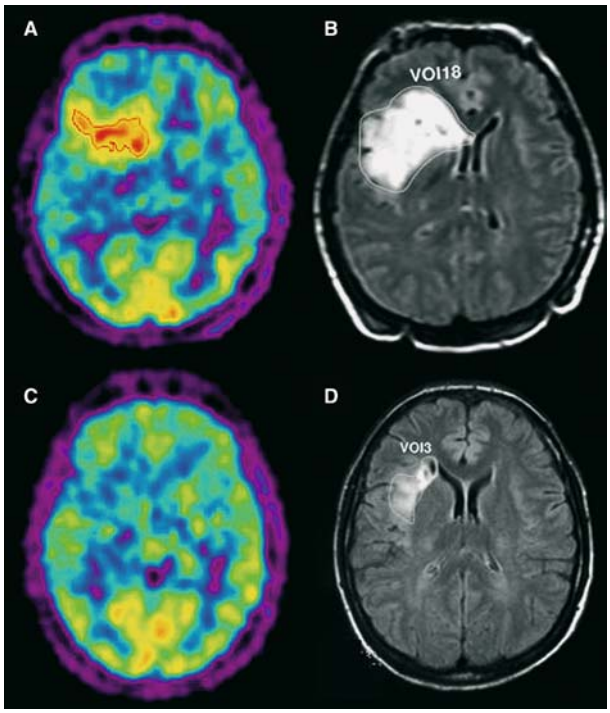

Figure 2. Patient 4 treated by PCV chemotherapy after diagnostic biopsy of an ODG: PET-MET before chemotherapy showing an area of moderate uptake in the right fronto-temporal region (A). Corresponding MR images before chemotherapy (B). After completion of treatment, no tumor activity is detected on PET-MET (C) whereas abnormal FLAIR signal is decreasing but still present on MRI images (D). ROI on the PET-MET slices are obtained by a thresholding method (red line). Boundaries of the tumor are traced considering areas of high signal intensities on FLAIR images (white line).

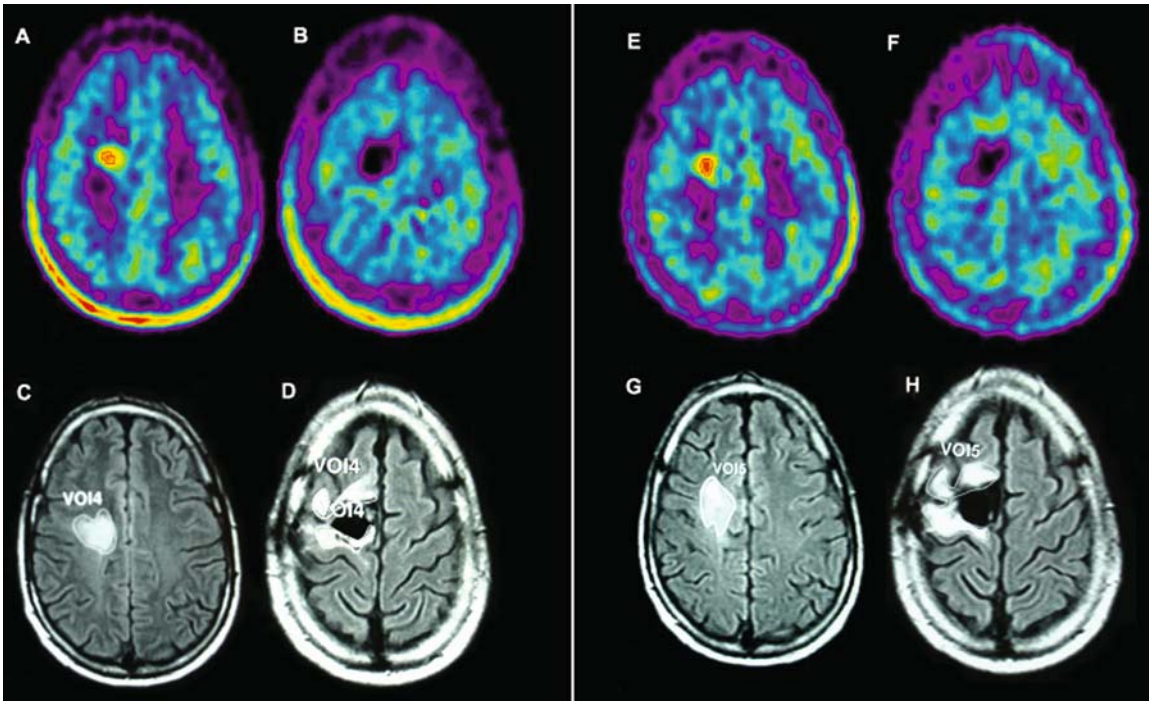

Figure 3. Patient 7 treated by PCV chemotherapy after resection of an ODG: PET-MET before chemotherapy showing an area of increased uptake in the right subcortical frontral region (A, B). Corresponding MR images before chemotherapy (C, D). After completion of treatment, slight increase in tumor activity is detected on PET-MET (E, F) and MR images (G, H). Increase in FLAIR signal is found at the level of the resection site borders (G compared to C) where no MET uptake is found on either PET-MET (A and E). ROI on the PET-MET slices are obtained by a thresholding method (red line). Boundaries of the tumor are traced considering areas of high signal intensities on FLAIR images (white line).

Table 2. PET-MET and MRI-FLAIR measurements and timing

Patient	Successive scans	PET-MET (AVI)					FLAIR (volume)				
		Prior initiation of PCV		Post-completion of PCV		% of initial AVI	Prior initiation of PCV		Post-completion of PCV		% of initial volume
		Time (month)	AVI (cm^3)	Time (month)	AVI (cm^3)		Time (month)	Volume (cm^3)	Time (month)	Volume (cm^3)	
I	1	2.27	20.13			100	2.20	30.56			100
	2			−4.70	4.12	20.45			−4.70	29.23	95.63
	3			3.87	0.16	0.79			3.93	22.01	72.01
	4			17.63	0.11	0.55	–	–	–	–	–
II	1	1.73	33.95			100	1.17	120.23			100
	2			−0.13	4.61	13.58			0.03	35.80	29.78
	3			8.70	4.05	11.92			7.26	24.40	20.29
III	1	4.13	1.95			100	4.13	94.88			100
	2			17.47	0	0			16.97	37.56	39.59
	3			21.50	0	0			20.23	38.87	40.96
IV	1	3.30	9.67			100	1.20	97.68			100
	2			7.50	0	0			7.50	54.26	55.54
	3			16.3	0	0			16.30	32.68	33.41
V	1	3.50	12.01			100	3.50	78.57			100
	2			7.60	0.60	5.00			7.60	33.99	43.27
	3			19.87	0.02	0.15			17.90	25.10	31.94
VI	1	4.87	12.68			100	4.87	40.11			100
	2			22.33	0.56	4.38			22.33	28.13	70.13
	3			26.77	0.11	0.86			26.77	31.47	78.47
VII	1	0.97	0.20			100	0.23	13.63			100
	2			13.93	0.25	127.7			13.93	19.23	141.11

[a] Time before completion of PCV treatment.

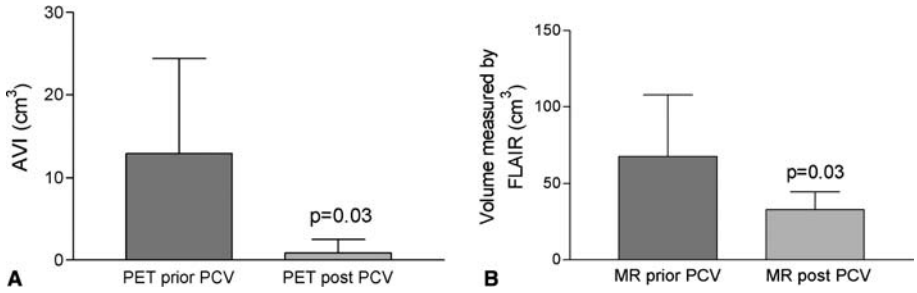

Figure 4. PET-MET and MRI-FLAIR tumor analyses before and after PCV. Results are expressed as mean ± SD ($n = 7$). AVI measurement on PET-MET (A) and volume measurement on MRI-FLAIR (B) significantly decrease after PCV treatment.

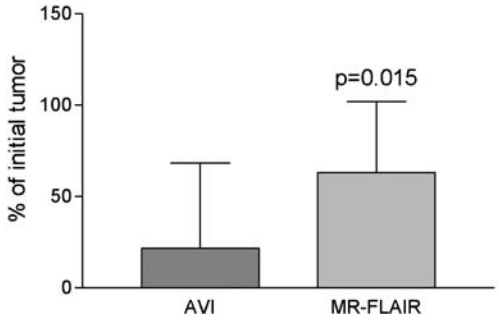

Figure 5. Comparison of PET-MET AVI and MRI-FLAIR volume calculations in response to PCV chemotherapy. Decrease in AVI is significantly more pronounced than decrease in volume measurement on MRI-FLAIR. Variation is expressed in % change in comparison to pre-treatment value (mean ± SD, $n = 7$).

by chemotherapy, AVI appears a practicable and sensitive index of ODG evolution.

Compared to astrocytomas, the high sensitivity of ODG to PCV therapy is well established but not fully understood**.** One of the most relevant prognostic factors for this responsiveness is the molecular pattern of ODG. Loss of chromosomes 1p and 19q, a combined marker of ODG [23], indeed correlates with exceptional responsiveness and prolonged survival [24–26].

If the benefits of PCV chemotherapy in patients with ODG are recognized, the accurate monitoring of this treatment remains problematical. Morphological imaging methods are difficult to interpret for this follow-up. This difficulty probably partly explains the high variablility of responsiveness rate based on clinical follow-up and morphological imaging. For this evaluation, MRI and ECT rely on changes in tumor size since a large number of these tumors do not present contrast enhancement [9]. Metabolic assessment of responsiveness, as tested in the present study, appears therefore attractive. It has already been applied for gliomas of a different type and grade, i.e. the high grade astrocytomas. SPECT with ^{201}Tl, a tracer known to accumulate in gliomas partly through an ATPase active transport [27], has indeed demonstrated decreased volume and intensity of uptake in patients with malignant astrocytoma treated with PCV. As reported by the authors these changes were more pronounced than morphological findings and ^{201}Tl-SPECT results after completion of chemotherapy correlated with clinical findings during follow-up [28]. For the evaluation of low-grade ODG, PET study of MET uptake was considered the method of choice in view of the high sensitivity of this tracer for this tumor, particularly in comparison to FDG. In line with this assumption, recent data indicated that MET uptake measurement is more suitable than FDG uptake for monitoring therapeutic effect in low-grade gliomas treated by brachytherapy [19]. In addition, a recent case report describes a patient with anaplastic astrocytoma in whom favorable response to PCV is accompanied by a continuous decline in MET uptake [29].

To establish an observer-independent method of PET-based evaluation of therapeutic response, we used a thresholding procedure to delineate the tumor area. Prior chemotherapy, all ODG tumors in our study presented a high level of uptake of MET. This avidity of low grade ODG for MET has been reported in the literature [14,20]. We made use of this feature to set a constant threshold for tumor evaluation at 120% of a control area (cerebellum). The threshold was chosen on the basis of our large experience acquired with PET-guided brain biopsies (more than 150 PET-guided procedures during the last 10 years) [30]. The index of metabolic activity, here defined as AVI, takes into consideration both volume and activity level of the tumor. It appears indeed essential to integrate these two variables since tumor cells response to treatment is expected to influence the evolution of both their total mass and metabolic activity. AVI provides a characterization of tumor features independently from morphological data. Tumor delineation is indeed intrinsic to the metabolic imaging modality and avoids subjective delineation on PET or co-registered MRI. Obviously, the thresholding technique does not ensure that infiltrated cells in the surrounding brain tissue are integrated in the evaluation but visual inspection of the ROI obtained indicated that in all cases the core of the tumor was accurately tested. As a matter of fact, neither PET-MET with the threshold here used nor FLAIR changes on MRI ensure accurate delineation of the tumor and its extensions in the infiltrated brain. Concerning this question of tumor

delineation, it is noteworthy that, as illustrated on Figure 1, FLAIR signal is highly sensitive to post-operative changes such as inflammation or hemorrhage, and therefore certainly less accurate than PET-MET.

The mechanisms of MET uptake in gliomas is known to depend on MET diffusion across the blood–brain barrier, activation of carrier-mediated transport at the same level [31] and transcellular system L-like transport. The latter system of transport depends on the proliferation rate of human glioma cells *in vitro* as the MET uptake decreases by 73% when the cells shift from the exponential growth phase into the plateau phase [32]. Therefore, in our patients, we suggest that the important reduction of MET uptake is a clue for major metabolic disturbances of ODG when exposed to alkylating drugs. The metabolic inhibition here demonstrated is expected to involve diverse cell functions including proliferation. The metabolic reaction is obviously earlier than the consequent cell death that leads to tumor volume reduction. This explains the more pronounced changes detected by AVI compared to FLAIR. In addition, the FLAIR signal probably overestimates tumor volume by the assimilation of the inflammatory and gliotic reactions. In fact, areas of high signal intensities on FLAIR images were inhomogeneous within the tumor mass. Unfortunately, there is no criterion available to differentiate on these images tumor from inflammatory changes within the tumor boundaries or the surrounding tissue [33]. It has been also described that, in the postoperative phase, FLAIR imaging is unable to suppress the signal related to cerebrospinal fluid because of the presence of protidic cell components and blood within the resection cavity [34]. The multiple factors that influence AVI and FLAIR changes probably evolve on different time scales. The present study did not specifically address the question of differences in kinetics between PET-MET and FLAIR changes on MRI. Still, it is worth noting that in the patient who was assessed before completion of the PCV cycles, AVI decreased to 20% of the initial tumor level when the FLAIR volume had not yet changed.

The clinical relevance of AVI evaluation of ODG response to treatment certainly requires further studies. As a first approach, it is noteworthy that no patient with AVI decrease in the present series presented neurological sign of relapse during the follow-up period. Based upon the imaging techniques, to distinguish responders from non-responders we applied the criterion of 25% decrease of the initial value of AVI and/or FLAIR. Six of our patients presented this response and one did not. However, the prognostic value of the AVI response in terms of time of relapse is an aspect that the study has not addressed. A multi-centric study is needed to establish by ROC curve analysis the accurate cut-offs to separate responder and non-responder groups. Three patients presented no relapse in tumor activity more than 1.5 year post-treatment but longer follow-up in a larger population will be necessary to investigate this point.

Conclusion

This study, based on limited number of patients and follow-up period indicates that AVI derived from PET-MET analysis may provide a sensitive and objective marker of ODG response to PCV chemotherapy. Volumetric data from MRI-FLAIR provide concordant information on ODG response to PCV treatment, though PET-MET appears significantly more sensitive. The two imaging techniques obviously provide information of different nature and larger multi-centric studies should establish their respective usefulness, particularly in term of prognostic value.

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Address for offprints: Bich-Ngoc-Thanh Tang, Hospital Erasme, route de Lennik 808, 1070 Brussels, Belgium; Tel.: +32-2-555-3111, ext. 5727; Fax: +32-3-555-6800; E-mail: Thanh.Tang@ ulb.ac.be